The Impact of Fertility Changes on Maternal Mortality

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I, Wei Huang, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

ABSTRACT

As less developed countries experience lower fertility, the age/parity distribution of pregnancies may shift. While these shifts may affect maternal mortality levels, their exact impact remains largely unknown. The aim of this thesis is to quantify the impact of fertility changes on maternal mortality.

First, the literature was systemically reviewed for the strength of association between maternal age/parity and the maternal mortality ratio. Second, a retrospective cohort study utilised data from Matlab, Bangladesh to investigate the relationship between maternal age/gravidity and the pregnancy-related mortality ratio (PRMRatio) using logistic regressions. Lastly, the impact of observed (in Matlab) and theoretical shifts in childbearing composition on pregnancy-related mortality indicators was modelled using a compartmental model.

The systematic review, including 62 studies, found that the risk of maternal death was higher for very young adolescents, older women and nulliparas. However, it was difficult to disentangle the confounding effect of age and parity.

The retrospective cohort study found that the odds of pregnancy-related death was four times higher for women at the extreme maternal ages, even after adjustment for confounders, including gravidity. Nulligravidas were at increased risk of pregnancy-related death (adjusted OR=1.63, CI: 1.24-2.16), but multigravidas were not. The adverse effect of first pregnancies was more pronounced for older women.

The compartmental model suggests that the fertility decline in Matlab between 1983-1993 and 2000-2005 accounted for a 30% reduction in the pregnancy-related mortality rate (PRMRate). However, it made no contribution to the reduction in the PRMRatio observed during this period.

Reducing or eliminating pregnancies at extreme ages and high gravidity could reduce the PRMRatio by 1-17% and the PRMRate by 1-50%. If all women had a maximum of one pregnancy each, the PRMRate would decrease by 74%. However, the PRMRatio would increase by 32% due to higher risk of first pregnancies.

Fertility changes have limited impact on maternal mortality ratios, but can have substantial effect on the maternal mortality rate.

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ACRONYMS AND ABBREVIATIONS

CI	Confidence interval
CEMD	Confidential Enquiry into Maternal Deaths
COR	Crude odds ratio
DHS	Demographic and Health Surveys
GFR	General fertility rate
HDSS	Health and Demographic Surveillance System
ICDDR,B	International Centre for Diarrhoeal Disease Research, Bangladesh
ICD-10	International Statistical Classification of Diseases and Related Health Problems (10th Revision)
MCH-FP	Maternal and Child Health and Family Planning Programme
MMRate	Maternal mortality rate
MMRatio	Maternal mortality ratio
MeSH	Medical Subject Heading
OR	Odds ratio
PRMRate	Pregnancy related mortality rate
PRMRatio	Pregnancy related mortality ratio
RAMOS	Reproductive age mortality studies
TFR	Total fertility rate
UCI	Uncertainty interval
UN	United Nations
WHO	World Health Organization

1 INTRODUCTION

In 2008, around 350,000 women died globally from complications relating to pregnancy or childbirth [1-2].Of all the human development indicators, maternal mortality shows one of the widest differences between rich and poor countries. Less developed countries are burdened with 99% of all maternal deaths. Women in Africa face an obstetric risk of 620 maternal deaths per 100,000 live births, whilst the corresponding risk for European women is 21 [2]. These differences mask extensive variations between and within countries. The reduction of maternal mortality was adopted as part of the Fifth Millennium Development Goal by the United Nations [3]. One of its aims is to reduce the maternal mortality ratio by 75% between 1990 and 2015.

Pregnancies to very young, very old, primiparous or multiparous women are often quoted as at increased risk of maternal death [4]. Fertility changes that shift pregnancies away from high risk groups could potentially decrease the maternal mortality levels. In addition, fertility decreases achieved through the use of effective contraception can affect maternal mortality levels through the removal of exposure to unintended pregnancy for women who want no more children. Without unintended pregnancies there will be few or no maternal deaths as a result of unsafe abortions.

The traditional high risk groups are widely acknowledged, but the evidence for their effects on maternal mortality was often based on past investigations focused primarily on crude relationships [5-6]. The examination of childbearing composition (maternal age and parity) as the main determinant of maternal mortality has been neglected in more recent decades.

There are a limited number of existing studies that have investigated the impact of fertility changes on maternal mortality. These models have a number of limitations as will be shown later. None of these models took account of the close association between maternal age and parity, and some models eliminated births without taking account that women must start their childbearing with a first birth. Since women in the model were not closely followed through their reproductive lives, the exact fertility assumptions made were unclear. While they have the advantage of being easily replicable, they lack the ability for precise manipulation of the parameters. In addition, none of the studies took account of the fact that uncertainty in the

maternal mortality estimates may affect the magnitude of the impact of fertility changes on maternal mortality.

As less developed countries continue to experience fertility transitions, it is important that we understand the impact of fertility changes on maternal mortality through changes in the age and parity distribution of births.

1.1 Aims and objectives

The overall aim of this study is to investigate the impact of changes in fertility on maternal mortality levels as measured by different maternal mortality indicators.

The first objective is to systematically review the literature on the strength of the association between maternal age, parity and the maternal mortality ratio. I am especially interested in any studies that adjusted for both maternal age and parity, and studies that adjusted for other confounders when investigating these relationships. If a sufficient number of studies that have adjusted for confounders are included in the meta-analysis, the independent effects of maternal age and parity can be separated. In addition, the summary adjusted results can be used to partly parameterise the compartmental model developed later.

The second objective is to examine the strength of the association between maternal age and parity and the maternal mortality ratio in a cohort study using data from the Matlab Health and Demographic Surveillance System in Bangladesh. The Matlab site provides high quality prospective data on maternal mortality and offers the largest data set from developing countries to examine these associations. The large sample size and the availability of information on the socio-economic characteristics of households provide the opportunity to investigate the relationship between maternal age/parity and the maternal mortality ratio including an examination of possible confounders and effect modifiers. Thus the effects of maternal age and parity may be disentangled. The Matlab dataset also includes sufficient data to calculate the pregnancy rates which can be used to parameterise the compartmental model developed later. This dataset can also be used to calculate maternal mortality ratios needed to parameterise the compartmental model if only a small number of studies are found in systematic review.

The third objective is to construct a compartmental model to assess the impact of fertility changes on the maternal mortality indicators through using different fertility scenarios. These

include the impact on the absolute number of maternal deaths, the maternal mortality ratio, the maternal mortality rate, the lifetime risk of maternal mortality and the proportionate mortality ratio.

1.2 Structure of the thesis

The thesis begins with some broad maternal mortality and fertility concepts. Then it moves on to an overview of the relationship between fertility and maternal mortality, including a review of the risk factors.

The next three chapters (3-5) present the analyses for each of the objectives of the thesis as described in section 1.1. Each chapter includes background information when appropriate, the methods used for the analysis, the results and a discussion of the findings.

Chapter 3 reports on the systematic review. The results for the strength of the association between maternal age and the maternal mortality ratio are reported first. This is followed by the association between parity and the maternal mortality ratio.

Chapter 4 presents the analysis of the cohort study using the Matlab surveillance data. This chapter begins with some background information on the study site. The observed childbearing pattern trends are reported first, followed by the results from the logistic regressions that investigated the relationship between maternal age/ gravidity and the pregnancy related mortality ratio.

Chapter 5 presents the methods and results of the compartmental model used to assess the impact of fertility changes on the pregnancy related mortality indicators. The method section describes the techniques used to set up the compartmental model before moving on to the calculations used to estimate the model parameters. The impact of the observed and theoretical fertility changes on pregnancy related mortality indicators are then presented.

The thesis concludes with Chapter 6 which includes some overall conclusions and discussion. This final chapter also includes policy recommendations and future research steps.

2 BACKGROUND

2.1 Maternal mortality concepts

2.1.1 Defining maternal mortality

The International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, second edition (ICD10) defines a maternal death as *"the death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and the site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes"* [7].

Maternal deaths are further divided into two subgroups – direct and indirect obstetric deaths. Direct obstetric deaths encompass deaths *"resulting from obstetric complications of the pregnant state (pregnancy, delivery, and postpartum), from interventions, omissions, incorrect treatment, or from a chain of events resulting from any of the above"*. Indirect obstetric deaths are *"those resulting from previous existing disease, or diseases that developed during pregnancy, and which were not due to direct obstetric causes but aggravated by physiological effects of pregnancy"* [7].

Maternal deaths may be difficult to categorise into direct, indirect and accidental or incidental causes, especially in developing countries with a high proportion of home births and low quality information on causes of death in civil registrations. To minimise the potential misclassification of the various categories of maternal deaths, a related definition from ICD10 can be used - pregnancy related death. A pregnancy related death is defined as *"death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the cause of death (obstetric and non obstetric)"* [7]. This alternative definition is often used in surveys where relatives are asked about the pregnancy status of deceased women of reproductive age, at the time of their death. No further questions are asked which may elucidate the cause of death.

"The death of a woman from direct or indirect obstetric causes more than 42 days after termination of pregnancy, but less than one year postpartum" is defined by ICD10 as late maternal death. This definition of maternal death is often included in civil registrations of more developed countries, where advances in modern medicine and equipment may delay a

maternal death beyond 42 days postpartum. The term late pregnancy related death was used in this thesis as the death of a woman from any causes (obstetric or non obstetric) more than 42 days after termination of pregnancy, but less than one year postpartum.

Other variations in the maternal mortality definition include the inclusion of deaths within 90 days of termination of pregnancy [8-10].

The Centers for Disease Control in the US, and the American College of Obstetricians and Gynecologists use the term "pregnancy related deaths" as the equivalent to the ICD10 definitions of maternal deaths and late maternal deaths combined, i.e. excluding accidental or incidental causes, within 1 year of termination of pregnancy. They use the term "pregnancy associated deaths" as the equivalent to the ICD10 pregnancy related and late pregnancy related deaths, i.e. including incidental and accidental deaths, within 1 year of termination of pregnancy [11]

2.1.2 Causes of maternal mortality

A recent World Health Organisation (WHO) systematic review on the causes of maternal mortality found the majority of deaths were due to direct obstetric causes. Haemorrhage, sepsis, hypertensive disorders, obstructed labour and abortion were the five most common causes [12].

There were regional variations between the relative contributions of these causes, with haemorrhage as the largest contributor of maternal deaths in Africa and Asia, accounting for over 30% of maternal deaths. In Latin America and the Caribbean, the leading cause of death was hypertensive disorders (26%). In more developed countries, hypertensive disorders (16%) and embolism (15%) were the leading causes of maternal death.

The regional differences observed are partly due to real differences in the availability and use of obstetric services, and partly due to paucity of quality data, differential reporting and disease epidemiology [13]. For example, there is a severe shortage of quality data from sub-Saharan African countries [14]. Some countries have the double burden of high HIV prevalence, which can be an indirect cause of maternal mortality. An estimated 9% of maternal deaths in sub-Saharan Africa are thought to be due to HIV/AIDS [2].

2.1.3 Maternal mortality indicators

Aside from the absolute number of maternal deaths, there are four other indicators used to measure slightly different dimensions of the maternal mortality burden.

The most commonly used indicator is the maternal mortality ratio (MMRatio) which measures the risk of maternal mortality once a woman is pregnant, i.e. the risk associated with a single pregnancy. The MMRatio is one of the progress indicators used to track Millennium Development Goal five. It is defined as the number of maternal deaths in a population divided by the number of live births in the same population over the same period. It is generally expressed per 100,000 live births.

The maternal mortality rate (MMRate) is defined as the number of maternal deaths in a population divided by the number of women of reproductive age in the same population over the same period. The MMRate reflects a combination of the obstetric risk per pregnancy and the level of fertility in the population. Mathematically, the maternal mortality rate is the product of the maternal mortality ratio and the general fertility rate.

The adult lifetime risk of maternal death indicates the accumulated risk of dying due to maternal causes over a woman's reproductive life. It takes account of both obstetric risk and fertility levels. The lifetime risk can be calculated using either the maternal mortality ratio or the maternal mortality rate and several methods can be used to estimate the lifetime risk. The WHO estimates the adult lifetime risk of maternal death using the following formula:

$$\text{Adult lifetime risk of maternal mortality} = \frac{T_{15} - T_{50}}{l_{15}} \times \text{MMRate},$$

where l_{15}, T_{15} and T_{50} are quantities from a life table for the female population.

Another alternative maternal mortality indicator is the proportionate mortality ratio which is the proportion of all female deaths during reproductive age that is attributable to maternal causes.

2.2 Measurements of obstetric history

The terms gravidity and parity are often used to describe information on a woman's past pregnancies and deliveries. While the definition of the term gravidity is more consistent across different studies in different fields, the definition of parity may be less consistent.

2.2.1 Definition used in obstetrics and midwifery

In both obstetrics and demography the definition of gravidity is similar. Stedman's medical dictionary (27th edition) defines gravidity as *"the number of pregnancies (complete or incomplete) experienced by a woman" [15].*

In the obstetrics literature, the confusion regarding the definition of parity revolves around two issues. These relate to how to classify a woman's parity when she has a multiple gestation pregnancy and the definition of viability of a foetus.

Stedman's medical dictionary (27th edition) defines parity as *"the condition of having given birth to an infant or infants, alive or dead; a multiple birth is considered as a single parous experience" [15].* This definition clearly defines multiple gestation births as one parous event, and most recommendations in the literature suggest that multiple gestation pregnancies should be counted as single parous events [16-17].

Other definitions of parity use a gestational threshold, for example, in Essential Obstetrics and Gynaecology (3rd edition) parity is defined as *"the number of times a women has given birth to a viable infant (gestational age of >24 weeks and birth weight >500g)"*[18]. This definition addresses the issue of viability of infants, but suggests that multiple gestation pregnancies should be counted as multiparous events. Some definitions of parity use a lower gestational threshold of 20 weeks, which may cause confusion as to the classification of induced abortions which may occur between gestational period of 20-24 weeks [16].

A third issue less discussed in the medical literature is how to define a woman's parity if she dies undelivered after a gestational period of 24 weeks. By the two above definitions of parity, the phrase "given birth" suggests that her parity should remain the same as her parity prior to her current pregnancy since she will not have expelled or given birth to the foetus (which remains in her uterus when she dies undelivered).

Parity is defined as *"the number of pregnancies that have completed at or after the point of viability"* in Williams Obstetrics [19]. This definition suggests the woman dying undelivered discussed above would have a higher parity than prior to her current pregnancy. Given the general consensus among obstetricians and midwives that parity *"should be defined as the number of pregnancies that attained the gestation of viability irrespective of outcome" [17],* then when a woman dies undelivered her current pregnancy should count in her parity definition if it passes some pre-defined gestational period.

The optimal definition of parity in obstetrics would be similar to the definition given in Williams Obstetrics, *"the number of pregnancies that have completed at or after the point of viability"*, with the additional information that a multiple birth is considered as a single parous experience. This avoids confusion regarding multiple pregnancies or when a woman dies undelivered. There is still some contention with the definition of viability, and this may need to vary between countries due to different legal definitions of stillbirths and laws relating to induced abortion.

2.2.2 Definitions used in demographic and epidemiological studies

In demographic and epidemiological studies there is generally a lack of accurate information on gestational age of pregnancies and gestational age is not explicitly mentioned when defining parity. A pragmatic way of dealing with this is to count the number of live births (including still births if such information is available), much like the definition used in Stedman's medical dictionary given above (*the condition of having given birth to an infant or infants, alive or dead; a multiple birth is considered as a single parous experience).*

While it may be argued that the definition of parity counting the number of live births and stillbirths strives to estimate the obstetric definition of considering certain pregnancies past a gestational period, the practical implications of using this definition still need to be considered.

Parity is defined as *"the number of children a woman has borne"* in the Handbook on the Collection of Fertility and Mortality Data by the Department of Economic and Social Affairs Statistics Division of the United Nations [20].

"The term parity is used by demographers to denote the number of children a woman has had" is given in Demographic Methods by Andrew Hinde [21].

Clausson and colleagues define parity as *"the number of births before the index pregnancy"* in a population based cohort study in Sweden on perinatal outcome of small for gestational age births [22].

All three definitions given above may misclassify the parity as a result of a multiple gestation pregnancy because every birth is counted. However, the proportion of births which is multiple gestations is low. Of all maternities (confinements resulting in the birth of one or more live born or still born children) in England and Wales in 2008, 1.6% were multiple births [23]. It is noted that the in certain African populations, the prevalence of non-identical twins is higher.

The consideration of women who die undelivered may be problematic when defining parity as the number of births, especially when investigating maternal deaths. Women who die undelivered make up a substantial proportion of all women who die due to pregnancy related causes, especially in less developed countries. Of all pregnancy related deaths in the United States between 1991 and 1999, 10% were to women who died undelivered [24]. A facility based study of maternal deaths in Nigeria, between 1985 and 2001, found 21% of deaths were to women who died undelivered [25]. This means that using a definition of parity that counts the number of births may potentially underestimate the parity of women who die undelivered.

Similar to Clausson's definition, a definition of parity which specifies how to deal with the index pregnancy is likely to resolve the confusion in demographic and epidemiological studies. Since there is no physical foetus to count if a woman dies undelivered, defining parity as the number of live births and still births prior to (or excluding) the index pregnancy should lead to less misclassification in demographic and epidemiological studies. For consistency gravidity may also be defined excluding the index pregnancy, i.e. it may be defined as the number of pregnancies a woman has had excluding the index pregnancy if applicable.

2.2.3 Definitions used in this thesis

Ideally, a standard definition of parity should be used to allow comparability between studies. In the systematic review, I reported the definitions used by various authors, and I tried to arrive at some form of standardisation (see sections 3.2.1 and 3.2.3 below). In general the definitions used in the demographic and epidemiological studies included in the review counted the number of live births. There is substantial variation between studies however, and standardisation proved to be difficult (see section 3.2.3 below). For the systematic review, I strived to standardise the definition of parity as the number of previous live births (and stillbirths if information was available), excluding the index pregnancy. For the Matlab cohort study and the compartmental model, I used gravidity rather than parity due to the lack of data. Gravidity was defined the number of previous pregnancies a women has experienced excluding the index pregnancy (if applicable) to be consisted with the definition of parity above (see sections 4.2.3 and 5.1.1 below).

2.3 Fertility concepts

The classic demographic transition theory attempts to explain the period when a country moves from high to low fertility and mortality rates [26]. The first stage of the transition is

characterised by high mortality and birth rates, with couples making no conscious decision to limit family size. Children are generally seen as economic assets being able to contribute to household chores or income from an early age. In addition they are the primary source of old age insurance for parents. The second stage of the transition is characterised by decreasing mortality rates, achieved by more stable food sources and public health improvements. This leads to an increase in population as more children survive into adulthood. With increasing urbanization and schooling, children become an increasing economic burden and the demand for children falls. Couples start to limit their family size through contraceptives (both modern and traditional methods), leading to a fall in the birth rate in the third stage. Population equilibrium is reached in stage four when both the mortality and birth rates are low.

Further stages to the original transition have been suggested to include the phenomenon of sub-replacement fertility (< 2.1 children per woman) observed in most European and some East Asian countries [26-27].

The classic demographic transition theory was developed with an aim to explain historic European demographic changes. This focus is now seen by some as a limitation of this framework to explain transitions in less developed countries [26]. More significantly, the demand focus of the theory does not take account of cultural and ideational differences, and fails to explain the historic differences in the "natural" fertility of Europe. However, the classical theory is still popular due to its ability to predict future population trends and its coherence at explaining the observed demographic changes.

2.3.1 Fertility behaviour trends

Prior to the 1960s, two distinct demographic groups divided the world; more developed countries with total fertility rates of below 3.5 children per woman, and less developed countries with total fertility rates above 5 children per woman [28]. Over the past five decades, the total fertility rates decreased in all regions, but the rate and timing of the reductions varied. By 2005, Eastern, Middle and Western Africa were the only regions with a total fertility rate of more than five children per woman. In contrast, more developed countries faced fertility rates below replacement level (<2.1 children per woman) [28].

Since the 1970s, there have been declines in adolescent fertility throughout more developed regions, and in many parts of less developed regions such as North Africa and Asia [29-30]. In many more developed regions, the rate of decline in adolescent fertility was greater than

declines in general fertility. For example, between 1975 and 1995, the adolescent fertility rate in the UK reduced by 22% whilst the corresponding reduction for the total fertility rate was 7% [30]. The declines were less prevalent in sub-Saharan Africa and Latin America. In much of Latin America and the Caribbean, the fertility declines in older women were much greater than among adolescents. However, declines in adolescent fertility in some parts of sub-Saharan Africa were observed prior to declines in older maternal ages [29].

Much of the early childbearing in less developed countries takes place within marriages or unions. Often women are expected to start childbearing soon after marriage due to the high value placed on children. In some cultures, a marriage is not formalised until proof of fertility by a live birth [31]. Due to the temporal links between age of marriage and first birth, the factors associated with early marriage may also be important to adolescent childbearing.

Delayed childbearing is almost universal in all more developed countries, due to longer periods in education, more opportunities for women to enter the work force and the instability of the labour market [32-33]. In most Western, Northern and Southern European countries, the average age at first birth for women was around 28-29 in 2005, increased from around 24-25 in the early 1970s [32, 34]. In the US, the average age at first birth was 26 years in 2006, compared to 21.4 years in 1970 [35].

It is important to recognise that fertility behaviours can vary dramatically even between areas with similar levels of total fertility rate.

2.4 Risk factors of fertility and maternal mortality

Maternal age and parity shifts as a result of fertility changes are the main exposures of interest in this research. The main aim of this section is to summarise factors associated with maternal age/parity at pregnancy and maternal mortality in order to identify potential confounders and effect modifiers. A possible confounder was considered to be a variable that is associated with maternal age or parity, an independent risk factor for maternal death, and not on the casual pathway between the two variables. A variable was considered to be an effect modifier if the statistical association between maternal age/parity and maternal mortality differs for different levels of this variable.

To identify the major risk factors for fertility and maternal mortality, I started from known review articles. These review articles (not original research) were identified through PubMed

using Medical Subject Heading Terms for maternal mortality and fertility, limited to review citations, focusing on human females, published in English. These reviews were supplemented by the course reading lists for "Current issues in safe motherhood and perinatal health" and "Extended demography" at the London School of Hygiene and Tropical Medicine.

I also checked for referenced articles and articles which referenced these reviews for inclusion. Articles that were identified as relevant were checked for further references, thereby creating a snowball effect. This review did not aim to provide a systematic review of the literature. Rather I aimed to present an overview of the types of risk factors for maternal age and parity at pregnancy, and maternal mortality, their plausible pathways and typical findings in the literature.

The determinants of maternal death were succinctly summarised in a conceptual framework by McCarthy and Maine in their review article "A framework for analyzing the determinants of maternal mortality" [36]. For fertility, Davis and Blake [37] first described the mechanism by which distal factors such as social, economic and cultural conditions affect fertility through intermediate factors. In 1978, Bongaarts developed a model to estimate the relative effects of these variables on fertility at the population level [38]. This has been updated several times in light of changes in fertility behaviour e.g. by Stover in 1998 [39].

The conceptual framework in Figure 2.1 summarises the distal and intermediate risk factors that were identified to be associated with both maternal age/parity and maternal mortality. In addition, the possible pathways in which maternal age, parity can affect maternal mortality were also included. These are discussed in detailed below.

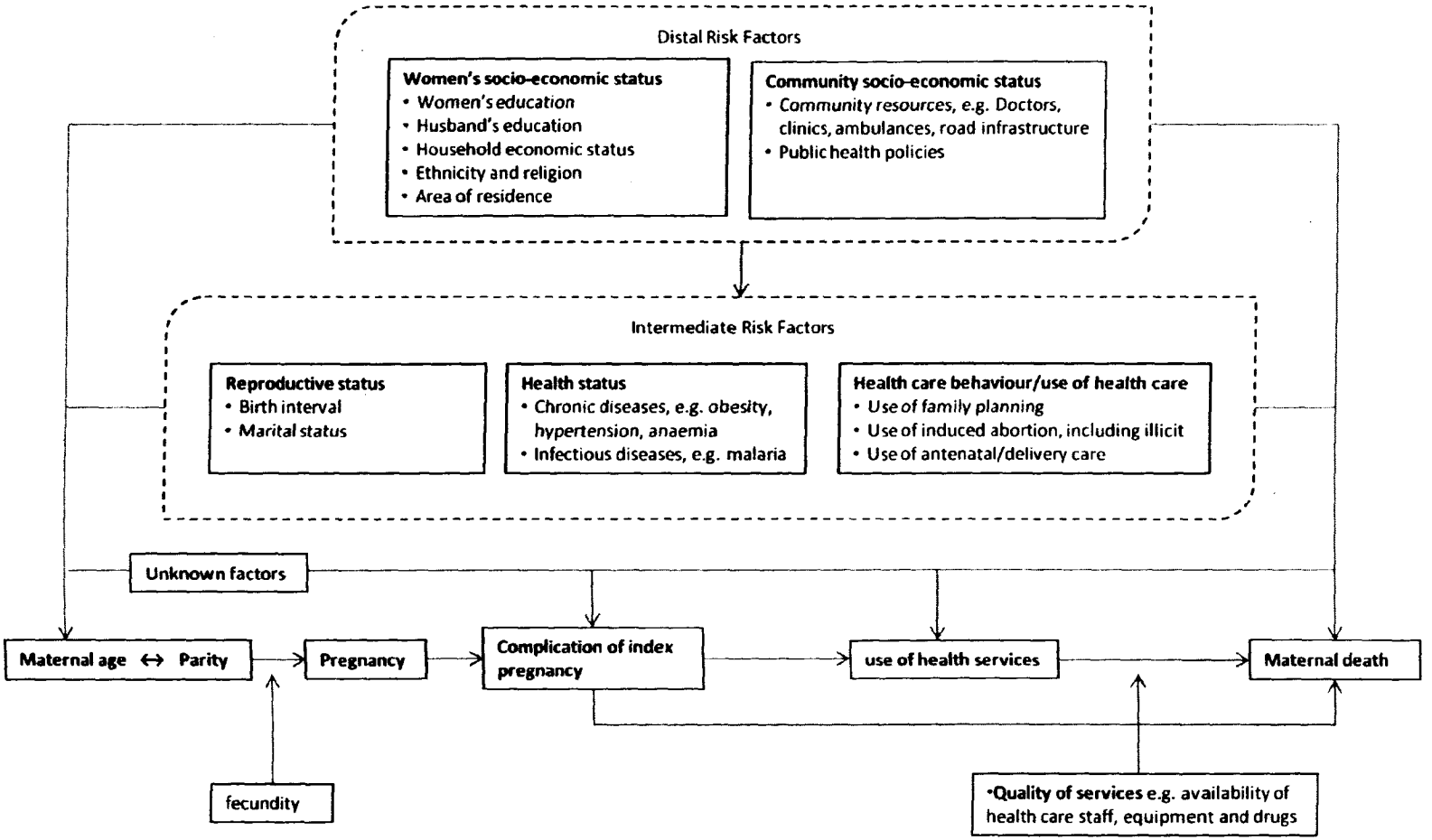

Figure 2.1: A framework for analysing the relationship between maternal age, parity and maternal mortality.

2.4.1 Maternal age, parity and maternal mortality

A prerequisite for maternal death must be pregnancy, and therefore how maternal age and parity affect the likelihood of pregnancy was explored first. Once pregnant, a woman's age or parity may be associated with the likelihood of experiencing a complication during her pregnancy that may lead to her demise.

Maternal age and parity were considered to be reproductive status variables which are intermediate risk factors of maternal mortality. Maternal age and parity are clearly related, with adolescents more likely to have first pregnancies and older women more likely to be higher parity pregnancies. The effects of parity and maternal age on maternal mortality will be further explored in a systematic review in chapter 3.

Maternal age and pregnancy

Maternal age may affect the risk of pregnancy through biological or behavioural factors. Biologically, fecundability is generally lower and pregnancy losses higher at extreme ages. The physiological capacity for childbearing in women starts from the age of first ovulation and the age at menarche is a sufficient proxy for this. The age at menarche varies within and between populations, with studies reporting a mean age at menarche between age 12 and 16 in contemporary populations [40]. Once the start of ovulation occurs in adolescents there is a period of sub-fecundity due to irregular ovulation [41]. In addition the necessary hormonal changes for a successful pregnancy may not accompany each ovulation, and this may also increase the risk of miscarriages.

The end of the childbearing period is less well understood. The proxy used to measure the end of ovulation is menopause, which is not a well defined event. In addition, menopause may not be a good indicator for the end of fecundity since it is thought to cease before menopause [41]. Most researchers agree that fecundity reduces as women age due to reduced oocyte quantity and quality [42-43]. Increased prevalence of chromosome abnormalities with age is thought to increase the risk of miscarriage.

The ability to conceive is coupled with behavioural factors such as coitus frequency, use of contraception and induced abortion to affect fertility. Coitus frequency is often found to decrease with age [44].

Older women may have more knowledge, confidence and resources to obtain effective contraceptives compared to adolescents. For example, misconceptions between the link of modern contraceptives and increased infertility often result in lower uptake of contraceptives, especially among young women [45-46].

Most studies show lower rates of contraceptive use among adolescents [47-49]. However, contextual factors may explain this relationship. For example, in societies that highly value childbearing, married adolescents are generally expected to start childbearing soon after marriage and therefore are less likely to use contraceptives [50]. Younger women may have higher rates of contraceptive failures due to less compliance with user dependent methods, increased fecundity and higher coitus frequency.

Maternal age and obstetric complications/mortality

Adolescent girls may be at a higher risk of obstetric complications and/or mortality for a number of reasons. Once an adolescent is pregnant, her physical and biological immaturity may hinder maternal adaptation to the physiological demands of pregnancy [51]. Nutritional competition between the mother and foetus may occur if the mother is still growing [52]. A study from the United States found growing adolescent girls have higher pregnancy weight gain and postpartum weight retention compared to their older counterparts, but the birth weights of their infants were lower [53]. The effect of competition may disproportionally affect pregnant adolescents in less developed countries as a smaller proportion of girls reach their adult height at menarche [54].

The pelvic bone has a longer growth period compared to other long bones in the body [55]. Contracted pelvis may result in obstructed labour, leading to higher risk of infection and prolonged labour that may increase the risk of maternal death.

Adolescence is often reported as a risk factor for obstructed labour [56-58]. However, studies which adjusted for confounders, such as parity and height, suggest that adolescents were not at increased risk of cephalopelvic disproportion [57] or prolonged/obstructed labour [59] in less developed countries. Very few studies looked at very young adolescents (<15 years old).

Hypertensive disorders of pregnancy are often reported as one of the complications affecting adolescent pregnancies. However, a systematic review on the risk factors of pre-eclampsia at

antenatal booking did not find young maternal age as a risk factor [60]. Some authors suggest that young girls may also have immature immunity leading to higher rates of infections [61-62].

Older maternal age at childbearing may affect the risk of maternal death due to biological changes as women age. Age related degenerative loss of muscle mass and strength may decrease myometrial efficiency. This could lead to higher rates of uterine atony, which is a major risk factor for postpartum haemorrhage. Gestational diabetes, pre-eclampsia and placenta praevia may be secondary to age related vascular endothelial damage [63]. Incidence of uterine fibroids increase with age, and this may also contribute to uterine atony. In addition, uterine fibroids were also found to increase the risk of placental abruption, dysfunctional labour, foetal malpresentation and caesarean delivery [64-65].

Parity and pregnancy

Higher parity women may have already reached their desired family size, and are thus more likely to use contraceptives. The desired family size is based on the number of currently living children rather than parity which may include stillbirths. So the number of living children and contraceptive use is usually investigated.

Most studies have found a higher rate of contraceptive use among women with higher number of living children [47, 66-67] and this relationship may strengthen after adjustment for confounders [68]. The gender composition of the living children may also be particularly important, especially in societies with gender preferences. In South Asia where a strong son preference exists, studies have found either no association or a positive association between the number of sons and contraceptive use [69].

Parity and obstetric complications/mortality

Pregnancies are physiologically demanding on the mother, requiring adaptation to almost every system in the body. Previous successful adaptation suggests the woman's body is able to make the transition for pregnancy, and therefore could partially explain why nulliparous women are at increased risk of maternal death.

A recent systematic review on the relationship between nulliparity and pre-eclampsia found nine studies that reported adjusted results [70]. Studies adjusted for factors such as maternal age, body

mass index, smoking or chronic hypertension. All studies found increased risk of pre-eclampsia in first pregnancies with adjusted odds ratios ranging from 1.30-5.40, but the result was non-significant for one study. The nine studies were almost exclusively based on populations from more developed countries; six studies from the US, the rest were from Norway, Taiwan and Finland. The exact mechanisms for increased risk of gestational hypertension in nulliparas remain unclear. Possible pathways include maternal naivety to paternal antigens, less favourable angiogenic factor profile and/or greater reactivity to insulin resistance in early pregnancy for first pregnancies compared to subsequent pregnancies [71-73].

Women giving birth for the first time a have higher risk of prolonged labour, which is a risk factor for uterine atony that could lead to postpartum haemorrhage. A study using Demographic and Health Surveys (DHS) found the higher risk of prolonged labour in first births persisted after adjustment for maternal age in Niger, Nigeria and Tanzania [59].

Multiparas are often observed to have higher risk of placental abruption, placenta praevia, postpartum haemorrhage, uterine rupture, hypertensive disorders of pregnancy and malpresentation, with many of these complications also associated with maternal age [5, 74-79].

Possible biological mechanisms include increased hypertension leading to placenta abruption. Placenta praevia, a risk factor for malpresentation, may be due to changes in blood vessel at previous placental attachment sites, resulting in decreased blood flow [80]. To maintain adequate blood flow, the placenta must spread over a larger area, increasing the risk of implantation in the lower uterine segment and resulting in placenta praevia [81]. Repeated demands on the uterus may lead to inefficient contractility of the uterine muscles [4], a risk factor for postpartum haemorrhage. Uterine scarring, especially from previous caesarean sections, is a major risk factor for uterine rupture. In addition, nulliparas and multiparas respond differently to obstructed labour, with multiparas more likely to develop uterine rupture and nulliparas more likely to develop obstetric fistulas [82].

Examining studies which adjusted for confounders, most studies do not find an association between higher parity and many of the complications mentioned above. One study found increased levels of placenta praevia and placental abruption among higher parity women aged 20–25 only, and the authors suggested that short birth spacing or other confounders may be responsible [83].

An age matched case control study of 1,242 women found women of parity five or higher were not at increased risk of pre-eclampsia or pregnancy induced hypertension, and they were found to be at decreased risk of intrapartum complications such as instrumental deliveries and emergency caesareans after adjusting for smoking, alcohol consumption, chronic hypertension and chronic diabetes [84]. No increased risk of gestational diabetes were found for women parity five or higher once weight before and after pregnancy were taken into account [84].

Another age matched case control study of 764 US women did not find any increased risk of pre-eclampsia, placenta abruption, malpresentation, dysfunctional labour or postpartum haemorrhage in women of parity five or over [85].

A study of 510,989 pregnancies from Australia, however, found the increased risk of gestational diabetes persisted after adjusting for age, maternal smoking, insurance status and non-English speaking background, but no increased risk was found for postpartum or antepartum haemorrhage [86].

The role of delivery care in the association between maternal age/parity and maternal mortality

The use of delivery care should mitigate some of the adverse effect of pregnancy complications. We have extensive medical knowledge to treat most obstetric complications to prevent deaths [87-88]. For example, haemorrhage related maternal mortality can be largely avoided if women can access timely and competent obstetric care [87]. Similarly, caesarean section is a life saving intervention in women with placental abruption, placenta praevia and obstructed labour. Therefore the effect maternal age or parity may be modified by the use of delivery care.

The effect modification of delivery care, however, may vary depending on contextual factors. The use of delivery care as a means to prevent maternal deaths depends on of the availability of good quality of care with sufficiently trained staff working in an enabling environment with the necessary drugs, equipment, supplies and functional referral system. The availability of good quality health services may depend on community resources. In many less developed countries, there is a shortage of trained medical staff, especially in rural areas. In addition, many rural health hospitals lack the facilities for life saving procedures such as caesarean sections and blood transfusions.

2.4.2 Intermediate risk factors

Reproductive status

Birth interval

Young women are more fecund and may therefore have shorter birth intervals. In addition age or parity may affect the birth interval length through related fertility behaviour such as contraceptive use, breastfeeding practices and coital frequency.

Younger women and lower parity women have generally been found to have shorter birth intervals in crude analyses [89-91]. However, in regions with higher prevalence of delayed childbearing, some studies have found older women and higher parity women have shorter birth intervals, especially for women who delayed childbearing [92-94].

Most studies do not take account of contraceptive or breastfeeding practices when investigating these relationships. One study using birth intervals between two consecutive live births for women in Malaysia, found that older women are less likely to have shorter birth interval after taking account of breastfeeding and contraception practices [89].

Maternal depletion has been put forward as a possible explanation for the presumed relationship between multiple short birth intervals and adverse maternal outcomes. It postulates that multiple short birth intervals do not allow women enough time to restore their nutrition reserves after pregnancy and breastfeeding [95-97]. However, there is still debate on the exact definition of maternal depletion syndrome and the literature on maternal depletion has yielded conflicting results [98], with most studies investigating the effect of just one interval prior/preceding the index pregnancy.

A high quality systematic review was conducted in 2007 by Conde-Agudelo and colleagues on the effect of birth intervals on maternal health, including maternal mortality [99]. They searched through six electronic databases using medical subject headings and key words. Only original studies that adjusted for at least maternal age were included in the review. Two investigators assessed the citations against the inclusion/exclusion criteria and extracted the data independently. Of the 635 citations found, 22 studies conducted in 27 countries were included in the review.

Conde-Agudelo and colleagues found that women with longer birth intervals (>5 years) were at increased risk of pre-eclampsia. There was also emerging evidence that women with longer intervals were at increased risk of labour dystocia. In addition, women with shorter birth intervals were associated with uteroplacental bleeding disorders, and with uterine rupture for women attempting vaginal births after previous caesareans sections [99]. The evidence for birth intervals length and anaemia was unclear.

The authors found five studies which investigated the relationship between birth interval length and maternal mortality [100-104]. All studies controlled for at least maternal age, some also controlled for parity, socio-economic status and other potential confounders. The studies reported inconsistent findings for the association between short intervals and maternal mortality, and the authors concluded *"Less clear is the association between short intervals and the risks of maternal death and..."* Only three studies investigated longer birth intervals and maternal death, and two out of three studies did not find an association.

Three out of five studies, including one high quality study, did not find any association between women with short birth intervals and maternal mortality [102-104]. The remaining two studies, found a 2.5 fold increase in the risk of maternal death for women with shorter birth intervals (inter-pregnancy interval < 6 months and birth interval < 24 months) [100-101]. However, it was unclear whether matched analysis was used for the matched case control study conducted in India [100]. Extremely short inter-pregnancy intervals of less than 6 months are infrequent in any population, and lengthening this interval is unlikely to have a major impact on the overall maternal mortality indicators.

Marital status

In almost all countries in South Asia with a Demographic and Health Survey conducted since 2005, the proportion of currently married women increased with age, reaching a peak around 30-39 years [105-109].

Parity of women may be associated with marital status since marital fertility rates are generally higher in most countries, especially for societies where premarital sex and childbearing outside of marriage is a taboo [110]. This is still observed in more developed countries where marriage is no longer a prerequisite for childbearing. In England and Wales, 55% of all births were to women who were married, although this has been falling for the last three decades[111].

Some studies show that coitus frequency decreases with duration of marriage and this may have an impact on fertility [112-114].

Being unmarried would not necessarily increase the risk of obstetric complications or deaths. However, it may affect the risk of death if being unmarried is related to care seeking. Unmarried pregnant women may avoid seeking care in an effort to hide their pregnancies, especially in communities where childbearing outside of marriage is stigmatised. They may lack the resources to seek appropriate care compared with married women e.g. antenatal care or for treatment if any complications arise [115]. However, in some societies they may have greater autonomy than currently married women [115] and this may encourage higher uptake of maternal health care.

Studies investigating the crude relationship between marital status and maternal mortality have either found no association or increased risk for unmarried women [24, 116-117]. Few studies adjusted for confounders. In the United States, the effect of marital status was modified by race, with only increased risk of maternal death to unmarried Caucasian women [118]. Never married and divorced/widowed women were at higher risk of non-abortion related maternal death in Ethiopia, but these associations disappeared after adjusting for antenatal care, income and occupation [116].

Health Status

Pre-existing conditions that worsen due to pregnancy or delivery account for about 20% of maternal deaths globally [119]. However there are wide regional variations due to differences in disease prevalence and availability and quality of health services in different parts of the world [12].

Chronic diseases

Older women are likely to have pre-existing health problems prior to pregnancy such as diabetes, chronic hypertension, cardiac or neurological disorders [120-121]. These are risk factors for pregnancy related complications such as hypertensive disorders of pregnancy. In addition, the pre-existing conditions may worsen due to the stress of pregnancy.

Obesity: over nutrition can lead to obesity which is generally associated with age [122-123]. Some studies have reported associations between parity and obesity [124-125].However this association was driven by changes in lifestyle after pregnancy rather than parity per se [126].

Pregnant obese women are at increased risk of obstetric complications such as hypertensive disorders of pregnancy, gestational diabetes, venous thromboembolism, infections, induction of labour and caesarean sections [127-131].

In the UK, thromboembolism and cardiac disease were the leading direct and indirect cause of maternal mortality respectively for the period 2003 and 2005 [132]. Obese women are at higher risk of developing both conditions compared to normal weight women. Larson and colleagues found obese women to be at over five times the odds of developing venous thromboembolism in pregnancy and postpartum after adjustment for confounders such as age, parity, smoking, diabetes and infertility treatment [133].

Obesity is associated with other intermediate risk factors; for example it is a major risk factor for diabetes [134], which is also associated with obstetric complications.

Anaemia: over 40% of all pregnant women are estimated to be anaemic worldwide, although the prevalence and severity varies between regions [135]. One of the commonly reported complications during adolescent pregnancies is increased anaemia [136]. Studies have found either no association [55] or increased risk of anaemia among pregnant adolescents [61, 137].

For women with higher parity pregnancies, past studies have found either no association [138-139] or increased risk [78] of anaemia. However, few studies adjusted for confounders. A study in Oman found that the increased risk of anaemia in pregnancy for women of higher parities persisted after adjustment for maternal age and socio-economic variables [140]

Iron deficiency anaemia may result in impaired immune responses leading to increased risk of infection [141-142]. The case fatality of haemorrhage may be higher for anaemic women since they cannot tolerate the same amount of blood loss compared to non anaemic women. Severe anaemia is a medical emergency and can result in cardiac failure.

There is still ongoing debate on the exact effect of anaemia on maternal mortality including the mechanisms underlying the relationship. Currently, there is a lack of high quality studies, especially from less developed countries, where there are higher prevalence of severe anaemia

[143]. In addition, there is no international agreed method of attributing death to anaemia, and so studies may not be comparable [144]. Based on current evidence, the consensus is that the risk of maternal mortality is increased for women with severe anaemia in developing countries [143-145], although this relationship may not be casual [143].

Infectious diseases

Malaria:

Pregnant women are more susceptible to malaria compared to non pregnant women, possibly due to a combination of immunity and hormone changes during pregnancy [146]. First pregnancies especially are associated with increased malaria risk in both high and low transmission areas, although this effect is less marked for low transmission areas [147]. Young age (<20 years) has been found to be a risk factor for malaria, independent of parity, in some studies [148-150]

Pregnant women with malaria are more likely to suffer from severe anaemia since they can suffer from sequestration of malaria infected blood cells in the placenta and the spleen [151]. Links between malaria and pre-eclampsia were reported in some studies, but they were conducted in high transmission regions only [152-153].

In malaria endemic areas, direct and indirect malaria related maternal deaths account for between 2.9% and 17.6% of all maternal deaths in community based studies [154].

Health care behaviour/use of health care

Use of family planning

Just over 200 million recognisable pregnancies are estimated to occur every year [155-156]. Of these about 40% are estimated to be unintended pregnancies [155].

There are obvious fertility implications for women who choose to use effective family planning. With no pregnancy there can be no maternal death. The relationships between maternal age, parity and the use of family planning have been discussed previously, in section 2.4.1.

Use of induced abortion

Around 22% of all pregnancies globally are estimated to result in termination by induced abortion [155]. Even in regions with no access to legal abortion, women often seek unsafe abortion to end their unintended pregnancies.

Maternal age is generally associated with the use of induced abortion, although the pattern of association varies by region, and is heavily dependent on the access and availability of effective contraception [157]. In addition, in countries with restricted abortion laws, there is a lack of accurate abortion data. Most figures are from hospitals that deal with complications of unsafe abortions, and thus may be not be representative [157-158].

A review studying the percentage distribution of induced abortions found that older women obtained the lowest proportion of all abortions, and adolescents do not obtain a disproportional share of induced abortion in most countries (more and less developed) [159]. However, in 9 out of 56 countries, adolescents were overrepresented. Based mainly on more developed countries with sufficient data to calculate the age specific abortion ratio, either a "U" or a monotonic increase pattern was found for abortion ratio by age [159]. Few studies have adjusted for confounders, such as parity, socio-economic status or education when investigating this relationship. A study conducted in Matlab Bangladesh found younger and older women were more likely to seek induced abortion even after adjustment for pregnancy order, marital status, education, dwelling space and service area [160].

Bankole reported more than half of all abortions were to women with at least one live birth in most countries, both more and less developed. However, there were wide variations between countries [159]. Using data from more developed countries with sufficient data to calculate parity specific abortion ratios, the induced abortion ratio was higher for women of higher parities. Again, few studies adjusted for confounders. Studies conducted in Matlab, Bangladesh found women of higher parities were more likely to seek induced abortion even after adjustment for confounders such as maternal age [160-161].

The use of illicit unsafe abortion may have serious adverse effect on the mother. Around 13% of all maternal deaths are estimated to be due to complications resulting from unsafe abortions [157], although the exact proportions are unknown. It is estimated the case fatality rate of unsafe abortion is 300 per 100,000 unsafe abortions globally, and this ranges from 750 per 100,000

unsafe abortions in sub-Saharan Africa to 10 per 100,000 in developed regions [162]. The regional differences are possibly due to the variation in the methods use, severity of complications and access to care.

Use of antenatal/delivery care

Older women may use maternal health care more frequently due to previous experience of health care. In addition they may be more confident or have more influence in household decision making compared to younger women. However, they may belong to a more tradition cohort and have a preference for home delivery. This age effect may be especially pronounced in the least developed countries where the economic cost of maternal health care is a higher proportion of household resources [163-165]. Additional reasons for decreased use of health care for adolescents may be denial of pregnancy or to hide their pregnancies leading to avoidance/delay in care seeking [52].

A study using Demographic and Health Surveys from 21 sub-Saharan African countries did not find a clear crude association between maternal and late initiation of antenatal care [166]. Older women (≥35 years) and sometimes adolescents (<20 years) were more likely to have inadequate number of antenatal care visits, and older women were more likely to deliver without skilled attendance. However, after adjusting for confounders such as parity, premarital births and educational attainment, the authors found that only adolescents were more likely to initiate antenatal care late, have inadequate antenatal care visits and deliver outside of a health facility.

Another study using Demographic and Health Surveys from 15 countries in Africa, Asia and Latin America did not find an age difference in use of antenatal care or skilled delivery care after adjustment for parity, marital status, education and residence for the five sub-Saharan African countries included [167]. For the five south and south-east Asian countries included, adolescents from three countries were less likely to use both skilled antenatal and delivery care.

In a recent literature on the determinants of delivery care in less developed countries, the authors found either no age associated or increased skilled delivery care use among older women compared to young women in studies reviewed which adjusted for confounders including parity [115].

In more developed countries, the use of delivery care is almost universal, and so there are less age differentials. Adolescents are often noted to initiate antenatal care late or have inadequate number of visits [168]. However, younger women were least likely to have a planned home delivery in the US and Netherlands [169-170]. After adjustment for confounders such as parity and socio-economic status, women older than 35 were more likely to have a planned home delivery compared to women aged 25-35 in Sweden [171].

Women experiencing first pregnancies may be more likely to attend antenatal/delivery services due to lack of previous experience. Higher parity women may feel more confidence and have greater experience, in addition to greater household responsibilities, leading to decreased health care use during pregnancy. In addition, doctors may be more likely to advise nulliparous women to deliver in a hospital.

Most studies have found increased antenatal care and delivery care for women having their first pregnancies after adjustment for confounders such as maternal age and maternal education [172-174]. However in Ethiopia, higher parity women were more likely to use antenatal care services, but less likely to use delivery care after adjustment for confounders [175]. In more developed countries, very few women do not seek antenatal or delivery care. Studies have found multiparous women are more likely to plan to deliver at home with a midwife [169-170, 176]. This effect persisted after adjustment for confounders such as maternal age and socio-economic status in Sweden [171].

Antenatal care provides an opportunity for contact with health care professionals, who may encourage women to delivery with a skilled birth attendant. The antenatal care provider may explicitly recommend delivery with skilled birth attendants for higher risk pregnancies. However, the evidence suggests that antenatal care have limited impact on the maternal mortality [177-178].

The relationship between the use of delivery care and maternal mortality has been discussed previously in section 2.4.1.

2.4.3 Distal risk factors

Many social, economic and contextual factors influence fertility and maternal mortality through intermediate variables. Distal risk factors such as women's and husband's education, household

economic status and ethnicity/religion reflect the socio-economic status. The relationship between the distal factors, fertility and maternal mortality are explored in this section.

Socio-economic status

Household and individual socio-economic status is an artificial construct used to measure both social and economic circumstances of living. Factors that present different, but related aspects of these circumstances include income, ownership of assets, consumption, wealth, occupation type, education, religion/ethnicity and place of residence. Only a selection of these factors is discussed below, and many other factors may affect fertility or maternal mortality.

Many of the distal risk factors may be associated. For example women's education may be associated with their husbands' education, the household economic status or their ethnicity/religion.

Women's education

Women's education may affect fertility and maternal mortality through various pathways.

Education leads to increased literacy, cognitive development and exposure to new ideas or opinions. This may result in higher receptivity to educational materials that challenge social norms, such as adolescent childbearing, large families or a preference for home delivery without birth attendants.

More educated women may be more knowledgeable about health issues, such as contraception and their efficient use, the benefits of using skilled birth attendants or danger signs of pregnancy complications that could lead to prompt care seeking. In addition, they may be more confident and better communicators so that they are better equipped to negotiate and demand services such as contraceptives or skilled birth attendants from their household head or public health services.

Women with higher educational attainment stay in education for a longer period of time, decreasing the likelihood of adolescent childbearing. More educated women may have higher labour force participation and are in jobs with higher salaries, thereby increasing the opportunity costs of childbearing and rearing children compared to less educated women. They may have higher aspirations for their children, increasing the cost of child rearing. In addition, more

educated women may experience higher survival rates of their offspring. These factors may decrease the likelihood of high parity births for women with higher educational attainment.

Women's education may also be associated with other socio-economic variables, such as husband's education or better household economic status. For example education may improve economic opportunity, and increase social mobility and resources. In addition, selective matching suggests that women with higher educational attainment are more likely to have husbands who are also more educated.

One of the most consistent factors associated with adolescent pregnancy for all countries is lower educational attainment [29, 179-183].

In more developed countries, most studies have found a positive relationship between higher educational attainment and delayed childbearing, having fewer children and being more likely to remain childless [184-188]. Using data from the Demographic and Health Surveys of 26 countries, Castro Martin found that higher education was consistently associated with lower fertility [189]. In some least developed countries, there was a curvilinear relationship between education and fertility- women with primary school education have the highest fertility and women with secondary or higher education have the lowest. Jejeebhoy came to similar conclusions when investigating the relationship between education and fertility in several developing countries [190].

Studies investigating the crude relationship between maternal education and maternal mortality have generally found either no association [191-192] or decreased risk of maternal death for women with higher educational attainment [9, 193]. A study conducted in Bangladesh adjusted for the confounding effect of maternal age, parity, asset quintile and residence, and found that women of higher educational attainment still had lower risk of maternal death [9]. Women with lower educational attainment were at the highest risk of maternal death in China after taking account of residence and calendar month of maternal death [194].

Husbands' or partner's education

Similar to women with higher education, better educated husbands and partners may be more likely to challenge social norms on adolescent childbearing or large families. They may be better aware of the benefits of using skilled delivery care for their wives.

A husband's education may be a strong determinant of the household's economic status and commodities the household consumes, such as family planning and health care. This is especially true in highly gender stratified societies where women have non monetary employment.

When complications occur during a pregnancy, a timely decision to seek care by the husband, with sufficient funds to pay for the provider fees and transportation costs is vital for a woman's survival, especially in the context of low status for women.

A husbands' education may not affect fertility in the exact same pathways as women's education since there is lower opportunity cost of childbearing involved for men compared to women in most societies. In addition, some researchers argue that male education status is more indicative of household financial resources and schooling facilities rather than diffusion of innovations or attitudes [195]. This is because education for men is rarely against cultural or social norms, which education for women can be.

There is less research conducted on husbands' or partners' education and fertility or maternal mortality. Studies have found either husband's education has similar effect as women's education or no association with fertility [196]. In a matched case control study conducted in India, women with husbands who had less than 5 years of schooling were at increased risk of maternal death, compared to women with husbands who had more than 10 years of schooling (matched on residence or complication) [197]. In contrast, there was no association between having an illiterate husband and maternal mortality in a study conducted in Pakistan, similar to the results found for women's literacy status [191].

Household economic status

Access to financial resources is obviously important for a good standard of living. In most countries health service fees, including the cost of contraceptives, is high relative to the average income of a family. Even nominal fees may be a challenge to the extremely poor [163-164]. In addition, provider fees do not take account of the indirect financial burden, such as the cost of transport, medications, opportunity cost of lost wages for the care seeking individual and any accompanying family members.

Bollen found that higher permanent income was negatively associated with fertility in Ghana and Peru [198]. A study using asset quintiles in 56 developing countries found almost universal

association between greater asset ownership and lower overall and adolescent fertility. In more developed countries, lower income is consistently associated with teenage childbearing [29, 179-181]. The relationship between pregnancies at older maternal age and socio-economic status is less clear [199].

Studies focusing on economic disparities in maternal mortality have generally found the women from the highest economic group experience the lowest maternal mortality [9, 200-203]. However, there were studies that found either no association or an inverse relationship between economic status and maternal mortality [204-205]. This may not be surprising since the economic status operates through a set of intermediate variables that affect maternal mortality. For example, in the late 19th century in Britain, richer women had higher risk of maternal mortality compared to poorer women. This was because richer women could afford to deliver with physicians who used procedures causing higher rates of iatrogenic deaths, compared to the midwives that the poorer women used [36].

Household economic status is often linked with other factors such as education, ethnicity and place of residence, and thus may act on fertility or maternal mortality through these factors.

Ethnicity/religion

Different ethnicities or religions may have distinct beliefs that may influence fertility and health care use including during pregnancy. For example, Jehovah's Witnesses believe blood transfusion should be refused, even in a medical emergency. This may have obvious adverse effects for cases of severe postpartum haemorrhage.

Minority ethnic or religious groups are often marginalized, and may live in more remote regions with poorer infrastructure, both in terms of health care and transportation networks. In many contexts, ethnicity and religion are closely associated with lower socio-economic status. For example, in the United States, race is often used as a proxy for socio-economic position [206].

Crude relationships generally suggest that minority ethnicities and women belonging to religious groups are more likely to have a higher number of children [207-211]. There was less consistent evidence on the effect of religion/ethnicity on the age at childbearing [212-214].

Most studies investigating crude relationship between ethnicity/religion and maternal mortality found conflicting results [24-25, 192]. In the US, African-American women were found to have a

2.5 fold increased odds of maternal death compared to Caucasian women even after adjusting for maternal age, income, gestation of pregnancy, hypertension and care status[215].

2.4.4 Summary of risk factors of fertility and maternal mortality

A high quality systematic review conducted in 2007 found inconsistent evidence for an association between short birth intervals and maternal mortality [99]. Only two out of five studies found evidence of increased risk of maternal mortality for shorter birth intervals, while the other three studies did not find an association. One high quality study from Latin America found increased risk of maternal death for women with an inter-pregnancy interval of less than 6 months, but such short intervals are extremely rare.

As a result of the above systematic review, due to the inconsistent evidence in addition to the very small number of women affected, my research will not further address the possible effect of very short intervals on maternal mortality. I only focused on the effects of maternal age and parity on maternal mortality.

This literature review suggests there are numerous potential confounding factors between maternal age/parity and maternal mortality. Factors such as current health status, use of delivery care, maternal and husband's education, household economic status and ethnicity/religion may be related to both age/parity and maternal mortality and may thus confound the association between age/parity and maternal mortality. The strength and direction of the associations differed between studies. For example, in sub-Saharan African countries, studies have found adolescents (<20 years) to have no association or decreased use of skilled delivery care after adjustment for confounders such as parity and education [166-167]. In contrast, in Sweden, older women (>35 years) were more likely to have a planned home delivery after adjusting for confounders such as parity, education and income [171]. This further suggests the importance of contextual factors in examining the role of confounding in the association between age/parity and maternal mortality.

The use of delivery care was considered as a possible effect modifier in the relationship between maternal age/parity and maternal mortality. Access to competent obstetric care should decrease the case fatality of most obstetric complications. However, access to care can be influence by contextual factors.

A systematic review was not undertaken for this literature review, which meant that it was carried out in a fraction of the time required for a systematic review. The aim of this review was to identify the major risk factors for fertility and maternal mortality rather than create an exhaustive list of all risk factors or to summarise the magnitude of the associated relative risks. The conceptual framework, which builds on the variables identified in this review, was only used as a guide to the possible confounders between the relationships between maternal age/parity and maternal mortality.

However, since the review was not systematic, potential biases need to be considered.

The original reviews were identified through a relatively limited search strategy and therefore other reviews may have been missed, especially review articles not published in English. The snowballing technique may also have resulted in selection bias if researchers were more likely to reference studies that supported their own conclusions. However, most review studies identified very similar risk factors, and it is unlikely that any of the major risk factors would have been missed.

2.5 Models on the impact of changes in fertility on maternal mortality

I identified studies which modelled the impact of fertility changes on maternal mortality through the searches described in section 2.4 above, the search results of the systematic review in chapter 3 and talking to experts in the field of maternal health and fertility at the London School of Hygiene and Tropical Medicine. I also screened the references for the most recent model published in 2010 by Stover and Ross.

I only found four studies that have modelled the impact of fertility changes on maternal mortality. All four studies focused on the effect of hypothetical or observed changes in the maternal age and parity distribution of births on the maternal mortality ratio (and the maternal mortality rate).

Two analytic approaches have been used. First, the indirect standardisation approach uses a set of standard age or parity specific maternal mortality ratios, and applies these ratios to births with different age and parity distributions. Second, the direct standardisation approach uses a standard age and parity birth distribution, and different age or parity specific maternal mortality ratios are applied to births distributed as the standard age and parity distribution. Three studies used indirect standardisation and one study used direct standardisation.

The focus of this section is to present and examine the methodologies used in these four studies, and therefore the results of the studies are omitted. The results are presented in chapter 5 , along with comparisons to the results of my compartmental model.

2.5.1 Indirect standardisation

Trussell and Pebley 1984

Trussell and Pebley investigated hypothetical changes in the maternal age and parity distribution of live births on the maternal mortality ratio and rate [216]. The standard set of maternal mortality ratios used were the age and parity specific maternal mortality ratios reported in a published study, conducted in Matlab, Bangladesh, which used data on 20,816 live births and 119 maternal deaths between May 1968 and April 1970 [8].

The expected number of maternal deaths for each age group of the theoretical scenarios was calculated by applying the standard age specific maternal mortality ratio for that age group to the number of theoretical live births in that age group. The expected number of maternal deaths by parity group was calculated using a similar method. The expected maternal mortality ratio was calculated as the total number of expected maternal deaths divided by the number of theoretical of live births.

The maternal mortality rate was calculated as the product of the maternal mortality ratio and the general fertility rate. Two values of the maternal mortality rate were calculated for each scenario. One assumed no change in the observed general fertility rate for Matlab, and one assumed a 25% reduction in the observed general fertility rate. These two values were multiplied by the expected maternal mortality ratio to obtain two different maternal mortality rates. The authors did not calculate a general fertility rate based on the theoretical number of live births as a result of theoretical fertility changes.

The authors investigated four theoretical changes to the age/parity distribution of live births and their impact on the maternal mortality indicators. Scenario I completely eliminated live births to women younger than 20 and older than 39 without redistributing the eliminated births.

Scenario II eliminated all live births above parity five, without redistributing the eliminated births.

Scenario III eliminated live births to women younger than 20 and older than 39 as in scenario I and redistributed all these live births to women aged 20-39. The theoretical assumptions were: 1) all original live births to women aged 10-19 were redistributed to the 20-29 group, 2) all original live births to women aged 40-49 were redistributed to the 30-39 group ,and 3) half of the original live birth to women aged 20-29 were redistributed to the 30-39 group. The expected number of maternal deaths was then calculated using the original observed crude age specific maternal mortality ratios (the standard set of mortality ratios).

The final, scenario IV, eliminated all live births to women younger than 20 and older than 39 within each parity group. In addition all live births to parity six or higher women of any age were eliminated.

The authors acknowledged that the first two scenarios did not take account of the close association between maternal age and parity.

Scenario III does not explicitly control for parity, even though the authors suggest that the model takes account of parity. In this scenario, it is implicitly assumed that the parity distribution of live births to 10-19 year olds and 20-29 year olds are the same. However, this is not the case. The expected number of maternal deaths for the new live birth distribution was calculated using the original crude age specific mortality ratios. However, a higher proportion of the original births to women aged 10-19 would have been first births, which have a higher risk of maternal death. Redistributing these births to women aged 20-29 may underestimate the number of maternal deaths since the original crude age specific maternal mortality ratio for 20-29 year olds were based on a smaller proportion of first births. Over the study period of 1968-1970 in this population in Matlab, 60% of live births to 10-19 year olds were first pregnancies, while this dropped to 4% of all live births to 20- 29 year olds.

Scenario IV also failed to address the issue of first pregnancies. This scenario eliminated 85% of the observed live births that were first pregnancies. So these higher risk first pregnancies were lost when calculating the expected number of maternal deaths, and therefore the maternal mortality ratio would be underestimated. In addition, this assumption is unrealistic since any childbearing must start with a first birth and these cannot be eliminated if women want to have children.

In this study, it is unclear why the authors choose to assume constant or a 25% reduction in the general fertility rate since the theoretical reduction of the general fertility rate can be estimated

more accurately using the number of theoretical live births in each scenario. In addition, it is also unrealistic to assume constant general fertility rate if live births were eliminated.

Fortney 1987

Fortney extended the work by Trussell and Pebley using the same methods and data. Scenario IV in the paper by Trussell and Pebley was expanded to two further scenarios "eliminating births to women <20, >39, or P(arity)>5 and redistributing original number of births to ages 20-39" and "eliminating all births to women <20, >39 or P(arity)> 5, and redistribute a reduced number of births to parities <6 and to ages 20-39" [217]. However, in both cases it was unclear from the article exactly how the births were redistributed to different parities.

This study would suffer from similar shortcomings as the study by Trussell and Pebley. It is difficult to comment on whether the association between maternal age and parity was taken into account since it was unclear how the live births were redistributed.

Stover and Ross 2010

Stover and Ross used indirect standardisation to investigate the impact of observed age or parity distribution changes in live births on the maternal mortality ratio [218]. The authors used the parity specific maternal mortality ratio from Honduras (1990-1997), and the observed changes in the live birth order distribution of live births in consecutive Demographic and Health Surveys for 46 countries. Similar methods were used to investigate the age distribution changes in childbearing on the maternal mortality ratio. However, it was unclear which set of standard age specific maternal mortality ratios was used.

No attempts were made to take account for the association between maternal age and parity. In addition, the crude age specific maternal mortality ratios may be context specific as suggested by the review of the risk factors of fertility and maternal mortality in section 2.4. Therefore it may not be appropriate to apply the parity specific maternal mortality ratios from Honduras to all 46 countries.

2.5.2 Direct standardisation

Högberg and Wall used historic data from Sweden to examine the effect of observed age and parity distribution changes in births on the number maternal deaths, and the maternal mortality

ratio [219]. To investigate the effect of age changes on the number of maternal deaths in the 20th century, the standard age distribution of births was taken to be the age distribution of births in 1911-1915.

For each 5 year period after 1915, the expected number of maternal deaths was calculated by applying the observed age specific maternal mortality ratios for a given 5 year period to the observed live births in that period distributed according to the age distribution of births in 1911-1915. Thus the difference between the expected and observed number of maternal deaths would be the number of "prevented" maternal deaths. This method obviously does not take account of the association between maternal age and parity.

Further in the study, an age-parity adjusted maternal mortality ratio was calculated using direct standardisation. The authors used the age-parity distribution of births in 1800-99 as the standard. The percentage reduction in the number of maternal deaths attributed to age and parity distribution changes in births between 1800-99 and1951-1980 was then calculated.

The direct standardisation method used by Högberg and Wall could be used to study the observed changes in the age and parity distribution in live births, and their subsequent impact on maternal mortality. However, it would be harder to use this method to study any theoretical changes in age and parity distribution of births since a standard birth/parity distribution of birth must be used. Direct standardisation requires estimation of a series of age-parity specific maternal mortality ratios for different periods, and this may produce a series of imprecise estimates due the rarity of maternal deaths.

2.5.3 Summary of studies modelling impact of fertility changes on maternal mortality

Very few studies examined the impact of fertility changes on maternal mortality, and all studies had important methodological limitations. The direct standardisation approach is attractive because it can estimate the impact of fertility changes on maternal mortality taking account of the joint distributions of maternal age and parity. However, this can only be used to study observed age-parity distribution changes of births due the restriction of having to use a standard age-parity distribution. In addition, this method requires a series of age-parity specific maternal mortality ratio estimates, which may all suffer from imprecision due to small numbers.

The studies which used the indirect standardisation approach did not explicitly control for the association between of maternal age and parity, thereby limiting their possible application. Some

attempts were made by redistributing eliminated live births from the extreme age groups to women aged 20 to 39, but the authors implicitly assumed that the parity distribution of live births for women of different ages were the same, thereby underestimating the proportion of first births. As a result, the effect on maternal mortality may have been overestimated.

None of the studies investigated the effect of fertility changes on the lifetime risk of maternal mortality or the proportionate mortality ratio. In addition none of the studies explored how uncertainties in the maternal mortality estimation may affect the magnitude of the impact of fertility changes on maternal mortality.

I will address the shortcomings of existing studies in a number of ways. First, using a compartmental model to track women through their reproductive lives to ensure all pregnancies at different gravidities and the age at which women give birth can be progressively recorded. This ensures all women have a first pregnancy, giving a more accurate and realistic estimation of the population level parameters. Second, the impact on the maternal mortality rate will be examined more accurately using the expected number of births resulting from any theoretical fertility changes assumed. Third, the effect of maternal age and parity changes on the lifetime risk of maternal mortality or the proportionate mortality ratio will be investigated. Finally, I will explore how uncertainties in the maternal mortality estimation may affect the magnitude of the impact of fertility changes on maternal mortality indicators. The use of a compartment model to assess the impact of fertility changes on maternal mortality indicators is presented chapter 5.

3 SYSTEMATIC REVIEW OF CHILDBEARING COMPOSITION AND MATERNAL MORTALITY

This review assessed the effect of maternal age and number of previous pregnancies on maternal mortality at the population level.

3.1 Methods

3.1.1 Criteria for considering studies for this review

Inclusion Criteria

Types of studies - A study was eligible for inclusion if it was a cross sectional, cohort or case-control study. Randomised controlled trials or special investigations into maternal deaths, e.g. reproductive age mortality studies (RAMOS) or confidential enquiries into maternal deaths (CEMD) were also eligible [220].

Studies without empirical data, with estimates solely derived from modelling of other variables or extrapolation from other populations were excluded. Studies using the indirect sisterhood method to ascertain maternal deaths were excluded because they lack the age distribution of sisters to allow age specific maternal mortality ratio (MMRatio) calculations. Studies using the direct sisterhood method were included if sufficient information was reported to allow the calculation of age specific MMRatios and corresponding 95% confidence intervals.

The aim of the study was to produce population-based estimates. Only hospital studies in settings with skilled birth attendant coverage of 95% or over were included in the review to avoid selection bias. Skilled birth attendant coverage figures were obtained from the World Health Organisation (WHO), United Nations (UN), World Bank or Demographic and Health Surveys (DHS). No estimates of the skilled birth attendant coverage were available prior to the early 1980s; therefore only hospital studies after the 1980s were considered in this review.

Studies using data purely based on civil registrations were included if the study country was rated as having a high quality civil registration by recent WHO assessments [221-222]. The WHO

reviewed country civil registrations based on the most recent year available at the time of the reviews. The earliest available calendar year reviewed was 1990 [221], and therefore only studies using data purely based on civil registrations with a study period from 1990 onwards were included.

Types of participants – Study participants included ever pregnant women who experienced a pregnancy within the study period. Studies with participants only based on a specific health condition or intervention were excluded (e.g. investigations into maternal mortality among HIV positive women only).

Types of outcome measures – Studies with a maternal mortality definition that fell within the definition for a pregnancy related or late pregnancy related death. This includes the death of a woman while pregnant or within one year of termination of pregnancy, irrespective of the duration and site of the pregnancy or the cause of death [7].

The term "maternal mortality" used in this review encompasses all definitions found in the studies.

Studies investigating only a specific cause of maternal mortality were excluded, e.g. maternal deaths due to postpartum haemorrhage only.

Types of exposure measures – Studies that gave any information on the maternal age at the time of the pregnancy outcome or conception were included.

Studies that gave any information on the past pregnancy history of the women were included regardless of the definition of pregnancy history used, with or without explicitly definition of the study measurement used. For example, definitions of the exposure to previous pregnancies/live births (and stillbirths) include parity, gravidity, pregnancy order or live birth order. Sometimes, the index pregnancy is included in the definition. The term "number of previous pregnancies" was used in this review to encompass all different definitions used in the studies.

Exclusion criteria

The aim of the exclusion criteria was to ensure this review included high quality studies which have sufficient power to enable comparisons of the risk of maternal death between different exposure categories.

Studies were excluded if any of the following applied: i) total number of maternal deaths was less than 20, ii) exposure variables were grouped and there were less than three categories for maternal age and previous number of pregnancies, iii) there was more than 20% exposure information missing, iv) there were insufficient data to calculate the strata-specific odds ratios of maternal death and corresponding 95% confidence intervals, v) cases and controls in the study were from different underlying populations.

The quality of the studies included in the review was also rated using the Newcastle-Ottawa Scale (see section 3.1.3 below). This scale does not rate the level of missing exposures in the studies, so an exclusion criterion was developed for studies that were considered to have too much information missing.

There are no universally agreed criteria on acceptable levels of missing data (either in the exposure or outcome). In randomised controlled trials, an 80% follow up or at most 20% missing outcome data have been put forward as high quality evidence [223]. Kristman and colleagues found that if the outcome is not missing at random, as is the case in many studies, then a 20% loss to follow up may bias the estimates [224]. Missing exposure status may not be at random, and therefore studies with more than 20% exposure missing were excluded.

Duplicate data

If two studies included participants over the same area and time period, the study with the most appropriate exposure grouping was included. Otherwise, the study which adjusted for the most number of confounders, or had the largest study population was included.

3.1.2 Search methods for identification of studies

The review was carried out according to an a priori protocol. I searched studies published in English or Chinese using Pubmed, Embase and POPLINE up to 13 February 2009.

A comprehensive search strategy was used to identify all relevant studies. Search terms for the outcome of interest included the exploded Medical Subject Heading Term (MeSH) for maternal mortality, exploded thesaurus terms maternal mortal*, pregnancy-related death*, pregnancy-related mortal*, pregnancy-associated death* pregnancy- associated mortal*, obstetric mortal*, obstetric death* and the free text term, death of mother. Search terms for the exposures of

interest included exploded MeSH terms parity, gravidity, birth order, maternal age and age factors. Further free text and exploded thesaurus terms included number of child*, family size, parit*, gravid*, parity-specific, gravidity-specific, age of mother , mother's age, age-specific, age factor, adolescent and middle aged.

All names of the Demographic Surveillance Sites (DSS) of the International Network of field sites with continuous Demographic Evaluation of Populations and Their Health (INDEPTH) were searched using free text terms in combination with the maternal mortality hits. The INDEPTH network was first established in 1998 to provide a platform to share best practices between different demographic and health surveillance sites, and to encourage and facilitate the development and implementation of multi-site investigations. The INDEPTH network includes membership from 42 DHS systems from 19 countries [225].

To join the INDEPTH network, members must have a DSS where all births, deaths and migrations, in a geographically defined population, are monitored continuously and prospectively. This minimum requirement suggests that the INDEPTH DSS sites are more likely to include relevant information for this review, such as births and maternal deaths. The individual site web-pages were also checked for relevant publications [225]. For further details of the search strategies used for all databases, see Appendix A.1.

To ensure English and Chinese studies would not be excluded due to labelling errors, no language limits were placed on the search strategy. Any studies with English/Chinese titles and abstracts were included at the initial stages. They were later excluded if the full text was found to be in a different language or the labelling from the electronic databases indicated that the full text was in a different language. Citations found using the search strategies were checked to ensure relevant articles were included in the search results. References from articles retrieved were hand searched for further studies.

3.1.3 Data collection and analysis

Selection of studies and data extraction

First, the titles and abstracts were evaluated against the eligibility criteria. If insufficient evidence was provided by the title/abstract, the report was provisionally included. The second stage evaluated all remaining studies against the eligibility criteria based on the full text.

Standardised data forms were used to extract study information including the study population, study design, sample size, study definitions of maternal mortality and number of previous pregnancies, both crude and adjusted strata- specific odds ratios and 95% confidence intervals or the data to calculate these. The quality of the studies, including the ascertainment of maternal mortality and exposure information, loss to follow-up, proportion of missing information (for both maternal deaths and pregnancy survivors) and variables included in any multivariable analysis, were also extracted. Please see Appendix A.2 for a full version of the extraction form.

The selection of studies and data extraction was carried out by one reviewer (PhD student). A second reviewer (professor in Epidemiology) was consulted if the first reviewer was unclear on whether the study satisfied any stages of the selection or data extraction. Two independent reviewers were not used due to financial and time constraints.

Study quality assessment

Many tools have been developed to aid bias assessment for non-randomised studies. However, most are poorly developed and remain un-validated [226]. Of the 194 scales and checklists identified by Deeks and colleagues to assess non-randomised study quality, only 6 were suitable for use in a systematic review [226].

The Newcastle-Ottawa Scale (NOS) was designed for use in epidemiological systematic reviews [227], and has been used by the Cochrane Collaboration Non-Randomised Studies Method Group [228]. The NOS assesses three aspects of study quality: selection of study groups (maximum score of four stars), comparability of study groups (maximum score of two stars) and ascertainment of exposure or outcome (maximum score of three stars). The content validity and inter-user reliability has been found to be satisfactory, while the construction validity has yet to be assessed.

The NOS was considered to be an appropriate tool for study quality assessment for this research, with the following modifications to match research needs:

- The original section on selection of study groups included four items. However, since maternal death can only occur once, it cannot be present prior to its occurrence. Therefore the need to demonstrate that "outcome of interest was not present at the start of study" or "no history of disease (in controls)" was not applicable here. This item was

excluded; only a maximum score of three stars was achievable in this category for the review.

- The comparability of studies section requires the study to control for at least the most important confounder, and additional important confounders defined by the user. Based on the literature review, for the relationship between maternal age and maternal mortality, the most important confounder would be a measure of the number of previous pregnancies. For the relationship between the number of previous pregnancies and maternal mortality, the most important confounder would be maternal age. Other important confounders for both of these relationships would be a measure of socio-economic status, such as maternal education, household assets or income.
- For the number of previous pregnancies and maternal mortality review, an extra star was added to the comparability section when the definition of the previous pregnancy measurement was included in the study. One extra star was awarded if studies explicitly and clearly defined the study measurement used. A maximum score of three was achievable for studies on previous pregnancies for the comparability section, whereas only a score of two was achievable for maternal age studies.
- A follow up or response rate of 80% or more was considered adequate in the ascertainment of outcome selection (item 3). The rationale for this cut off has been discussed previously in section 3.1.1 above.

The modified ONS used for this research can be found in appendix A.3. A maximum of three stars was achievable for sections on the selection of the study groups and the ascertainment of outcome/exposure for both reviews. For the section on the comparability of study groups, a maximum of three stars was achievable for the number of previous pregnancies review, and two stars was achievable for the maternal age review as mention above. Therefore the total achievable score was nine stars for the number of previous pregnancies review, and eight for the maternal age review.

Studies with a score of 5-8 in the maternal age and maternal mortality review were considered to be of high quality. A score of 6-9 in the number of previous pregnancies and maternal mortality review was considered to be of high quality. The discrepancy in defining high quality studies in the two reviews was due to differences in the maximum score attainable between them mentioned above.

The effect of study quality on heterogeneity of the studies was explored in the analysis.

Statistical methods

Maternal age was grouped into five year age groups from age 10 to age 49. Number of previous pregnancies was grouped as single pregnancy events, e.g. no previous pregnancies, one previous pregnancy and so on, with seven or more previous pregnancies grouped together. Groups at the extreme ages or previous pregnancies were combined if there were insufficient numbers. Both maternal age and number of previous pregnancies were treated as categorical variables to avoid distributional assumptions. Women aged 20 to 24 years, and women with one previous pregnancy were used as the baseline exposures as these groups were generally found to have the lowest risk of maternal mortality in the past.

The measurement of effect used was the odds ratio. The 95% confidence interval and the chi^2 test for association were used to assess association. The number of women who survived their pregnancies was estimated by subtracting the number of reported maternal deaths from the number of live births (and stillbirths). If only the national age/previous pregnancies specific MMRatios or maternal deaths were reported, the appropriate denominator information was obtained from the relevant national statistics office or WHO reports for the study period where possible.

Heterogeneity

Studies were set in different regions in different calendar periods using different study methods. There may be variation in the economic development of study regions which may affect the availability and quality of maternity services leading to differences in the maternal mortality levels. Cultural differences that affect health care seeking behaviour and delivery practices may exist. Fertility behaviour may also differ due to cultural differences and attitudes regarding childbearing and the value of children that lead to differences in the age at pregnancy, and the number of pregnancies women have.

These differences may lead to heterogeneity between studies, particularly when confounders remain unadjusted. The use of a random effects model would be appropriate when there is heterogeneity between studies, since it assumes a different underlying effect for each study. The

resulting summary odds ratio should be interpreted as an average of these underlying effects [229].

I used two methods to assess heterogeneity between studies, the I^2 statistic and the chi^2 test of heterogeneity [228, 230]. I used the Inverse Variance fixed effect model for the meta-analysis when either of the following was true:

- $I^2 \leq 30\%$ (low inconsistency between the studies) OR
- $30\% < I^2 \leq 50\%$ (medium inconsistency between the studies) AND $p<0.1$ (no statistical evidence of heterogeneity between the studies)

Otherwise the DerSimonian and Laird random effects model was used [229, 231]. While the cut off points are to some extent arbitrary, they do provide a systematic method to assess heterogeneity and I have used the standard cut off points.

If both numerator and denominator information were available from the studies, continuity correction was applied to zero cells for the meta-analyses.

Subgroup analyses

Four a priori subgroup analyses were planned to explore the causes of heterogeneity between studies. First, a subgroup analyses by total fertility rate (TFR) of the study area was planned because women who have more children than 'average' may also have other characteristics that increase their risk of maternal death. So if, for example, the risk of maternal death begins at different parity cut offs for different TFR levels, then it may be that the selection of women into higher parity rather than the parity per se that increases the risk of maternal death. The TFRs were grouped as low fertility (TFR< 2.5), medium fertility (2.5≤ TFR< 5) and high fertility (TFR ≥5). When possible, the region specific TFR over the study period was obtained from the DHS or national statistical reports. Otherwise, the national TFR was obtained from the Population, Resources, Environment and Development database produced by the Population Division of the United Nations [232].

Second, a subgroup analysis was conducted by the definition of number of previous pregnancies used in the study, either parity or gravidity. For further details on the definitions of parity and gravidity, see section 3.2.3.

Third and fourth, differences in health care access and the quality of care given to pregnant women were also considered as important factors in explaining the heterogeneity between studies. Subgroup analyses by country development and by the maternal mortality ratio levels were considered. However, given the close association between higher levels of country development, lower MMRatio and lower TFR, subgroup analysis by TFR groups was believed to be sufficient. So these last two subgroup analyses were not conducted.

When significant heterogeneity between studies was present within one subgroup in a comparison, the random effects model was used for all subgroups.

Interaction

An interaction between TFR level and the effect of maternal age/previous pregnancy category on maternal mortality was tested using meta-regression, classifying the TFR as a categorical variable [231]. Similarly, an interaction between study definition used and the number of previous pregnancies was also tested using meta-regression.

Sensitivity analyses and publication bias

Studies do not always categorise their measurement of maternal age into 5 year age groups or group all previous pregnancies as single parous events. For example, some studies used 10 year age groups, and combined parity two to four together. In addition, studies do not always use women aged 20 to 24 years or women with one previous pregnancy as the baseline group. Sensitivity analyses were carried out restricting to studies that used the pre-defined 5 year age categories and women aged 20 to 24 as the baseline group. Similarly, sensitivity analyses were carried out restricting to studies with the number of previous pregnancies grouped as single parous events, using one previous pregnancy as the baseline group.

Publication bias was examined by Funnel plots and Begg's adjusted rank correlation test [231]. All statistical and graphical analyses were performed in Stata 11 [233].

3.2 Results

3.2.1 Description of studies

In total 7,845 citations were identified from the database search, of which 933 full texts were examined (Figure 3.1). Of these, 65 met the inclusion criteria. Three matched design studies did not report matched analyses, or the means to obtain matched odds ratios and so were excluded [234-236]. One further study was identified through hand searching of the references [237]. A total of 63 studies, including 65 cohorts of women were included in the review. When a study reported on more than one cohort of women, cohorts were included separately.

For the maternal age part of the review, 61 studies (63 cohorts) were included. A study conducted in Nepal only reported two categories for maternal age, and was excluded for the maternal age review. However there was sufficient information reported for parity in the study for its inclusion in the previous pregnancies review [204].

There was one case control study that was nested within a cross sectional survey conducted in Pakistan [191]. In this study, maternal age reported for the controls was not age of women at the time of last pregnancy outcome but age at the time of the survey. While for the cases, the maternal age reported were at the time of the fatal pregnancy. Given the survey asked for the pregnancy history of the women during the past five years, the ages of the controls could be biased upwards by as much as five years. Therefore this study was excluded from the maternal age part of the review. Gravidity was also reported in this study, and since the gravidity of the woman stays constant between pregnancies, this study was included in the number of previous pregnancies review.

Only 43 out of the original 63 studies reported the number of previous pregnancies. Of these, four studies were excluded because more than 20% of maternal deaths had missing information on previous pregnancy status [24, 238-240], and one study conducted in Egypt was excluded due to lack of appropriate denominator information [241]. A total of 38 studies, including 39 cohorts, were included in the previous pregnancies part of the review.

There were two studies conducted in Matlab, Bangladesh over the same period of 1976-1985 [9-10]. Chowdhury and colleagues used 10 year maternal age groups, whilst Koenig and colleagues used 5 year age groups. Koenig and colleagues categorised single parity groups, whereas Chowdhury and colleagues grouped gravidities together, e.g. gravidity 1-2, gravidity 3-4.

Therefore, the Koenig study can contribute to meta-analyses, such as for women aged 25-29 and women with two previous pregnancies, that were not possible for the study by Chowdhury and colleagues. The study by Chowdhury and colleagues included a larger cohort of women, and thus was given preference for inclusion when both studies qualified for inclusion into the analysis.

There were two articles reporting the same study in Ethiopia [116, 201]. One study reported on all maternal deaths and the other included only non-abortion related maternal deaths. Only the study investigating non-abortion related maternal deaths reported adjusted estimates [116]. The study reporting all maternal deaths, but no adjusted results was included in the meta-analysis. The study reporting on non-abortion related maternal death only, but including adjusted results was included in the part of the review that investigated adjusted results.

A study reported the age specific maternal mortality ratio by combining national statistics of European countries [242]. The authors split the combined statistics into two sets, one for the higher maternal mortality ratio countries, and one for the lower maternal mortality ratio countries. The figures from the lower maternal mortality ratio countries were excluded because they duplicated the CEMDs from the United Kingdom. Only the combined statistics from the higher maternal mortality ratio countries were included in this review.

Table 3.1 to Table 3.14 present the characteristics of studies included in the two reviews.

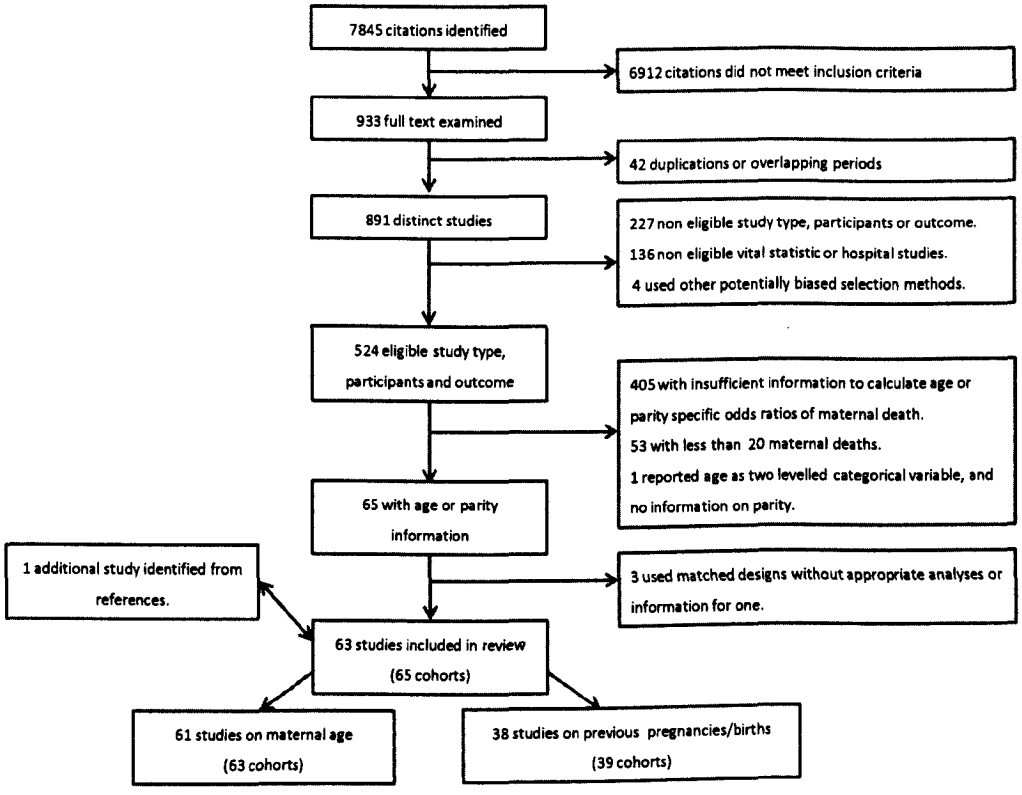

Figure 3.1: Flow chart to show the study selection process

Table 3.1: Characteristics of studies included in the systematic review of the association between maternal age/parity and maternal mortality.

First author, year of publication, (country of study)	Study design (year of study)	No. of maternal deaths	Variable used to estimate the no. of pregnant women	No. of pregnant women	Definition of maternal death	Definition of number of previous pregnancies	Variables included in multivariable analyses
TFR <2.5							
Arthure 75[243] (England and Wales)	CEMD - Active Surveillance (AS) (1970-72)	606	maternities[1] (parity: illegitimate births redistributed among parity groups)	2298198	Days postpartum: 365 Early deaths: included Incidental deaths: included Unknown cause: included	parity[1] - defined	none
Berg 03 [118] (US)	Active Surveillance (1991-97)	3201	registered live births	27834783[b]	Days postpartum: 365 Early deaths: included Incidental deaths: excluded Unknown cause: partially	live birth order[1] - defined	none
Chang 03 [24] (US)	Active Surveillance (1991-99)	4200	registered live births	35708897[b]	Days postpartum: 365 Early deaths: included Incidental deaths: excluded Unknown cause: partially	-	none
Dept. Health 91 [244] (UK)	CEMD - AS (1985-87)	249	maternities[1] (parity: illegitimate births adjusted using GHS[a] in England & Wales)	2231797	Days postpartum: 42 Early deaths: included Incidental deaths: excluded Unknown cause: included	parity[2] - defined	none
Dept. Health 94 [238] (UK)	CEMD - AS (1988-90)	277	maternities[1]	2360309	Days postpartum: 42 Early deaths: included Incidental deaths: included Unknown cause: included	-	none

maternities[1] : the number of women who gave birth to and registered one or more live or stillborn

parity[1]: number of previous pregnancies of 28 weeks gestation or over, regardless of outcome, plus the fatal pregnancy whatever its duration

parity[2]: number of previous registrable live and still births.

live birth order[1]: number of live births including the index pregnancy that the woman had delivered.

a:General Household Survey, conducted in England and Wales, sampling 10% of all births.

b:calculated from the maternal mortality ratio and the number of maternal deaths.

Table 3.2: Characteristics of studies included in the systematic review of the association between maternal age/parity and maternal mortality continued.

First Author, year of publication, (country of study)	Study design (year of study)	No. of maternal deaths	Variable used to estimate the no. of pregnant women	No. of pregnant women	Definition of maternal death	Definition of number of previous pregnancies	Variables included in multivariable analyses
TFR <2.5							
Dept. Health 96 [245] (UK)	CEMD - AS (1991-93)	228	maternities[1] (parity: illegitimate births adjusted using GHS[a])	2315204	Days postpartum: 42 Early deaths: included Incidental deaths: excluded Unknown cause: excluded	parity - undefined	none
Dept. Health 98 [239] (UK)	CEMD - AS (1994-96)	268	maternities[2]	2197640	Days postpartum: 42 Early deaths: included Incidental deaths: excluded Unknown cause: excluded	-	none
Dept. Health 01 [246] (UK)	CEMD - AS + Birth/Death (B/D) linkage (1997-1999)	242	maternities[2] (parity: illegitimate births adjusted using GHS[a])	2123614	Days postpartum: 42 Early deaths: included Incidental deaths: excluded Unknown cause: excluded	parity - undefined	none
Dept. Health 04 [247] (UK)	CEMD - AS + B/D linkage (2000-02)	261	maternities[2]	1997472	Days postpartum: 42 Early deaths: included Incidental deaths: excluded Unknown cause: excluded	-	none
Kaunitz 84 [248] (US)	Civil Registration (CR) (1974-78)	2555	registered live births	16131855	Days postpartum: 42 Early deaths: included Incidental deaths: excluded Unknown cause: excluded	-	none

maternities[1]: the number of women who gave birth to and registered one or more live or stillborn.

maternities[2]: pregnancies that result in live birth at any gestation or a stillbirth occurring 24 completed weeks gestation or later and are required to be notified by law.

a:General Household Survey, conducted in England and Wales, sampling 10% of all births.

Table 3.3: Characteristics of studies included in the systematic review of the association between maternal age/parity and maternal mortality continued.

First author, year of publication, (country of study)	Study design (year of study)	No. of maternal deaths	Variable used to estimate the no. of pregnant women	No. of pregnant women	Definition of maternal death	Definition of number of previous pregnancies	Variables included in multivariable analyses
TFR <2.5							
Koc 06 [249] (Turkey)	RAMOS (2005-06)	294[c]	estimated live births	763585	Days postpartum: 42 Early deaths: included Incidental deaths: included Unknown cause: included	-	none
Koonin 91[250] (US)	Civil registration (1979-86)	2644	registered live births	29269863[b]	Days postpartum: 365 Early deaths: included Incidental deaths: excluded Unknown cause: excluded	-	none
Koonin 97 [251] (US)	Active Surveillance (1987-90)	1459 (801 outcome= live births)	registered live births	15948217[b]	Days postpartum: 365 Early deaths: included Incidental deaths: excluded Unknown cause: excluded	live birth order – undefined	none
Lewis 07 [132] (UK)	CEMD - AS + B/D linkage (2003-05)	295	maternities[2]	2113831	Days postpartum: 42 Early deaths: included Incidental deaths: excluded Unknown cause: excluded	-	none
Nagaya 00 [252] (Japan)	Civil Registration (1991-92)	230	live births- source unknown	2432179	Days postpartum: 42 Early deaths: included Incidental deaths: excluded Unknown cause: excluded	-	None

maternities[2] : pregnancies that result in live birth at any gestation or a stillbirth occurring 24 completed weeks gestation or later and are required to be notified by law.

b:calculated from the maternal mortality ratio and the number of maternal deaths;

c:adjusted for disproportional allocation and non-sending.

Table 3.4: Characteristics of studies included in the systematic review of the association between maternal age/parity and maternal mortality continued.

First author, year of publication, (country of study)	Study design (year of study)	No. of maternal deaths	Variable used to estimate the no. of pregnant women	No. of pregnant women	Definition of maternal death	Definition of number of previous pregnancies	Variables included in multivariable analyses
TFR <2.5							
Ni 94 [194] (China)	Matched Case Control (1989-91)	456	-	-	Days postpartum: 42 Early deaths: included Incidental deaths: excluded Unknown cause: excluded	gravidity - undefined	Matched on town, date of deaths within 3 months.
Schuitemaker 98 [253] (Netherlands)	CEMD – AS + Civil Registration (CR) (1983-92)	180	live births - source unknown	1860807	Days postpartum: 42 Early deaths: included Incidental deaths: excluded Unknown cause: excluded	-	none
Scot H&H Dept 78 [254] (Scotland)	CEMD - AS (1972-75)	92	registered total births (parity: legitimate births only)	294519	Days postpartum: 365 Early deaths: included Incidental deaths: included Unknown cause: included	parity [3]- defined	none
Scot H&H Dept 87 [255] (Scotland)	CEMD - AS (1976-80)	64	maternities[1] (parity: illegitimate births adjusted using SMR2[d] forms)	328304	Days postpartum: 365 Early deaths: included Incidental deaths: excluded Unknown cause: excluded	parity [3]- defined	none
Scot H&H Dept 89 [256] (Scotland)	CEMD - AS (1981-85)	44	maternities[1] (parity: illegitimate births adjusted using SMR2[d] forms)	330746	Days postpartum: 365 Early deaths: included Incidental deaths: excluded Unknown cause: excluded	parity [3]- defined	none

maternities[1]: the number of women who gave birth to and registered one or more live or stillborn.

parity[3]: number of previous pregnancies ending in a registrable birth plus the fatal pregnancy irrespective of its duration.

d:SMR2 is the hospital discharge form.

Table 3.5: Characteristics of studies included in the systematic review of the association between maternal age/parity and maternal mortality continued.

First author, year of publication, (country of study)	Study design (year of study)	No. of maternal deaths	Variable used to estimate the no. of pregnant women	No. of pregnant women	Definition of maternal death	Definition of number of previous pregnancies	Variables included in multivariable analyses
TFR <2.5							
Temmerman 04 [257] (Belgium)	Civil Registration - B/D linkage (1991-00)	37	registered live births	639365	Days postpartum: 42 Early deaths: included Incidental deaths: included Unknown cause: included	-	None
Tomkinson 79 [258] (England & Wales)	CEMD - AS (1973-75)	390	maternities[1] (parity: illegitimate births redistributed)	1921569	Days postpartum: 365 Early deaths: included Incidental deaths: included Unknown cause: included	parity[1] - defined	none
Tomkinson 82 [259] (England & Wales)	CEMD - AS (1976-78)	427	maternities[1] (parity: illegitimate births redistributed)	1748851	Days postpartum: 365 Early deaths: included Incidental deaths: included Unknown cause: included	parity[1] - defined	none
Turnbull 86 [260] (England & Wales)	CEMD - AS (1979-81)	299	maternities[1] (parity: illegitimate births adjusted using GHS[a])	1923725	Days postpartum: 42 Early deaths: included Incidental deaths: included Unknown cause: included	parity - undefined	none
Turnbull 89 [261] (England & Wales)	CEMD - AS (1982-84)	243	maternities[1] (parity: illegitimate births adjusted using GHS[a])	1883754	Days postpartum: 42 Early deaths: included Incidental deaths: included Unknown cause: included	parity[1] - defined	none

maternities[1]: the number of women who gave birth to and registered one or more live or stillborn.

parity[1]: number of previous pregnancies of 28 weeks gestation or over, regardless of outcome, plus the fatal pregnancy whatever its duration.

a:General Household Survey, conducted in England and Wales, sampling 10% of all births.

Table 3.6: Characteristics of studies included in the systematic review of the association between maternal age/parity and maternal mortality continued.

First author, year of publication, (country of study)	Study design (year of study)	No. of maternal deaths	Variable used to estimate the no. of pregnant women	No. of pregnant women	Definition of maternal death	Definition of number of previous pregnancies	Variables included in multivariable analyses
TFR <2.5							
Walker 57 [262] (England & Wales)	CEMD (1952-54)	1351 (1198 non-abortion deaths)	registered births (parity: illegitimate births redistributed)	2079275	Days postpartum: 365 Early deaths: abortion deaths for maternal age only Incidental deaths: included Unknown cause: included	parity[4] - defined	none
Walker 60 [263] (England & Wales)	CEMD (1955-57)	1158	registered births (parity: illegitimate births redistributed)	2147247	Days postpartum: 365 Early deaths: partial Incidental deaths: included Unknown cause: included	parity[4] - defined	none
Walker 63 [264] (England & Wales)	CEMD (1958-60)	968	registered births (parity: illegitimate births redistributed)	2322229	Days postpartum: 365 Early deaths: partial Incidental deaths: included Unknown cause: included	parity - undefined	none
Wildman 04 [242] (Europe- higher MMRatio)	CR, B/D linkage, CEMD (1992-95)	160	registered live births	1707888[b]	Days postpartum: 365 Early deaths: included Incidental deaths: excluded Unknown cause: excluded	-	None
2.5<TFR ≤ 5							
Arthure 69 [265] (England & Wales)	CEMD - AS (1964-66)	755	maternities[1] (parity: illegitimate births redistributed)	2600367	Days postpartum: 365 Early deaths: included Incidental deaths: included Unknown cause: included	parity[1] - defined	none

maternities[1]: the number of women who gave birth to and registered one or more live or stillborn;

parity[1]: number of previous pregnancies of 28 weeks gestation or over, regardless of outcome, plus the fatal pregnancy whatever its duration.

parity[4]: number previous live and stillbirths, disregarding previous abortions and including the fatal pregnancy whatever its duration.

b:calculated from the maternal mortality ratio and the number of maternal deaths.

Table 3.7: Characteristics of studies included in the systematic review of the association between maternal age/parity and maternal mortality continued.

First author, year of publication, (country of study)	Study design (year of study)	No. of maternal deaths	Variable used to estimate the no. of pregnant women	No. of pregnant women	Definition of maternal death	Definition of number of previous pregnancies	Variables included in multivariable analyses
2.5<TFR ≤ 5							
Arthure 72 [266] (England & Wales)	CEMD - AS (1967-69)	698	maternities[1] (parity: illegitimate births redistributed)	2457444	Days postpartum: 365 Early deaths: included Incidental deaths: included Unknown cause: included	parity[1] - defined	None
Bhatia 88 [267] (India)	Case Control (1984- 85)	262	-	-	Days postpartum: 42 Early deaths: included Incidental deaths: excluded Unknown cause: excluded	pregnancy order - undefined	none
Boyd 88 [268] (Northern Ireland)	CEMD - AS (1978-84)	32	total births (parity: legitimate births only?)	193828	Days postpartum: 365 Early deaths: included Incidental deaths: included Unknown cause: included	parity - undefined	none
Chowdhury 07 [9] (Bangladesh)	Cohort (1976-05)	769	pregnancies to married women	215779	Days postpartum: 90 Early deaths: included Incidental deaths: excluded Unknown cause: excluded	pregnancy order – undefined	maternal age, pregnancy order, religion, SES, education, service area, delivery year
Christian 07 [204] (Nepal)	Cohort (1993-01)	185	pregnancies	25580	Days postpartum: 365 Early deaths: partial Incidental deaths: included Unknown cause: included	parity - undefined	maternal age, parity, mid upper arm circumference

maternities[1]: the number of women who gave birth to and registered one or more live or stillborn.

parity[1]: number of previous pregnancies of 28 weeks gestation or over, regardless of outcome, plus the fatal pregnancy whatever its duration.

Table 3.8: Characteristics of studies included in the systematic review of the association between maternal age/parity and maternal mortality continued.

First author, year of publication, (country of study)	Study design (year of study)	No. of maternal deaths	Variable used to estimate the no. of pregnant women	No. of pregnant women	Definition of maternal death	Definition of number of previous pregnancies	Variables included in multivariable analyses
2.5 ≤ TFR < 5							
Conde -Agudelo 05 [269] (Latin American countries)	Survey of health facility records (1985-03)	379	singleton pregnancies	854377	Days postpartum: 42 Early deaths: excluded Incidental deaths: excluded Unknown cause: unknown	-	parity, education, marital status, smoking, inter-pregnancy interval, pre-pregnancy BMI, weight gain during pregnancy, history of miscarriage, LBW, perinatal death, chronic hypertension, gestational age at first ANC attendance, no. of ANC visits, geographic area, hospital type, delivery year.

BMI: body mass index

LBW: low birth weight infant

ANC: antenatal care

Table 3.9: Characteristics of studies included in the systematic review of the association between maternal age/parity and maternal mortality continued.

First author, year of publication, (country of study)	Study design (year of study)	No. of maternal deaths	Variable used to estimate the no. of pregnant women	No. of pregnant women	Definition of maternal death	Definition of number of previous pregnancies	Variables included in multivariable analyses
2.5 ≤ TFR < 5							
Dunlop 74 [270] (Scotland)	CEMD - AS (1965-71)	188	total registered birth (parity: registered legitimate births)	662621	Days postpartum: 365 Early deaths: included Incidental deaths: included Unknown cause: included	parity[5] - defined	none
Egypt MoH 00 [237] (Egypt)	CEMD (2000)	585	live births	1752562	Days postpartum: 42 Early deaths: included Incidental deaths: excluded Unknown cause: excluded	-	none
Fortney 88 [271] (Indonesia)	RAMOS (1980-82)	278[f]	live births to married women	38727	Days postpartum: 42 Early deaths: included Incidental deaths: excluded Unknown cause: excluded	-	none
Ganatra 98 [197] (India)	Matched Case Control (1993- 95)	121	-	-	Days postpartum: 42 Early deaths: included Incidental deaths: excluded Unknown cause: excluded	gravidity - undefined	matched on complication or area
Kane 92 [241] (Egypt)	RAMOS (1985-1986)	156	live births	115727[b]	Days postpartum: 42 Early deaths: included Incidental deaths: included Unknown cause: unknown	-	none
Keeling 91 [272] (Jamaica)	RAMOS (1986-87)	62	estimated live births	54200	Days postpartum: 42 Early deaths: included Incidental deaths: included Unknown cause: included	parity – undefined	none

parity[5]: number of previous registrable birth, whether live or still, plus the mother's fatal pregnancy, irrespective of its duration.

b: calculated from the maternal mortality ratio and the number of maternal deaths;

f: adjusted for unidentified maternal deaths.

Table 3.10: Characteristics of studies included in the systematic review of the association between maternal age/parity and maternal mortality continued.

First author, year of publication, (country of study)	Study design (year of study)	No. of maternal deaths	Variable used to estimate the no. of pregnant women	No. of pregnant women	Definition of maternal death	Definition of number of previous pregnancies	Variables included in multivariable analyses
2.5 ≤ TFR < 5							
Kestler 00 [273] (Guatemala)	AS (1993-96)	435	registered live births	276432	Days postpartum: 42 Early deaths: included Incidental deaths: excluded Unknown cause: excluded	-	none
Kwast 86 [201] (Ethiopia)	Survey (1982-83)	45	for age: live births to resident Ethiopian women in survey for parity: pregnant resident Ethiopian women in survey	9154 live births to 9316 women	Days postpartum: 42 Early deaths: included Incidental deaths: excluded Unknown cause: excluded	parity - unclear	none
Kwast 88 [116] (Ethiopia)	Nested Case Control (1982-83)	29	-	-	Days postpartum: 42 Early deaths: abortion excluded Incidental deaths: excluded Unknown cause: excluded	parity[6] - defined	Maternal age, parity, ANC, occupation, Income, Education, Marital status
Mbizvo 93 [274] (rural area, Zimbabwe)	Matched Case Control (1989-90)	97	-	-	Days postpartum: 42 Early deaths: included Incidental deaths: excluded Unknown cause: excluded	parity - undefined gravidity - undefined live birth- undefined	One set of controls matched on level of care. Another set also matched on maternal age

Parity[6]: the number of previous births at least 20 weeks gestation, plus the index pregnancy, regardless of the period of gestation of the latter.

Table 3.11: Characteristics of studies included in the systematic review of the association between maternal age/parity and maternal mortality continued.

First author, year of publication, (country of study)	Study design (year of study)	No. of maternal deaths	Variable used to estimate the no. of pregnant women	No. of pregnant women	Definition of maternal death	Definition of number of previous pregnancies	Variables included in multivariable analyses
2.5 ≤ TFR < 5							
Mbizvo 93 [274] (urban area, Zimbabwe)	Matched Case Control (1989-90)	50	-	-	Days postpartum: 42 Early deaths: included Incidental deaths: excluded Unknown cause: excluded	parity - undefined gravidity - undefined live birth- undefined	One set of controls matched on level of care. Another set also matched on maternal age
Miller 73 [275] (Australia)	CEMD (1964-72)	44	confinements	124446	Days postpartum: 90 + any beyond if it has its origin in an illness related to pregnancy Early deaths: included Incidental deaths: included Unknown cause: included	-	none
NIPORT 01 [202] (Bangladesh)	Survey (1998-00)	131	live births	40785[b]	Days postpartum: 42 Early deaths: included Incidental deaths: excluded Unknown cause: excluded	-	none
Schaffner 77 [276] (US)	Active Surveillance (1950-71)	1341	live births	3988885[b]	Days postpartum: 90 Early deaths: included Indirect causes: excluded Incidental deaths: excluded Unknown cause: excluded	-	None

b: calculated from the maternal mortality ratio and the number of maternal deaths.

Table 3.12: Characteristics of studies included in the systematic review of the association between maternal age/parity and maternal mortality continued.

First author, year of publication, (country of study)	Study design (year of study)	No. of maternal deaths	Variable used to estimate the no. of pregnant women	No. of pregnant women	Definition of maternal death	Definition of number of previous pregnancies	Variables included in multivariable analyses
2.5≤ TFR< 5							
Viet Nam MoH 05 [277] (Viet Nam)	RAMOS (2000- 01)	80	live births	61341	Days postpartum:42 Early deaths: included Incidental deaths: excluded Unknown cause: excluded	-	none
Walker 66 [278] (UK)	CEMD (1961-63)	936	registered births (for parity, illegitimate births redistributed)	2550252	Days postpartum: 365 Early deaths: included Incidental deaths: included Unknown cause: included	parity[1] - defined	none
Walker 86 [240] (Jamaica)	CEMD (1981-83)	192	registered live births	178544	Days postpartum: 365 Early deaths: included Incidental deaths: included Unknown cause: included	-	none
TFR≥ 5							
Abdullah 92 [193] (Egypt)	Cohort and RAMOS (1987)	29	resident pregnant women	8656	Days postpartum: until delivery or end of pregnancy Early deaths: some included Incidental deaths: excluded Unknown cause: excluded	parity[7] - defined	parity, residence
Alauddin 86 [205] (Bangladesh)	Cohort (1982-83)	48	live births	8485	Days postpartum: 42 Early deaths: included Incidental deaths: included Unknown cause: included	parity - unclear gravidity - unclear	none

parity[1]: number of previous pregnancies of 28 weeks gestation or over, regardless of outcome, plus the fatal pregnancy whatever its duration.

parity[7]: number of previous births or deliveries

Table 3.13: Characteristics of studies included in the systematic review of the association between maternal age/parity and maternal mortality continued.

First author, year of publication, (country of study)	Study design (year of study)	No. of maternal deaths	Variable used to estimate the no. of pregnant women	No. of pregnant women	Definition of maternal death	Definition of number of previous pregnancies	Variables included in multivariable analyses
TFR≥ 5							
Bell 08 [200] (Burkina Faso)	Survey (2001-06)	385[g]	live births[g]	86033[g]	Days postpartum: 42 Early deaths: included Incidental deaths: included Unknown cause: included	-	none
Bouvier-Colle 01 [279] (West Africa)	Cohort (1994-96)	55	live births	17694	Days postpartum: 60 Early deaths: excluded Incidental deaths: excluded Unknown cause: excluded	parity[8]- defined	none
Chen 74 [8] (Bangladesh)	Cohort (1968-70)	119	live births to married women	20816	Days postpartum: 90 Early deaths: included Incidental deaths: included Unknown cause: included	parity[9] - defined gravidity[1]- defined no. of living children – undefined	None
Fikree 97 [191] (Pakistan)	Nested Case Control (1989-92)	196	-	-	Days postpartum: 40 Early deaths: included Incidental deaths: excluded Unknown cause: excluded	gravidity - undefined	distance, housing construction maternal , water supply
Fortney 88 [271] (Egypt)	RAMOS (1981-83)	385	live births	202806	Days postpartum: 42 Early deaths: included Incidental deaths: excluded Unknown cause: excluded	-	none

parity[8]: number of deliveries, the relevant pregnancy not included.

parity[9]: number of completed live birth experienced prior to the pregnancy associated with the death or birth event examined

gravidty[1]: no. of pregnancies prior to index pregnancy

g: adjusted for women who were absent at household interview

Table 3.14: Characteristics of studies included in the systematic review of the association between maternal age/parity and maternal mortality continued.

First author, year of publication, (country of study)	Study design (year of study)	No. of maternal deaths	Variable used to estimate the no. of pregnant women	No. of pregnant women	Definition of maternal death	Definition of number of previous pregnancies	Variables included in multivariable analyses
TFR≥ 5							
Hoj 02 [192] (Guinea-Bissau)	Cohort (1990-96)	85	pregnancies	10,846	Days postpartum: 91 Early deaths: included Incidental deaths: unknown Unknown cause: unknown	parity - undefined	none
Khan 86 [280] (Bangladesh)	RAMOS (1982-83)	58	live births	9137	Days postpartum: 42 Early deaths: included Incidental deaths: included Unknown cause: included	parity - undefined	none
Koenig 88 [10] (Bangladesh)	Cohort (1976-85)	387	live births to married women	70286	Days postpartum: 42 Early deaths: included Incidental deaths: included Unknown cause: excluded	parity - undefined gravidity - undefined	none
Rao 94 [281] (India)	Cohort (1970-73)	122	live births to married women	7139	Days postpartum: 42 Early deaths: partially Incidental deaths: excluded Unknown cause: excluded	-	none
Ronsmans 01 [282] (Senegal)	Cohort (1984-97)	317	live births[h]	16812	Days postpartum: 90 Early deaths: included Incidental deaths: included Unknown cause: included	-	none

h:inflated by 15% to account for miscarriages and stillbirths

Study setting

There were 61 studies, including 63 cohorts from non-overlapping populations and/or calendar periods. Of these, 41% of the cohorts were from Europe, 24% from Asia, 17% from Africa, 10% from North America, 6% from Latin America and Caribbean and 2% from Oceania. Of the 63 cohorts, 12 (19%) were from high fertility settings and 22 (35%) from medium fertility settings.

Study design

Of the 63 studies included, 27 were confidential enquiries into maternal deaths (CEMD) in the UK (23), the Netherlands, Australia, Jamaica and Egypt (Table 3.1 to Table 3.14). The live birth information in most of the CEMD studies was obtained from the relevant civil registration.

There were five studies with active surveillance (AS) systems for maternal deaths, four studies from the United States [24, 118, 251, 276] and one from Guatemala [273]. The live birth information for these studies was obtained from the relevant civil registration system for the US studies and live births were identified as part of the surveillance system in Guatemala.

Confidential enquiries into maternal deaths focus on the levels and causes of maternal deaths, in addition to drawing lessons on how to prevent future deaths. Extensive effort is usually taken to identify all maternal deaths for a confidential enquiry, although the exact methods vary from country to country. Active surveillance of maternal deaths is often an element included in a confidential enquiry. Active surveillance aims to identify all cases of maternal deaths as they occur within a region or country.

For the CEMD in the United Kingdom, health professionals are encouraged to actively report any maternal deaths to the confidential enquiry assessor, forwarding any medical records. More recently, a linkage between birth registration (from up to one year previously) and death registration of women of reproductive age was added to the CMED in the UK in an effort to identify further cases of maternal deaths. The confidential enquiries in Jamaica used a combination of active surveillance by health workers and reviews of hospital, police, coroner's and public mortuary records and registered deaths of women of reproductive age. Active surveillance in the United States combines reviews of death certificates, birth and death record linkages, active reports from health professionals, committees and the use of the media.

There were nine cohort studies, six from South Asia and three from West Africa. Most identified women of reproductive age and then followed them prospectively by regular visits

to ascertain the last menstruation date, pregnancy status and pregnancy outcome. The causes of death were generally identified through verbal autopsies and medical records where available. The number of births was also recorded in these studies which were then used to calculate the maternal mortality indicators.

Civil registration (CR) information was used in four studies, one from Japan [252], two from the United States [248, 250]and one from Belgium [257]. The number of live births by age of mother was also obtained from civil registration records.

There were seven reproductive age mortality studies, including eight cohorts of women, conducted in Turkey [249], Indonesia [271], Egypt [241, 271], Jamaica [272], Viet Nam [277] and Bangladesh [280]. Most studies used a combination of key informants and existing records to identify all deaths to women of reproductive ages. Maternal deaths were then identified through verbal autopsies. One of the weaknesses of the RAMOS is that often the denominator information required to calculate the maternal mortality indicators, e.g. the number of births was obtained from an alternative source. In one study (two cohorts) the source of the denominator information was unknown because it was not reported in the study [271]. Two studies used past censuses or Demographic Health Surveys of a different calendar period to the study period to estimate the number of live births by mother's age [249, 277]. Another study recorded all live births to women over a two months period (September – October) and extrapolated the number of live births for the 12 months study period without adjusting for seasonality [272]. The remaining three studies used either birth information collected concurrently with the maternal death or obtained civil registration information covering the same population over the same period.

There were three cross sectional surveys conducted in Ethiopia [201], Burkina Faso [172] and Bangladesh [105]. These studies generally included three surveys, one to identify all deaths in a household by a direct household death questionnaire. Further in-depth verbal autopsy questionnaires were conducted for deaths to women of reproductive age to identify maternal deaths. Finally a woman's questionnaire was conducted to women of reproductive age living in the household, to ascertain information on past reproductive history, and from this questionnaire the number of live births in the study period was identified.

There were six (seven populations) case control studies, three (four populations) of which were matched. Two unmatched case control studies were nested within cross-sectional surveys; one was conducted in Pakistan and one in Ethiopia [116, 191]. Two case control studies, conducted in India [197] and China [194], matched on residence. The Chinese study

also matched on the calendar month of maternal death (within three months). The Zimbabwean study matched on the level of care and had an additional control which matched on both level of care and maternal age (within 5 years) [274].

Of the remaining three studies, one study used pregnancy records from 1985 to 2003 from the Perinatal Information System in Latin America [269]. This is a database containing clinical records of pregnant women in 20 countries in Latin America [283]. This study was the only facility based study included in this systematic review.

Two other studies used mixed methods. One study combined national statistics from different European countries [242], and the maternal mortality collection methods depended on the country. The final study set in Egypt recruited women at antenatal care visits and followed these women up prospectively [193]. In addition, they identified pregnant women and maternal deaths through facility records, other official records and key informants. Pregnant women identified during the study were used as the denominator to calculate the risk of maternal death.

Study definition of maternal death

There were variations in the definition of maternal death between studies. The majority of studies (52%) defined maternal death up to 42 days postpartum and a third used a postpartum period of 365 days. Other periods included 40, 60, 90, 91 days postpartum or until the end of pregnancy. Almost all studies (60 studies) included all or some early pregnancy death. Over 40% of studies included incidental (29 studies) or unknown causes (27 studies) of death during the pregnancy period.

Measurement of the population at risk

The denominators used by studies to estimate the risk of maternal death included the number of live births, total births (live births and still births) or pregnancies. Some authors estimated the number of live births or limited it to live births to married women only. Twenty-four studies used the number of pregnancies as the denominator although sometimes this was limited to singleton pregnancies. Seven studies used the total number of births, including both live and stillbirths.

Quality of the studies

The overall study quality scores based on the Ottawa-Newcastle scale are shown in Table 3.15 to Table 3.20.

For the review of maternal age and maternal mortality, the scores of the 63 cohorts ranged from 1 to 6, with an average score of 4.3 out of a maximum of 8 (standard deviation=1.1). There were 28 cohorts with a score of 5 or more, indicating reasonably good methodological quality. Of these 28 cohorts, 16 were CEMDs from the UK, and another five were from other developed countries (four from the US and one from Belgium). Of the remaining 7 cohorts, 3 were from Bangladesh, and one from each of the following countries: Burkina Faso, Ethiopia and Jamaica. One study was conducted in several Latin American countries. Eighteen (64%) of the 28 cohorts were from low fertility countries. There were 8 cohorts from medium fertility settings, and 2 conducted in high fertility settings.

Four studies reported on the effect of maternal age on maternal mortality after controlling for the effect of number of previous pregnancies, and three studies adjusted for the confounding effect of socioeconomic status. Fifteen studies reported on the follow up/response rate and one case control study reported on the response rate by exposure groups.

For the review of number of previous pregnancies and maternal mortality, the scores of the 39 cohorts ranged from 2 to 7, with an average score of 5 out of a maximum of 9 (standard deviation =1.2). There were 13 cohorts with a score of 6 or more indicating reasonably good methodological quality. Of these 13 cohorts, 11 (85%) were CEMDs from the UK. There was also one cohort from Bangladesh and one from Ethiopia. 70% of the better quality studies were from low fertility settings (9 cohorts) and 4 were from medium fertility settings. There were no high quality studies from high fertility settings.

Comparison between maternal mortality and fertility levels

The relationship between the TFR and the MMRatio was investigated. Categorising the studies into low (MMRatio <100 per 100,000 live births), medium (100≤ MMRatio < 300 per 100,000 live births) and high (MMRatio ≥ 300 per 100,000 live births) levels, 44 out of 63 studies were in corresponding levels of TFR and the MMRatio. Discrepancies occurred most in medium fertility settings, where only 27% of the studies were also in the medium MMRatio category (Table 3.21).

Table 3.15: Quality of studies investigating the effect of maternal age on maternal mortality.

First author	Publication year	Country of study	Study design	Selection			Comparability		Outcome/Exposure			Total
				1	2	3	1a	1b	1	2	3	
TFR<2.5												
Arthure	1975	England and Wales	CEMD	*	*	*			*	*		5
Chang	2003	US	AS	*	*				*	*		4
DH	1991	UK	CEMD	*	*				*	*		4
DH	1994	UK	CEMD	*	*				*	*		4
DH	1996	UK	CEMD	*	*				*	*		4
DH	1998	UK	CEMD	*	*	*			*	*		5
DH	2001	UK	CEMD	*	*	*			*	*		5
DH	2003	UK	CEMD	*	*	*			*	*		5
Kaunitz	1984	US	CR	*	*				*	*	*	5
Koc	2006	Turkey	RAMOS	*		*			*	*		4
Koonin	1991	US	CR	*	*	*			*	*		5
Koonin	1997	US	AS	*	*	*			*	*		5
Lewis	2007	UK	CEMD	*	*	*			*	*		5
Nagaya	2000	Japan	CR	*	*				*	*		4
Ni	1994	China	Matched CC	*	*					*	*	4
Schuitemaker	1998	The Netherlands	CEMD	*	*					*	*	4
Scot H&H Dept	1978	Scotland	CEMD	*	*	*			*	*		5

CEMD- confidential enquiries into maternal deaths; AS- active surveillance; CR-civil registration; CC- case control

Selection 1 - representativeness of exposed maternal age cohort/adequate definition of maternal death; 2- selection of 20-24 year old group/representativeness of cases; exposure ascertainment/selection of controls

Comparability 1a-controlling for a measure of number of previous pregnancies; 1b-controlling for socio-economic status

Outcome/Exposure 1-outcome/exposure ascertainment; 2-sufficiently long follow up/same ascertainment methods of exposure for cases and controls; 3-follow-up/non-response rate

Table 3.16: Quality of studies investigating the effect of maternal age on maternal mortality continued.

First author	Publication year	Country of study	Study design	Selection			Comparability		Outcome/Exposure			Total
				1	2	3	1a	1b	1	2	3	
TFR<2.5												
Scot H&H Dept	1987	Scotland	CEMD	*	*				*	*		4
Scot H&H Dept	1989	Scotland	CEMD	*	*				*	*		4
Temmerman	2004	Belgium	CR	*	*				*	*	*	5
Tomkinson	1979	England and Wales	CEMD	*	*	*			*	*	*	6
Tomkinson	1982	England and Wales	CEMD	*	*	*			*	*	*	6
Turnbull	1986	England and Wales	CEMD	*	*				*	*	*	5
Turnbull	1989	England and Wales	CEMD	*	*				*	*	*	5
Walker	1957	England and Wales	CEMD	*	*	*			*	*		5
Walker	1960	England and Wales	CEMD	*	*	*			*	*		5
Walker	1963	England and Wales	CEMD	*	*	*			*	*		5
Wildman	2004	Europe	Mixed	*	*				*	*		4
2.5≤ TFR< 5												
Arthure	1969	England and Wales	CEMD	*	*	*			*	*	*	6
Arthure	1972	England and Wales	CEMD	*	*	*			*	*	*	6
Bhatia	1988	India	Case control		*	*			*			3
Boyd	1988	Northern Ireland	CEMD	*	*				*	*		4
Chowdhury	2007	Bangladesh	Cohort	*	*		*	*	*	*		6
Christian	2007	Nepal	Cohort	*	*		*		*	*		5

CEMD- confidential enquiries into maternal deaths; AS- active surveillance; CR-civil registration; CC- case control

Selection 1 - representativeness of exposed maternal age cohort/adequate definition of maternal death; 2- selection of 20-24 year old group/representativeness of cases; exposure ascertainment/selection of controls

Comparability 1a-controlling for a measure of number of previous pregnancies; 1b-controlling for socio-economic status

Outcome/Exposure 1-outcome/exposure ascertainment; 2-sufficiently long follow up/same ascertainment methods of exposure for cases and controls; 3-follow-up/non-response rate

Table 3.17: Quality of studies investigating the effect of maternal age on maternal mortality continued.

First author	Publication year	Country of study	Study design	Selection			Comparability		Outcome/Exposure			Total
				1	2	3	1a	1b	1	2	3	
2.5≤ TFR< 5												
Conde-Agudelo	2005	Latin American countries	Survey	*	*		*	*	*	*		6
Dunlop	1974	Scotland	CEMD	*	*	*			*	*		5
Egypt MoH	2000	Egypt	CEMD	*					*			2
Fortney	1988	Indonesia	RAMOS						*	*		2
Ganatra	1998	India	Matched CC	*		*						2
Kane	1992	Egypt	RAMOS	*					*	*		3
Keeling	1991	Jamaica	RAMOS	*		*			*	*		4
Kestler	2000	Guatemala	AS	*					*	*		3
Kwast	1986	Ethiopia	Survey	*	*	*				*		4
Kwast	1988	Ethiopia	Nested CC	*	*	*	*	*		*		6
Mbizvo	1993	Zimbabwe (urban and rural)	Matched CC	*	*				*			3
Miller	1973	Australia	CEMD								*	1
NIPORT	2001	Bangladesh	Survey	*	*	*			*	*	*	6
Schaffner	1977	US	AS	*	*				*	*		4
Vietnam	2005	Vietnam	RAMOS	*		*			*	*		4
Walker	1966	England and Wales	CEMD	*	*				*	*		4
Walker	1986	Jamaica	CEMD	*	*				*	*	*	5

CEMD- confidential enquiries into maternal deaths; AS- active surveillance; CR-civil registration; CC- case control

Selection 1 - representativeness of exposed maternal age cohort/adequate definition of maternal death; 2- selection of 20-24 year old group/representativeness of cases; exposure ascertainment/selection of controls

Comparability 1a-controlling for a measure of number of previous pregnancies; 1b-controlling for socio-economic status

Outcome/Exposure 1-outcome/exposure ascertainment; 2-sufficiently long follow up/same ascertainment methods of exposure for cases and controls; 3-follow-up/non-response rate

Table 3.18: Quality of studies investigating the effect of maternal age on maternal mortality continued.

First author	Publication year	Country of study	Study design	Selection			Comparability		Outcome/Exposure			Total
				1	2	3	1a	1b	1	2	3	
TFR ≥5												
Abdullah	1992	Egypt	Mixed	*	*					*	*	4
Alauddin	1986	Bangladesh	Cohort	*	*				*	*		4
Bell	2008	Burkina Faso	Survey	*	*	*			*	*		5
Bouvier-Colle	2001	West African countries	Cohort		*				*	*	*	4
Chen	1974	Bangladesh	Cohort	*	*					*		3
Fortney	1988	Egypt	RAMOS	*	*				*	*		4
Hoj	2002	Guinea Bissau	Cohort	*	*				*	*		4
Khan	1986	Bangladesh	RAMOS	*	*				*	*	*	5
Koenig	1988	Bangladesh	Cohort	*	*				*	*		4
Rao	1994	India	Cohort	*	*					*		3
Ronsmans	2001	Senegal	Cohort	*	*				*	*		4

CEMD- confidential enquiries into maternal deaths; AS- active surveillance; CR-civil registration; CC- case control

Selection 1 - representativeness of exposed maternal age cohort/adequate definition of maternal death; 2- selection of 20-24 year old group/representativeness of cases; exposure ascertainment/selection of controls

Comparability 1a-controlling for a measure of number of previous pregnancies; 1b-controlling for socio-economic status

Outcome/Exposure 1-outcome/exposure ascertainment; 2-sufficiently long follow up/same ascertainment methods of exposure for cases and controls; 3-follow-up/non-response rate

Table 3.19: Quality of studies investigating the effect of number of previous pregnancies on maternal mortality.

First author	Publication year	Country of study	Study design	Selection			Comparability			Outcome/Exposure			Total
				1	2	3	1a	1b	2	1	2	3	
TFR<2.5													
Arthure	1975	England and Wales	CEMD		*	*			*	*	*		5
Berg	2003	US	AS		*	*			*	*	*		5
DH	1991	UK	CEMD	*	*	*			*	*	*		6
DH	1996	UK	CEMD	*	*					*	*		4
DH	2001	UK	CEMD	*	*	*				*	*		5
Koonin	1997	US	AS	*	*	*				*	*		5
Ni	1994	China	Matched CC	*	*						*	*	4
Scot H&H Dept	1978	Scotland	CEMD		*	*			*	*	*		5
Scot H&H Dept	1987	Scotland	CEMD	*	*	*			*	*	*		6
Scot H&H Dept	1989	Scotland	CEMD	*	*	*			*	*	*		6
Tomkinson	1979	England and Wales	CEMD	*	*	*			*	*	*	*	7
Tomkinson	1982	England and Wales	CEMD	*	*	*			*	*	*	*	7
Turnbull	1986	England and Wales	CEMD	*	*	*				*	*	*	6
Walker	1957	England and Wales	CEMD	*	*	*			*	*	*		6
Walker	1960	England and Wales	CEMD	*	*	*			*	*	*		6
Walker	1963	England and Wales	CEMD		*	*				*	*		4
2.5≤ TFR< 5													
Arthure	1969	England and Wales	CEMD	*	*	*			*	*	*	*	7

CEMD- confidential enquiries into maternal deaths; AS- active surveillance; CR-civil registration; CC- case control

Selection 1 - representativeness of exposed maternal age cohort/adequate definition of maternal death; 2- selection of 20-24 year old group/representativeness of cases; exposure ascertainment/selection of controls

Comparability 1a-controlling for a measure of number of previous pregnancies; 1b-controlling for socio-economic status; 2- definition of number of previous pregnancies

Outcome/Exposure 1-outcome/exposure ascertainment; 2-sufficiently long follow up/same ascertainment methods of exposure for cases and controls; 3-follow-up/non-response rate

Table 3.20: Quality of studies investigating the effect of number of previous pregnancies on maternal mortality continued.

First author	Publication year	Country of study	Study design	Selection			Comparability			Outcome/Exposure			Total
				1	2	3	1a	1b	2	1	2	3	
2.5≤ TFR< 5													
Arthure	1972	England and Wales	CEMD	*	*	*			*	*	*	*	7
Bhatia	1988	India	Case control		*	*				*			3
Boyd	1988	Northern Ireland	CEMD	*	*					*	*		4
Chowdhury	2007	Bangladesh	Cohort	*	*		*	*		*	*		6
Christian	2007	Nepal	Cohort	*	*		*			*	*		5
Dunlop	1974	Scotland	CEMD		*	*			*	*	*		5
Ganatra	1998	India	Matched CC	*		*							2
Keeling	1991	Jamaica	RAMOS	*		*				*	*		4
Kwast	1986	Ethiopia	Survey	*	*	*					*		4
Kwast	1988	Ethiopia	Nested CC	*	*	*	*	*	*		*		7
Mbizvo	1993	Zimbabwe	Matched CC	*	*		*			*			4
Walker	1966	England and Wales	CEMD		*	*			*	*	*		5
TFR ≥5													
Abdullah	1992	Egypt	Mixed	*	*				*		*	*	5
Alauddin	1986	Bangladesh	Cohort	*	*					*	*		4
Bouvier-Colle	2001	West African countries	Cohort		*				*	*	*	*	5
Chen	1974	Bangladesh	Cohort	*	*				*		*		4
Fikree	1997	Pakistan	Nested CC	*	*	*				*			4
Hoj	2002	Guinea Bissau	Cohort	*	*					*	*		4
Khan	1986	Bangladesh	RAMOS	*	*					*	*	*	5
Koenig	1988	Bangladesh	Cohort	*	*					*	*		4

Please see footnote of the table above.

Table 3.21: The distribution of maternal mortality ratio levels for 63 non overlapping cohorts by different TFR levels.

Total Fertility Rate (no. of children)	Maternal Mortality Ratio (per 100,000 live births)			Total
	<100 (%)	100- 300 (%)	≥ 300 (%)	
< 2.5	28 (96.6)	1 (3.4)	0 (0)	29
2.5- 5	10 (45.4)	6 (27.3)	6 (27.3)	22
≥ 5	0 (0)	2 (16.7)	10 (83.3)	12
Total	38 (60.3)	9 (14.3)	16 (25.4)	63

3.2.2 Crude relationship between maternal age and maternal mortality

Adolescents aged < 20 years

Thirteen studies reported two adolescent groupings. They were mostly from the UK and the US, with one study conducted in Bangladesh and one in Latin America. The younger group was either grouped as girls under 15 or 16 years old.

Adolescents aged <15-16 years.

Twelve studies were included in the meta-analysis for the <15-16 group because one study reported insufficient denominator information. I compared the risk of maternal death for very young adolescents to both women aged 20 to 24 years and to older adolescents aged 15/16 to 19 years and found similar results (Figure 3.2 and Figure 3.3).

There was little statistical evidence of heterogeneity or inconsistency across the studies (p= 0.27, I^2 =17.8%). The crude summary odds ratio, when comparing to women aged 20-24, was 3.94 (95% confidence interval (CI): 3.18- 4.88, p<0.001, Figure 3.2).

Stratification by TFR did not change the findings using either baseline groups, although there was only one study for the high fertility group (Figure 3.2 and Figure 3.3). Combining the medium and high fertility groups together, there was some statistical evidence of an interaction with TFR levels (baseline group of 20-24 year olds: p=0.02; baseline group of 15-19 year olds: p=0.07). Using women 20-24 years old as the baseline group, the summary odds ratio was 2.21 (CI: 1.38- 3.55) for the low fertility setting, and 4.56 (CI: 3.54- 5.86) for medium fertility setting. Similar results were found using older adolescents as the baseline group (Figure 3.3).

There was no statistical evidence to suggest publication bias (Begg's test: p=0.45 for baseline as 20-24 years old; p=0.95 for baseline as 15/16- 19 years old).

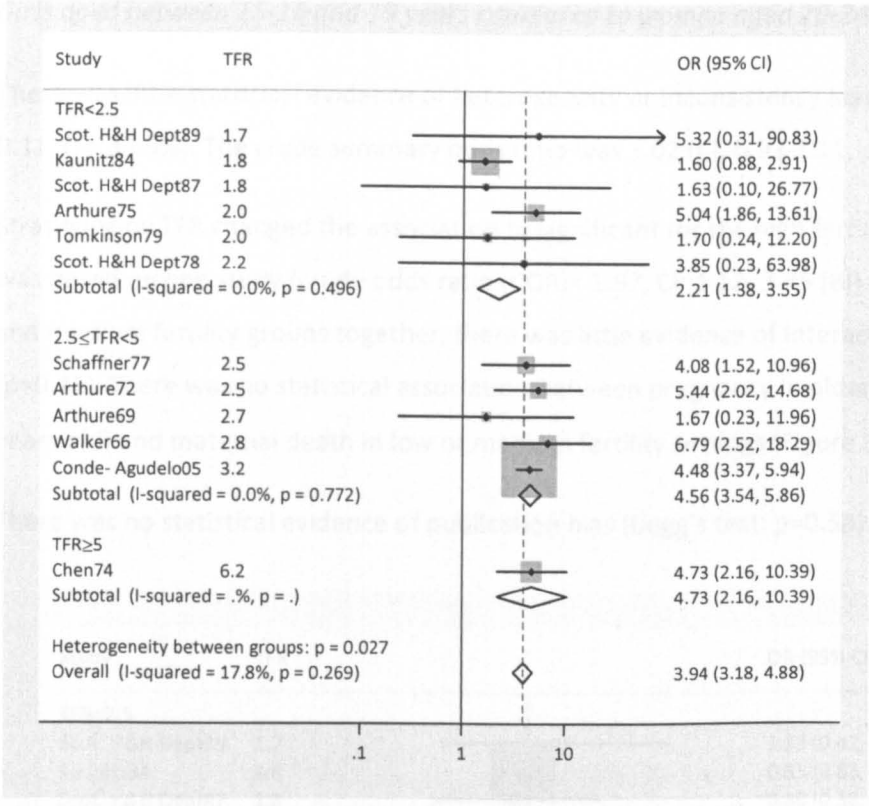

Figure 3.2: Crude odds ratios of maternal death comparing girls under 15 or 16 years old to women 20-24 years old in 12 studies, by fertility levels. The overall odds ratio was calculated using a fixed effect model.

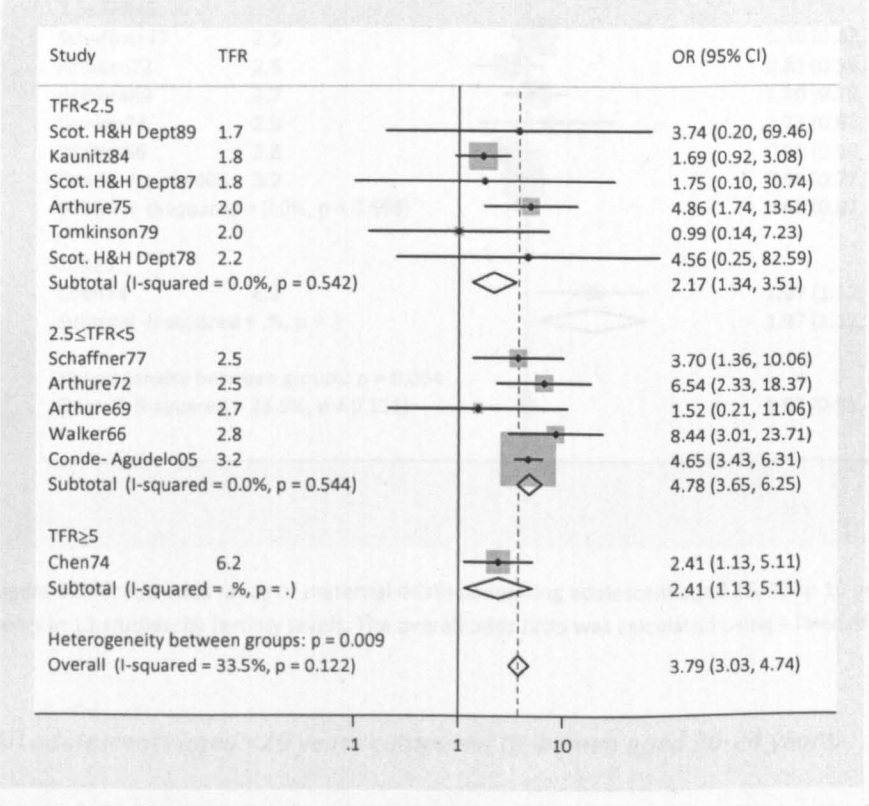

Figure 3.3: Crude odds ratios of maternal death comparing girls under 15 or 16 years to adolescents aged 15/16-19 years in 12 studies, by fertility levels. The overall odds ratio was calculated using a fixed effect model.

Girls aged between 15-16 and 19 years compared to women aged 20-24 years

There was little statistical evidence of heterogeneity or inconsistency across the studies (p= 0.11, I^2 = 33.9%). The crude summary odds ratio was 1.02 (CI: 0.93-1.11, p=0.70).

Stratifying by TFR changed the association to significant for the high fertility settings, but this was based on one study (crude odds ratio (COR)= 1.97, CI: 1.12- 3.45 [8]). Combining the high and medium fertility groups together, there was little evidence of interaction with TFR levels (p=0.71). There was no statistical association between pregnancy in older adolescents (15-19 years old) and maternal death in low or medium fertility settings (Figure 3.4).

There was no statistical evidence of publication bias (Begg's test: p=0.58).

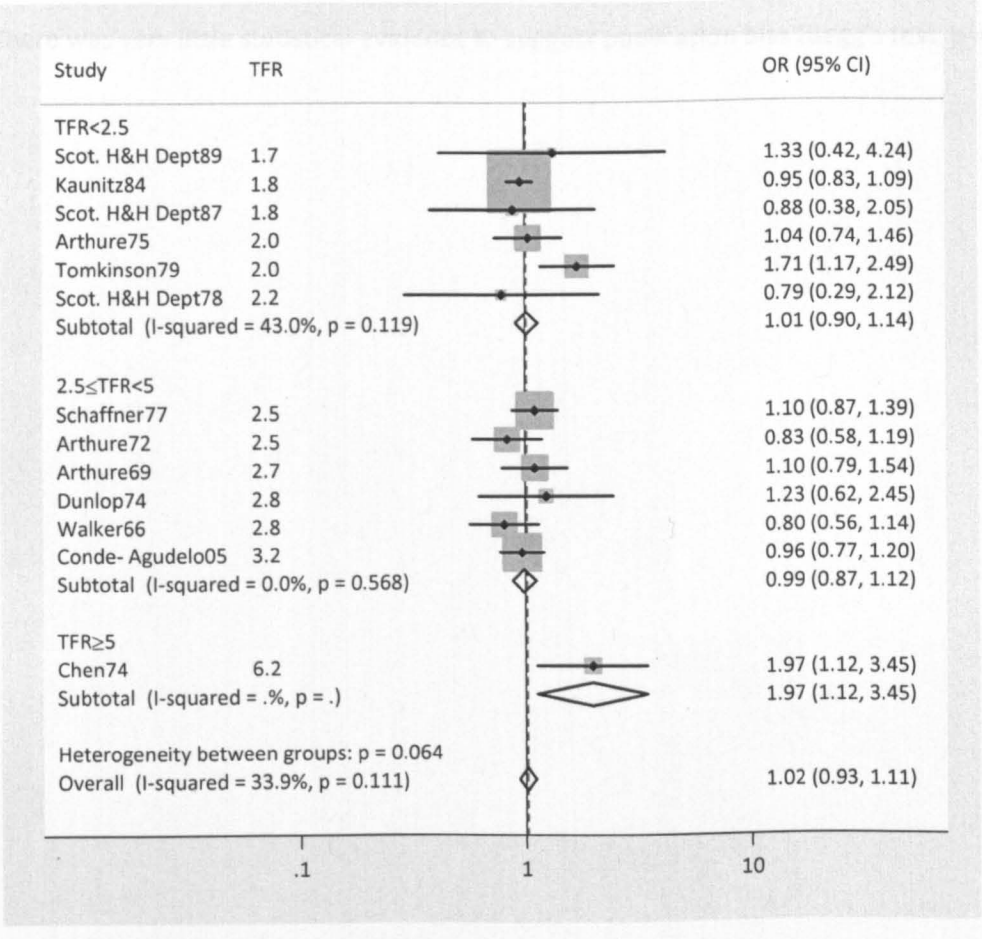

Figure 3.4: Crude odds ratios of maternal death comparing adolescent aged 15/16 to 19 years to women aged 20-24 years in 13 studies, by fertility levels. The overall odds ratio was calculated using a fixed effect model.

All adolescents aged <20 years compared to women aged 20-24 years.

Of the 54 cohorts included, 43 found increased odds of maternal death for adolescents younger than 20 years old, with 46 cohorts reporting a 95% confidence interval inclusive of

unity. There was evidence of heterogeneity and moderate inconsistency across the cohorts included (p=0.002, I^2= 39.8%). The crude summary odds ratio from a random effects model was 1.17 (CI: 1.08-1.26, p<0.001; Figure 3.5).

There was evidence of effect modification by TFR levels (p=0.04). Stratification by fertility levels changed the association to non-significant for women residing in low fertility settings (Figure 3.5). The crude summary odds ratio of maternal death increased with increasing TFR. They were 1.04 (CI: 0.98-1.10, p=0.21), 1.17 (CI: 1.01-1.35, p=0.03) and 1.51 (CI: 1.19-1.92, p=0.001) for low, medium and high fertility settings respectively (Figure 3.5).

Restricting to 52 cohorts that used the baseline age group of 20 to 24 year olds did not alter the overall findings.

There was very little statistical evidence to suggest publication bias (Begg's test: p=0.38).

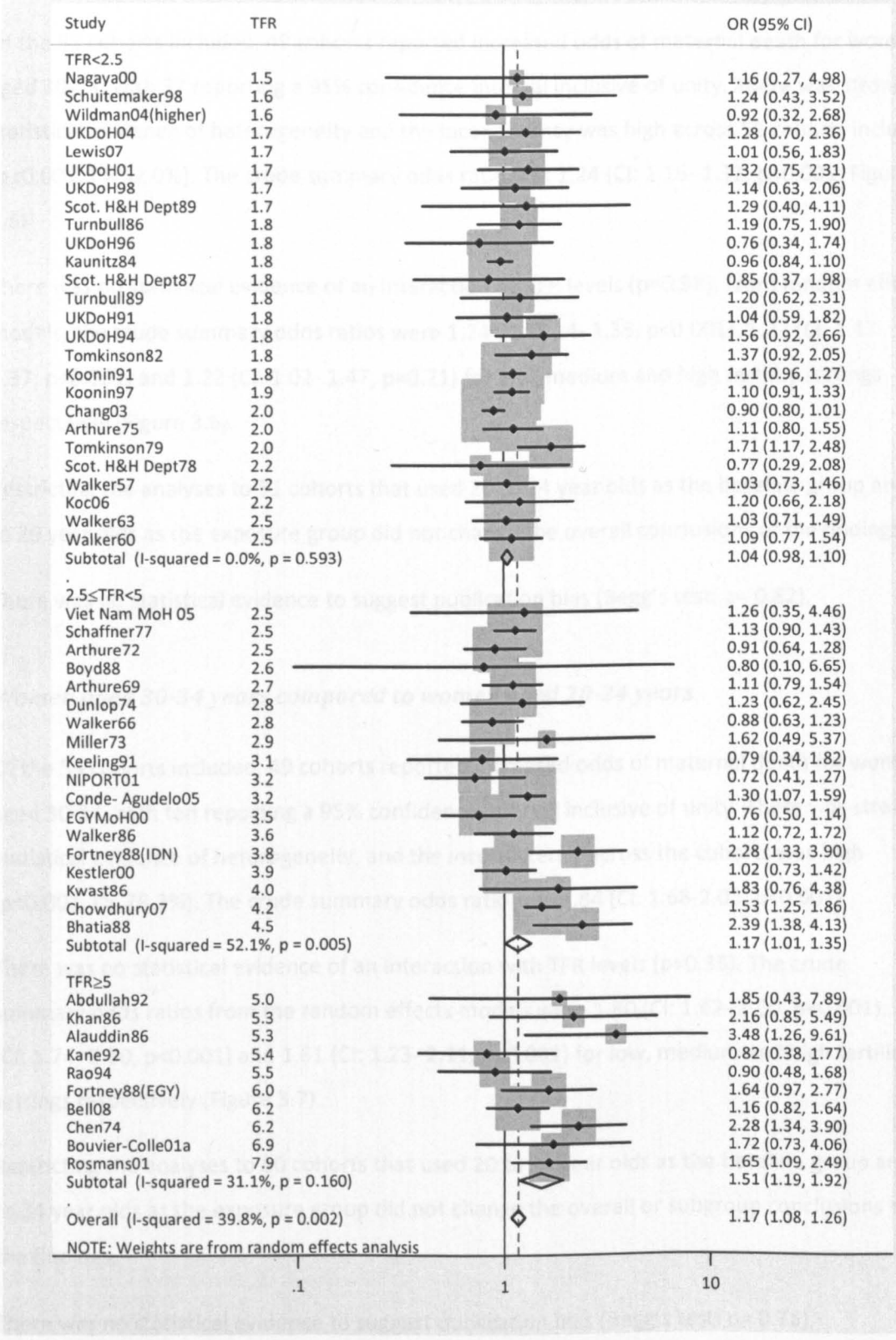

Figure 3.5: Crude odds ratios of maternal death comparing adolescents aged younger than 20 years to women aged 20-24 years in 54 cohorts, by fertility levels. The overall odds ratio was calculated using a random effects model.

Women aged 25-29 years compared to women aged 20-24 years

Of the 52 cohorts included, 49 cohorts reported increased odds of maternal death for women aged 30-34, with 37 reporting a 95% confidence interval inclusive of unity. There was strong statistical evidence of heterogeneity and the inconsistency was high across 52 cohorts included ($p<0.001$, $I^2= 52.0\%$). The crude summary odds ratio was 1.24 (CI: 1.16- 1.32, $p<0.001$; Figure 3.6)

There was no statistical evidence of an interaction by TFR levels ($p=0.98$). From random effects models, the crude summary odds ratios were 1.24 (CI: 1.14- 1.35, $p<0.001$), 1.27 (CI: 1.17- 1.37, $p<0.001$) and 1.22 (CI: 1.02- 1.47, $p=0.21$) for low, medium and high fertility settings respectively (Figure 3.6).

Restricting the analyses to 51 cohorts that used 20 to 24 year olds as the baseline group and 25 to 29 year olds as the exposure group did not change the overall conclusions of the findings.

There was no statistical evidence to suggest publication bias (Begg's test: $p= 0.82$).

Women aged 30-34 years compared to women aged 20-24 years

Of the 53 cohorts included, 49 cohorts reported increased odds of maternal death for women aged 30-34, with ten reporting a 95% confidence interval inclusive of unity. There was strong statistical evidence of heterogeneity, and the inconsistency across the cohorts was high ($p<0.001$, $I^2= 78.2\%$). The crude summary odds ratio was 1.84 (CI: 1.68-2.02, $p<0.001$).

There was no statistical evidence of an interaction with TFR levels ($p=0.35$). The crude summary odds ratios from the random effects models were 1.80 (CI: 1.62- 2.00, $p<0.001$), 2.09 (CI: 1.74- 2.50, $p<0.001$) and 1.61 (CI: 1.23- 2.11, $p<0.001$) for low, medium and high fertility settings respectively (Figure 3.7).

Restricting the analyses to 50 cohorts that used 20 to 24 year olds as the baseline group and 30 to 34 year olds as the exposure group did not change the overall or subgroup conclusions of the findings.

There was no statistical evidence to suggest publication bias (Begg's test: $p= 0.75$).

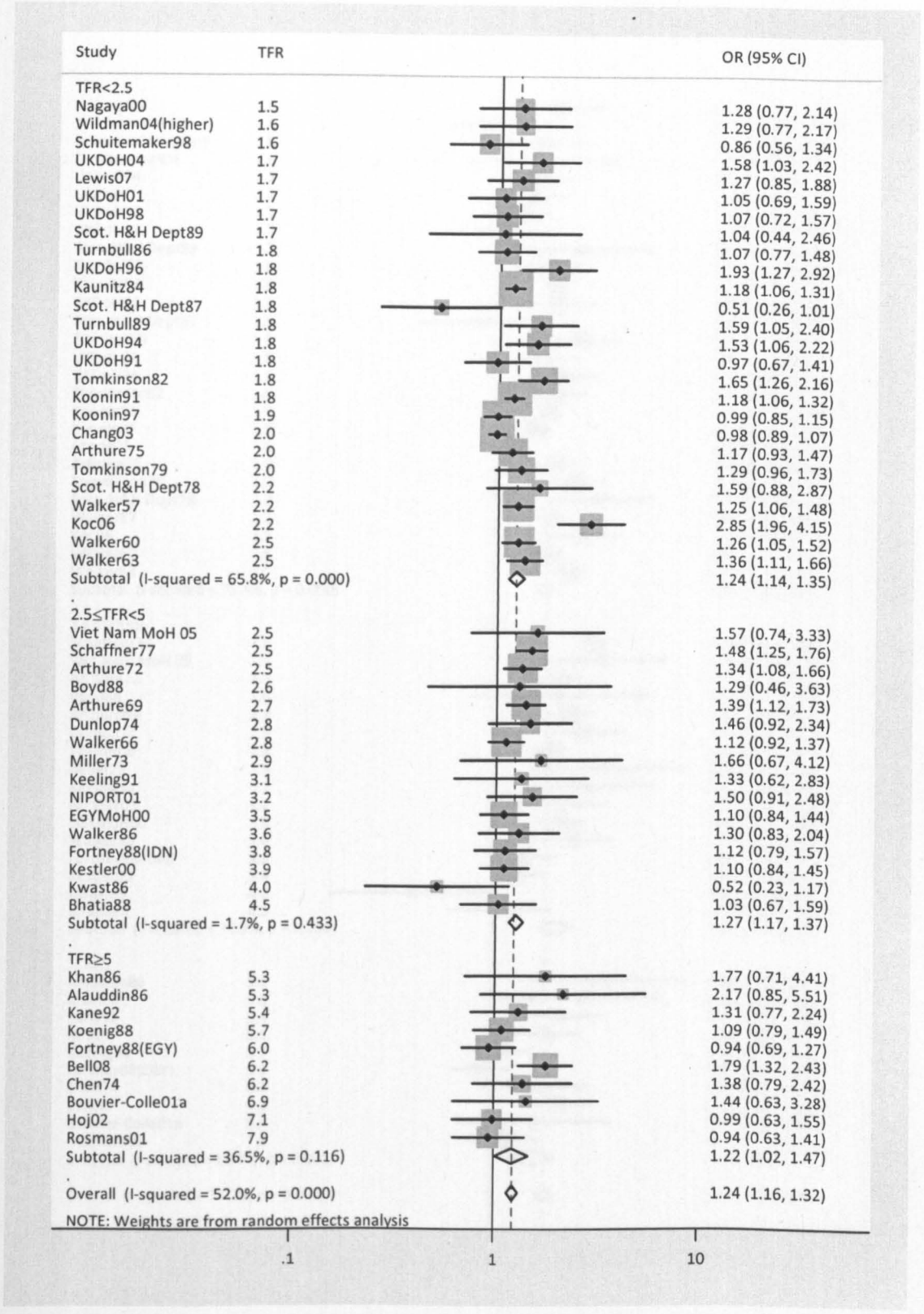

Figure 3.6: Crude odds ratios of maternal death comparing women aged 25-29 to women aged 20-24 years in 52 cohorts, by fertility levels. The overall odds ratio was calculated using a random effects model.

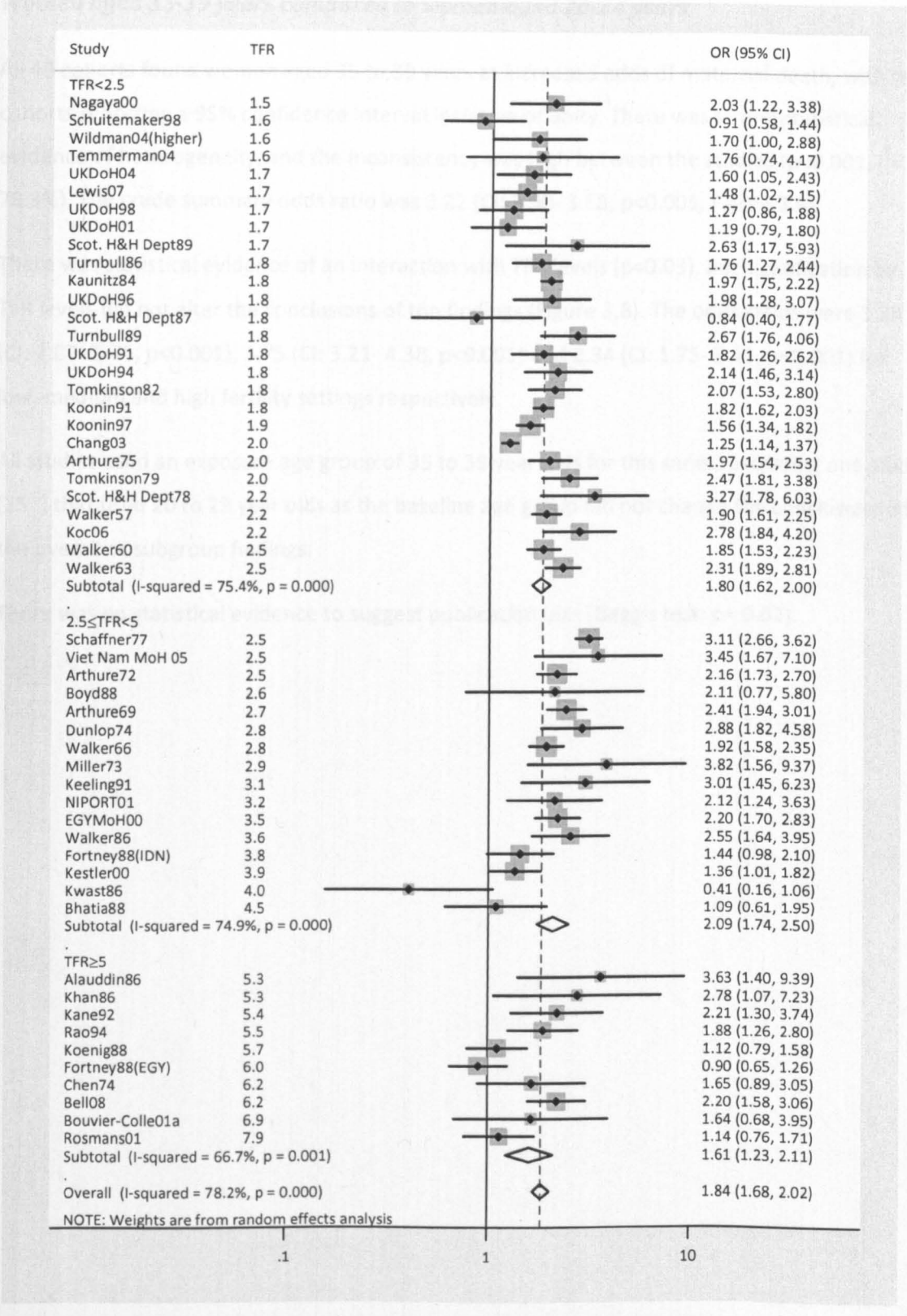

Figure 3.7: Crude odds ratios of maternal death comparing women aged 30-34 years to women aged 20-24 years in 53 cohorts, by fertility levels. The overall odds ratio was calculated using a random effects model.

Women aged 35-39 years compared to women aged 20-24 years

All 49 cohorts found women aged 35 to 39 years at increased odds of maternal death, with ten cohorts reporting a 95% confidence interval inclusive of unity. There was strong statistical evidence of heterogeneity, and the inconsistency was high between the studies ($p<0.001$, $I^2=$ 78.3%). The crude summary odds ratio was 3.22 (CI: 2.90- 3.58, $p<0.001$, Figure 3.8).

There was statistical evidence of an interaction with TFR levels ($p=0.03$), but stratification by TFR levels did not alter the conclusions of the findings (Figure 3.8). The odds ratios were 3.28 (CI: 2.87- 3.75, $p<0.001$), 3.75 (CI: 3.21- 4.38, $p<0.001$) and 2.34 (CI: 1.75- 3.15, $p<0.001$) for low, medium and high fertility settings respectively.

All studies used an exposure age group of 35 to 39 year olds for this series. Excluding one study [257] that used 20 to 29 year olds as the baseline age group did not change the conclusions of the overall or subgroup findings.

There was no statistical evidence to suggest publication bias (Begg's test: $p= 0.62$).

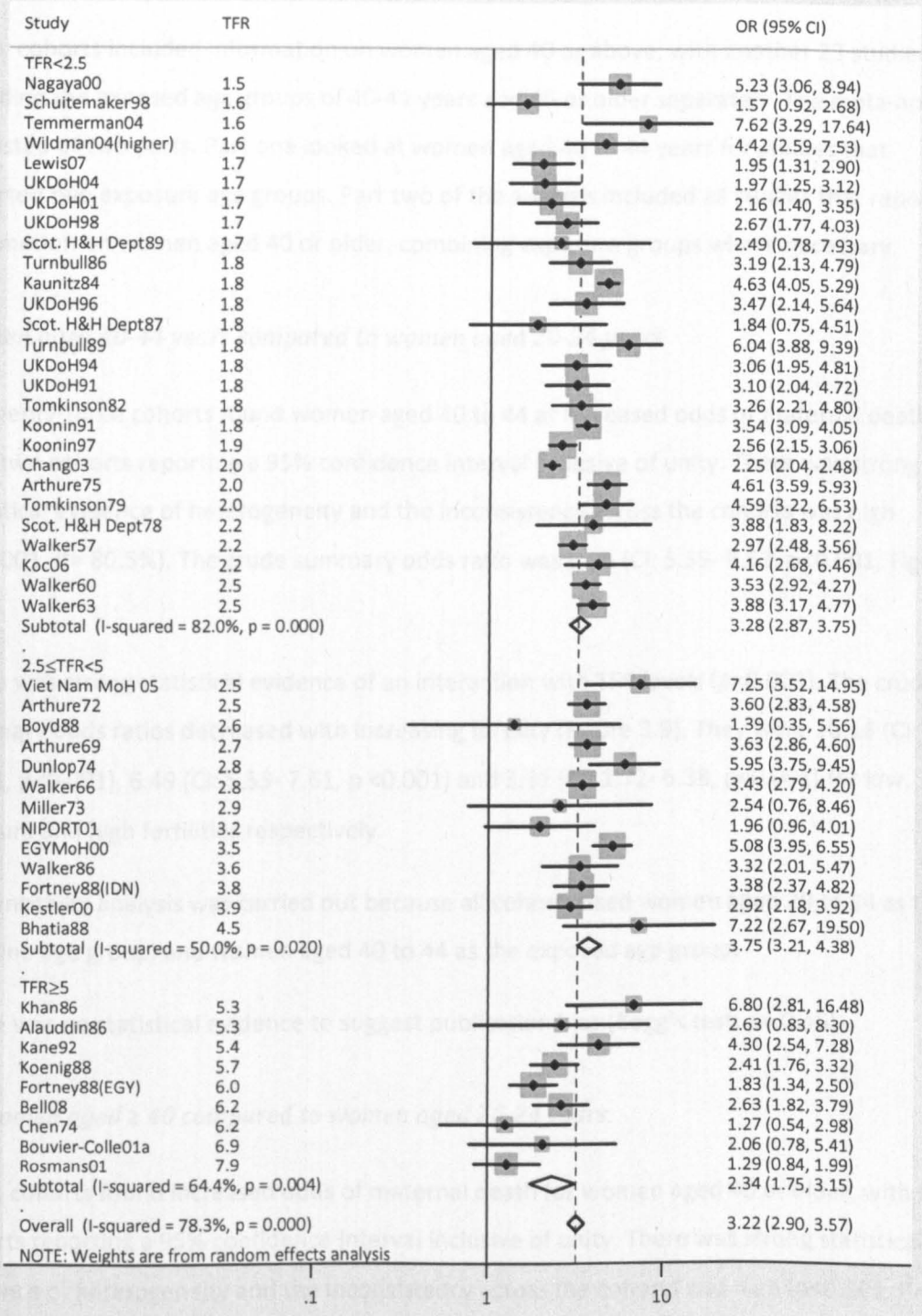

Figure 3.8: Crude odds ratios of maternal death comparing women aged 35-39 years to women aged 20-24 years in 49 cohorts, by fertility levels. The overall odds ratio was calculated using a random effects model.

Women aged ≥40 years compared to women aged 20-24 years

Thirty cohorts included information on women aged 40 or above, with another 23 studies including the exposed age groups of 40-44 years and 45 or older separately. The meta-analysis consisted of two parts. Part one looked at women aged 40 to 44 years for studies that reported two exposure age groups. Part two of the analysis included all studies that reported information on women aged 40 or older, combining exposure groups where necessary.

Women aged 40-44 years compared to women aged 20-24 years

All twenty-three cohorts found women aged 40 to 44 at increased odds of maternal death, with two cohorts reporting a 95% confidence interval inclusive of unity. There was strong statistical evidence of heterogeneity and the inconsistency across the cohorts was high ($p<0.001$, $I^2= 80.5\%$). The crude summary odds ratio was 6.95 (CI: 5.59- 8.63, $p<0.001$; Figure 3.9).

There was strong statistical evidence of an interaction with TFR levels ($p=0.003$). The crude summary odds ratios decreased with increasing fertility (Figure 3.9). They were 10.16 (CI: 7.64- 13.51, $p<0.001$), 6.49 (CI: 5.53- 7.61, $p <0.001$) and 3.31 (CI: 1.72- 6.38, $p<0.001$) for low, medium and high fertilities respectively.

No sensitivity analysis was carried out because all cohorts used women aged 20 to 24 as the baseline age group, and women aged 40 to 44 as the exposed age group.

There was no statistical evidence to suggest publication bias (Begg's test: $p= 0.46$).

All women aged ≥ 40 compared to women aged 20-24 years.

All 51 cohorts found increased odds of maternal death for women aged 40 or older, with three cohorts reporting a 95% confidence interval inclusive of unity. There was strong statistical evidence of heterogeneity and the inconsistency across the cohorts was high ($p<0.001$, $I^2= 82.5\%$). The crude summary odds ratio was 6.15 (CI: 5.36- 7.07, $p<0.001$; Figure 3.10).

There was very weak statistical evidence of an interaction with TFR levels ($p=0.10$). The summary odds ratios from random effects models decreased with increasing fertility levels (Figure 3.10). They were 7.13 (CI: 5.97- 8.51, $p<0.001$), 5.51 (CI: 4.24- 7.15, $p<0.001$) and 4.51 (2.91 – 7.00, $p <0.001$) for low, medium and high fertility settings respectively.

Restricting to 48 cohorts that used a baseline age group of 20 to 24 year olds did not change the conclusions of the findings.

There was little statistical evidence to suggest publication bias (Begg's test: p= 0.21).

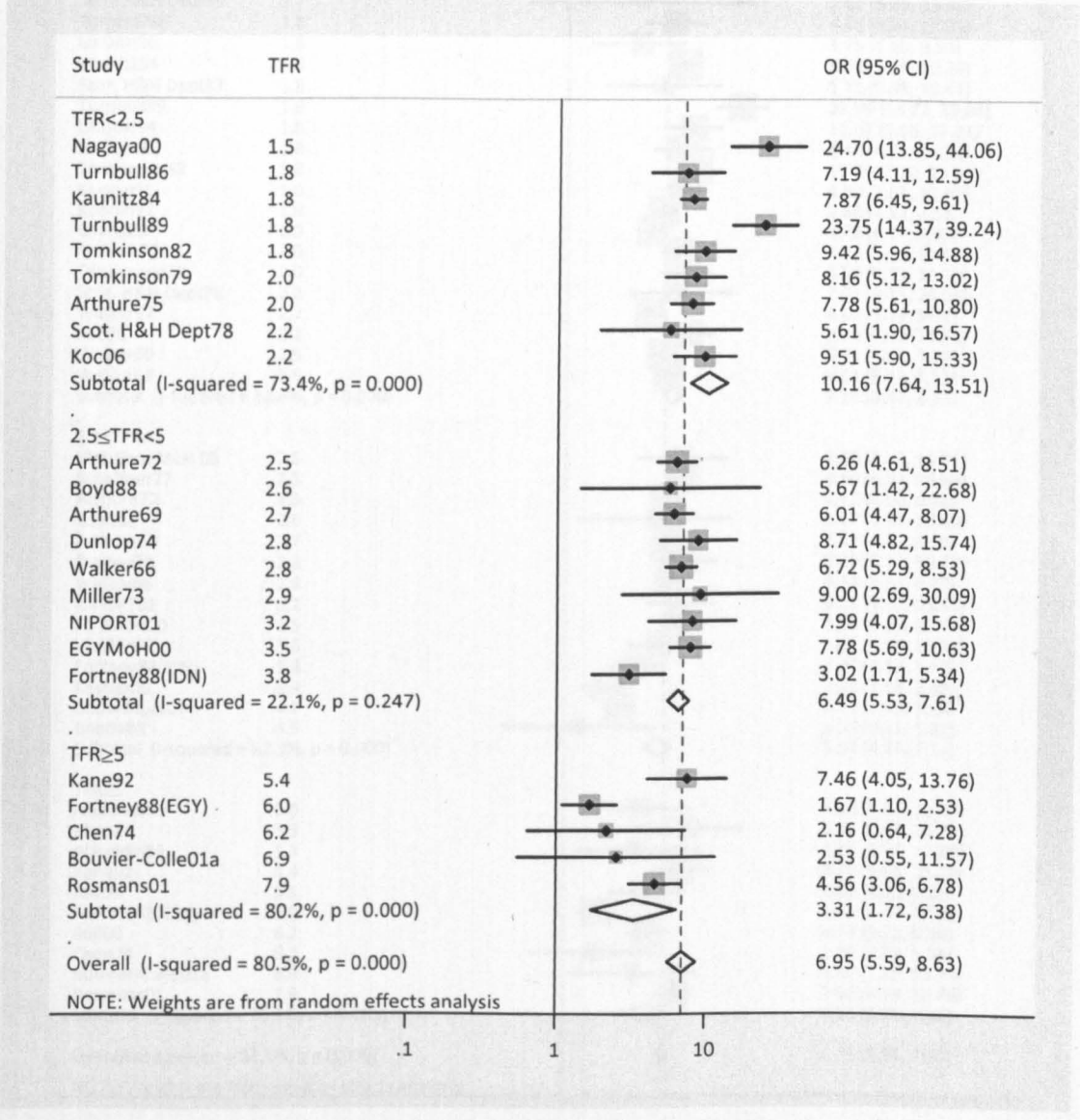

Figure 3.9: Crude odds ratios of maternal death comparing women aged 40-44 years to women aged 20-24 years in 23 cohorts, by fertility levels. The overall odds ratio was calcuated using a random effects model.

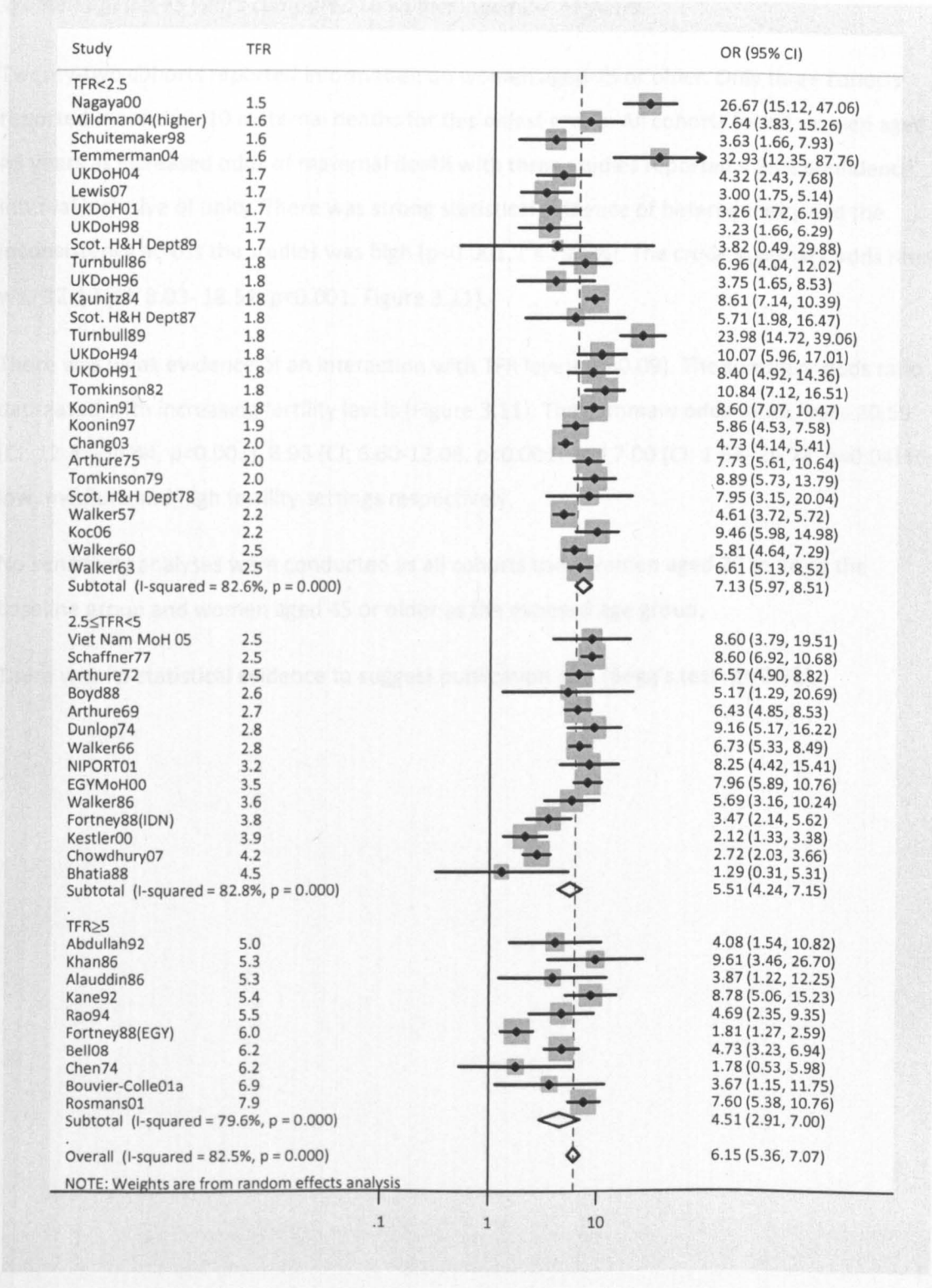

Figure 3.10: Crude odds ratios of maternal death comparing women aged 40 years or over to women aged 20-24 years in 51 cohorts, by fertility levels. The overall odds ratio was calcuated using a random effects model.

Women aged ≥ 45 years compared to women aged 20-24 years.

Twenty-two cohorts reported information on women aged 45 or older. Only three cohorts reported more than 10 maternal deaths for this oldest group. All cohorts found women aged ≥ 45 years at increased odds of maternal death with three studies reported a 95% confidence interval inclusive of unity. There was strong statistical evidence of heterogeneity and the inconsistency across the studies was high ($p<0.001$, $I^2= 79.6\%$). The crude summary odds ratio was 12.19 (CI: 8.03- 18.51, $p<0.001$; Figure 3.11).

There was weak evidence of an interaction with TFR levels ($p=0.09$). The summary odds ratio decreased with increasing fertility levels (Figure 3.11). The summary odds ratios were 20.59 (CI: 12.35-34.44, $p<0.001$), 8.93 (CI: 6.60-12.08, $p<0.001$) and 7.00 (CI: 1.83- 26.73, $p=0.04$) for low, medium and high fertility settings respectively.

No sensitivity analyses were conducted as all cohorts used women aged 20 to 24 as the baseline group and women aged 45 or older as the exposed age group.

There was no statistical evidence to suggest publication bias (Begg's test: $p= 0.93$).

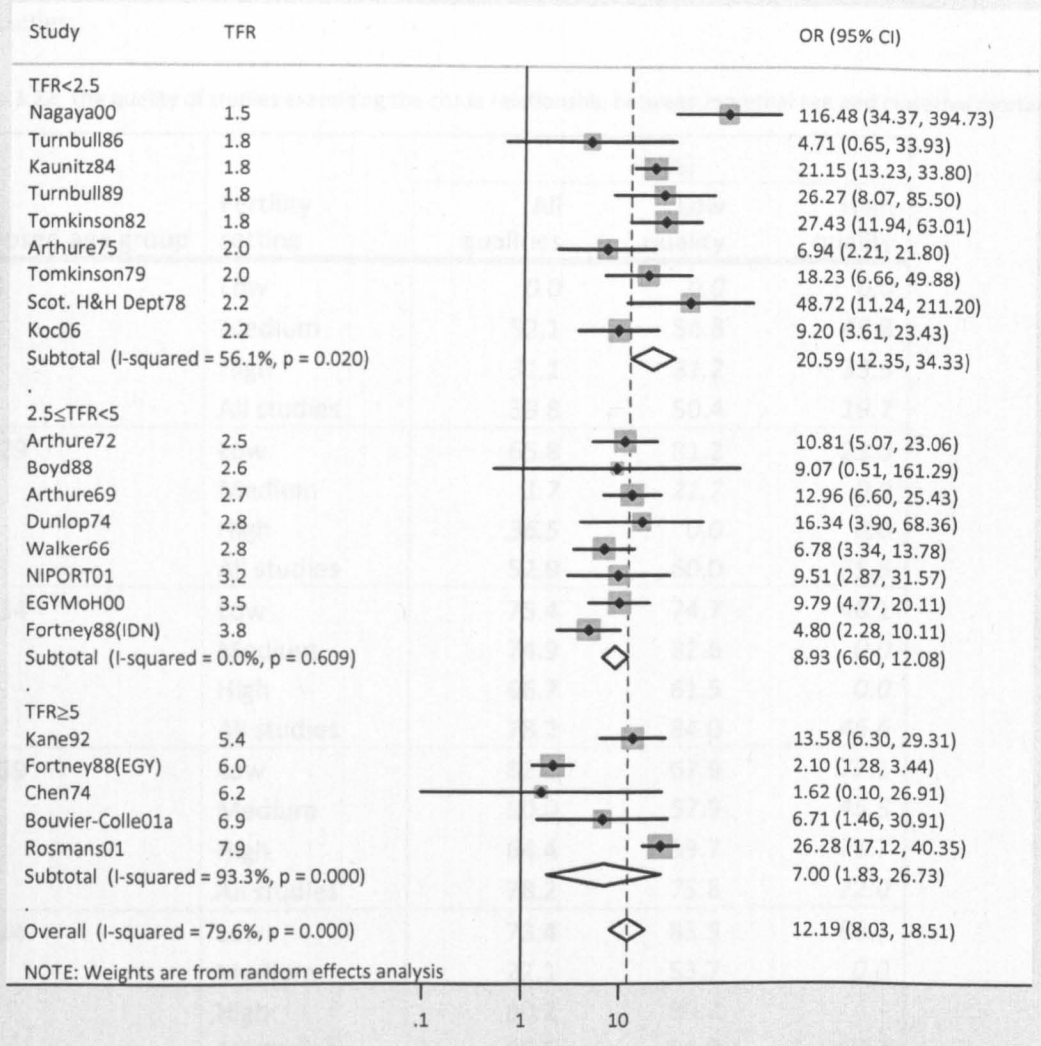

Figure 3.11: Crude odds ratios of maternal death comparing women aged 45 years or over to women aged 20-24 years in 22 cohorts, by fertility levels. The overall odds ratio was calculated using a random effects model.

Quality of the studies

The percentage of variation (I^2) or inconsistency between high quality studies was generally lower than between all studies combined for each maternal age group (Table 3.22). However, given most high quality studies were from the UK/US, this is not necessarily surprising.

There was no consistent pattern in the relationship between study quality and heterogeneity between studies, either overall or within different fertility groups. Please see Figure A.18 to Figure A.47 in Appendix A.6 for forest plots of study odds ratios by study quality. For age groups <20, 25-29 and 45 or over, the inconsistency between high quality studies was low/medium, while the inconsistency between all studies was high. For the other age groups,

the inconsistency between studies was high between high quality studies as well as between all studies.

Table 3.22: The quality of studies examining the crude relationship between maternal age and maternal mortality.

Exposed age group	Fertility setting	I^2 (%) All qualities	I^2 (%) Low quality	I^2 (%) High quality
<20	Low	*0.0*	*0.0*	*0.0*
	Medium	52.1	54.8	49.8
	High	*31.1*	*31.2*	*33.5*
	All studies	39.8	50.4	*19.7*
25-29	Low	65.8	81.2	*23.3*
	Medium	*1.7*	*21.7*	*0.0*
	High	*36.5*	*0.0*	*0.0*
	All studies	52.0	60.0	*25.5*
30-34	Low	75.4	74.7	48.1
	Medium	74.9	82.6	*0.0*
	High	66.7	61.5	*0.0*
	All studies	78.2	84.0	*46.6*
35-39	Low	82.0	67.9	77.1
	Medium	50.0	57.9	*45.5*
	High	64.4	59.7	73.7
	All studies	78.2	75.8	*72.0*
40-44	Low	73.4	83.9	66.7
	Medium	22.1	53.7	*0.0*
	High	80.2	80.2	-
	All studies	80.5	86.0	*60.2*
40+	Low	82.6	82.1	82.4
	Medium	82.8	83.4	82.7
	High	79.6	83.2	*38.1*
	All studies	82.5	83.0	*81.8*
45+	Low	56.1	90.5	*21.1*
	Medium	*0.0*	*0.0*	*0.0*
	High	93.3	93.3	-
	All studies	76.6	87.6	*12.9*

Text in italic indicates low inconsistency and heterogeneity between studies.
- where there were no or only one study in this category.

Summary

There was clear evidence that very young adolescents (10-14 years) had substantial increased odds of maternal death compared with women aged 20 to 24 years (Table 3.23). Girls aged 15-19, on the other hand, were not at increased odds of maternal death. From age 25 years

onwards the risk of maternal death increased with age, with the highest risk experienced by women at the end of their reproductive lives (Table 3.23).

The effect of higher maternal ages was associated with TFR levels from age 35 years onwards, generally with the lowest odds ratios in the high fertility settings (Figure 3.12).

The study quality did not consistently explain the heterogeneity between the studies.

Table 3.23: Summary odds ratios of maternal deaths comparing different age groups to women aged 20-24 years, using random effects models.

Age group (years)	Number of cohorts	Crude odds ratio (95% CI)	p-value for OR=1
<20	54	1.17 (1.08- 1.26)	<0.001
<15/16	12	3.94 (3.18- 4.88)	<0.001
15/16-19	13	1.02 (0.93- 1.11)	0.70
20-24	-	1	-
25-29	52	1.24 (1.16- 1.32)	<0.001
30-34	53	1.84 (1.68- 2.02)	<0.001
35-39	49	3.22 (2.90- 3.57)	<0.001
≥40	51	6.15 (5.36- 7.07)	<0.001
40-44	23	6.95 (5.59- 8.63)	<0.001
≥45	22	12.19 (8.03- 18.51)	<0.001

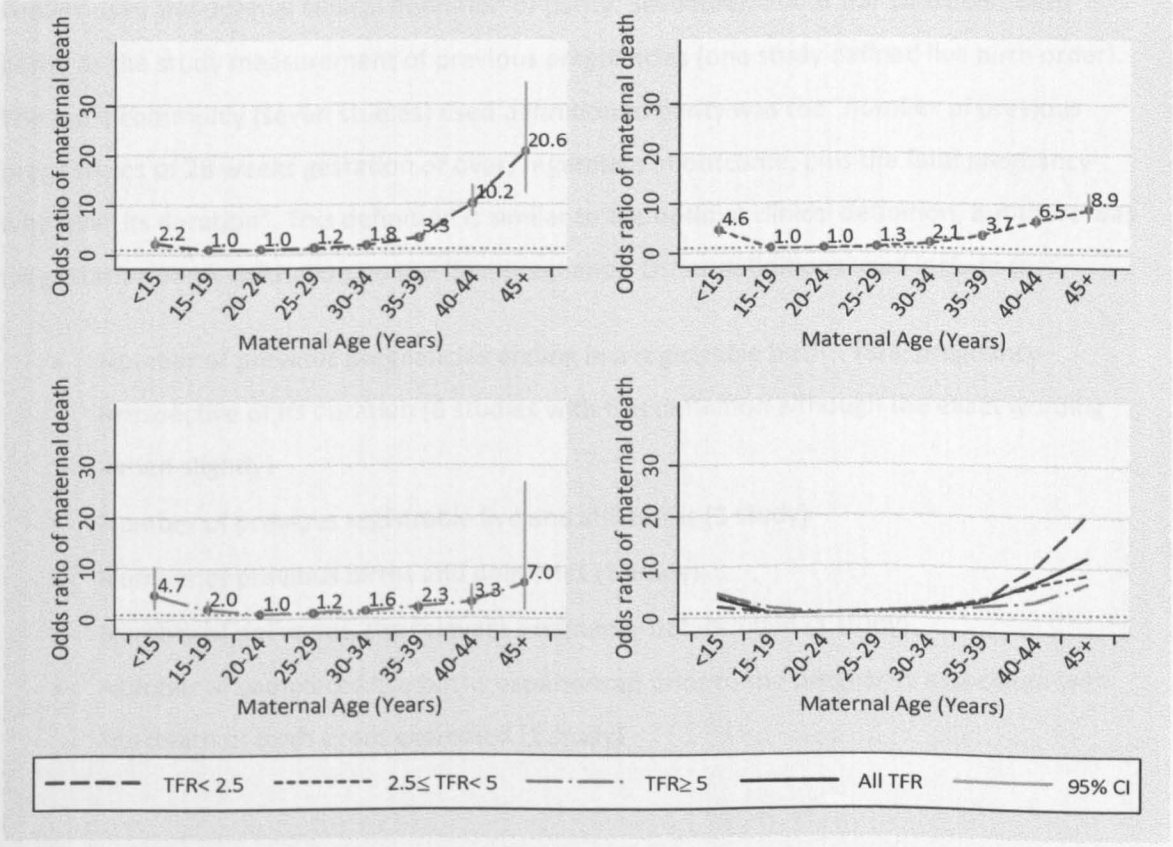

Figure 3.12: The crude summary odds ratios of maternal death from the meta-analyses, comparing various age groups to the baseline group of women aged 20-24 years by different TFR levels.

3.2.3 Crude relationship between the number of previous pregnancies and maternal mortality

Of the 38 studies included in the previous pregnancies review, 34 studies (34 cohorts) investigated the crude relationship between the number of previous pregnancies and maternal mortality.

The terminology used in studies for the number of previous pregnancies included parity, live birth order, gravidity, pregnancy order, and number of living children. They fell broadly into three categories – studies reporting parity (or live birth order) only; studies reporting gravidity (or pregnancy order) only; and studies that report both parity and gravidity (Table 3.24). The majority of studies reported on parity only (26 out of 34 studies).

The exact measurement of previous pregnancies varied between studies and the authors did not always explicitly define the measurement used. A total of 18 out of 34 studies explicitly and clearly defined their terminology used. Of these 18 studies, 14 were CEMDs from the United Kingdom.

For a list of definitions used in the studies, please see Table 3.1 to Table 3.14. None of the 34 studies used the optimal clinical definition of parity. Seventeen out of the 18 studies used parity as the study measurement of previous pregnancies (one study defined live birth order). The most commonly (seven studies) used definition of parity was the "number of previous pregnancies of 28 weeks gestation or over, regardless of outcome, plus the fatal pregnancy whatever its duration". This definition is similar to the optimal clinical definition, but there was no gestation week restriction on the final pregnancy. Other definitions used include the:

- Number of previous pregnancies ending in a registrable birth + fatal pregnancy irrespective of its duration (6 studies with this definition although the exact wording varied slightly)
- Number of previous registrable live and still births (1 study)
- Number of previous births and deliveries (1 study)
- Number of deliveries, the relevant pregnancy not included (1 study)
- Number of completed live births experienced prior to the pregnancy associated with the death or birth event examined (1 study)

Table 3.24: The three categories of terminologies used to measure number of previous pregnancies in the 34 studies included in the systematic review.

Terminology used in study	Terminology defined	Terminology undefined	Total number of studies
"Parity"			
parity	16	10[a]	26
live birth order	1	1	2
"Gravidity"			
gravidity	0	1	1
pregnancy order	0	2	2
"Parity and Gravidity"			
parity + gravidity	0	2[a]	2
parity + gravidity + no. of living children	1[b]	0	1
Total	18	16	34

a: includes one study with an unclear definition

b: the number of living children was not defined in the study

Of the 17 studies which explicitly defined the term "parity" used, 13 studies included the index pregnancy within their definition. However, ambiguity may arise in these definitions, particularly with regard to inclusion of the index pregnancy. For example, Alauddin reported "parity zero (no live births)" [205]. Consider two women who died as a result of their first pregnancy. The first died undelivered so producing no live births. She would be classified as parity zero. Assume the second woman died in the postpartum period after a live birth, and so she may be classified as parity one. There is a potential here for the two women to be classified under different parity categories even though both women died as a result of their first pregnancy. This ambiguity could be removed if the index pregnancy is excluded from the definition completely.

For the 16 cohorts that did not explicitly define the number of previous pregnancies, the definition was assumed to include the index pregnancy if the first category was reported as one. The definition was assumed to exclude the index pregnancy if the first category was reported as zero. The only exception was made for a study conducted in Ethiopia [201]. Out of 9,315 women aged 13-49 years, the author reported only 53 parity zero women, none whom had any live births. This proportion seemed unusually low for this population. In addition, the author reported high levels of abortion related maternal deaths (30% of maternal deaths). From the information available, I inferred that the "parity zero" women reported were a subgroup of women whose first pregnancy ended in an abortion. The deaths in this group were combined with deaths in the "parity one" group and I assumed the definition was inclusive of the index pregnancy.

To make the studies comparable, I excluded the index pregnancy in studies which included or were assumed to include the index pregnancy in the study definition of previous pregnancy. For example, if a study included the index pregnancy in its definition of gravidity, and reported on gravidity 1, gravidity 2, gravidity 3, etc, this was adjusted to gravidity 0, gravidity 1, gravidity 2, etc to exclude the index pregnancy.

Three quarters of the studies used para/gravida/live birth 1 women as the baseline group. The baseline group used by the rest of the studies ranged from 1-2 previous pregnancies to 1-6 previous pregnancies.

No previous pregnancies versus one previous pregnancy.

Thirty-three cohorts included information on women with no previous pregnancies compared to women with one previous pregnancy. There was strong evidence of heterogeneity and the inconsistency across studies was high ($p<0.0001$, $I^2= 64.4\%$). The crude summary odds ratio was 1.40 (CI: 1.28- 1.54, $p<0.0001$; Figure 3.13).

There was strong statistical evidence of an interaction with study definition used ($p=0.006$). From random effects models, the odds ratio of maternal death was the highest for gravidity studies (COR= 2.02, CI: 1.71-2.38, $p <0.0001$) and the lowest for parity studies (COR= 1.34, CI: 1.23-1.46, $p<0.0001$). The forest plots by study definitions of previous pregnancies are presented in Appendix A. The forest plot for the effect of no previous pregnancies on maternal mortality by study definition is shown in Figure A.72.

There was statistical evidence of an interaction with TFR levels ($p=0.06$). The crude summary odds ratios increased with TFR levels (Figure 3.13). They were 1.27 (CI: 1.17-1.39, $p<0.0001$), 1.57(1.32- 1.86, $p<0.0001$) and 1.74(1.16- 2.61, $p=0.007$) for low, medium and high fertility settings respectively.

All studies used no previous pregnancies as the exposed group. Restricting analyses to 24 studies using one previous pregnancy as the baseline group did not change the conclusions of the findings in the main or subgroup analyses

There was no statistical evidence to suggest publication bias (Begg's test: $p=0.11$).

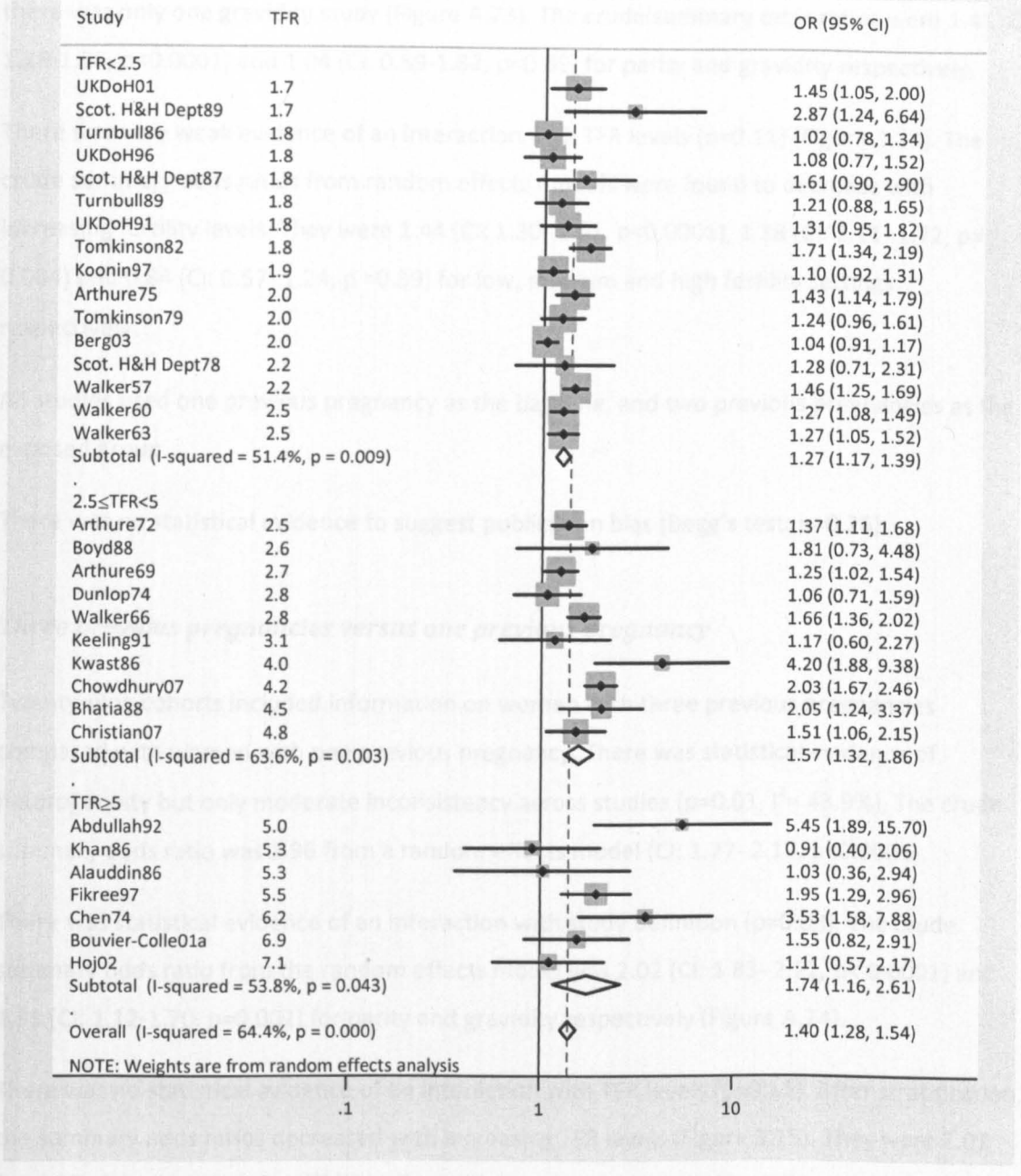

Figure 3.13: Crude odds ratios of maternal deaths comparing women with no previous pregnancies to women with one previous pregnancy in 33 studies, by fertility levels. The overall odds ratio was calculated using a random effects model.

Two previous pregnancies versus one previous pregnancy

Twenty five cohorts included information on women with two previous pregnancies compared to women with one previous pregnancy. There was strong evidence of heterogeneity and the inconsistency across studies was moderate (p=0.002, I^2= 50.3%). The crude summary odds ratio was 1.40 (CI: 1.27- 1.54, p<0.0001).

There was no statistical evidence of an interaction with the study definition (p=0.37). However, there was only one gravidity study (Figure A.73). The crude summary odds ratios were 1.41 (CI: 1.28-1.56, p<0.0001) and 1.04 (CI: 0.59-1.82, p=0.89) for parity and gravidity respectively.

There was very weak evidence of an interaction with TFR levels (p=0.11) (Figure 3.14). The crude summary odds ratios from random effects models were found to decrease with increasing fertility levels. They were 1.44 (CI: 1.30- 1.61, p<0.0001), 1.38 (CI: 1.11- 1.72, p= 0.004) and 0.84 (CI: 0.57- 1.24, p =0.39) for low, medium and high fertility settings respectively.

All studies used one previous pregnancy as the baseline, and two previous pregnancies as the exposed group.

There was no statistical evidence to suggest publication bias (Begg's test: p=0.26).

Three previous pregnancies versus one previous pregnancy

Twenty-nine cohorts included information on women with three previous pregnancies compared with women with one previous pregnancy. There was statistical evidence of heterogeneity but only moderate inconsistency across studies (p=0.01, I^2= 43.9%). The crude summary odds ratio was 1.96 from a random effects model (CI: 1.77- 2.17, p<0.0001).

There was statistical evidence of an interaction with study definition (p=0.03). The crude summary odds ratio from the random effects model was 2.02 (CI: 1.83- 2.22, p< 0.0001) and 1.38 (CI: 1.12-1.70, p=0.002) for parity and gravidity respectively (Figure A.74).

There was no statistical evidence of an interaction with TFR levels (p=0.15). After stratification, the summary odds ratios decreased with increasing TFR levels (Figure 3.15). They were 2.07 (CI: 1.83- 2.34, p<0.0001), 1.87 (CI: 1.54- 2.27, p<0.0001) and 1.33 (CI: 0.91- 1.94, p =0.15) for low, medium and high fertility settings respectively.

Restricting the analyses to 24 cohorts reporting an exposure group of three previous pregnancies and baseline of one previous pregnancy did not change the conclusions of the overall or fertility specific findings. There was only one gravidity study and this study found no association between gravidity three and maternal mortality (crude odds ratio= 1.51, CI: 0.78- 2.93, p = 0.22).

There was no statistical evidence to suggest publication bias (Begg's test: p=0.57).

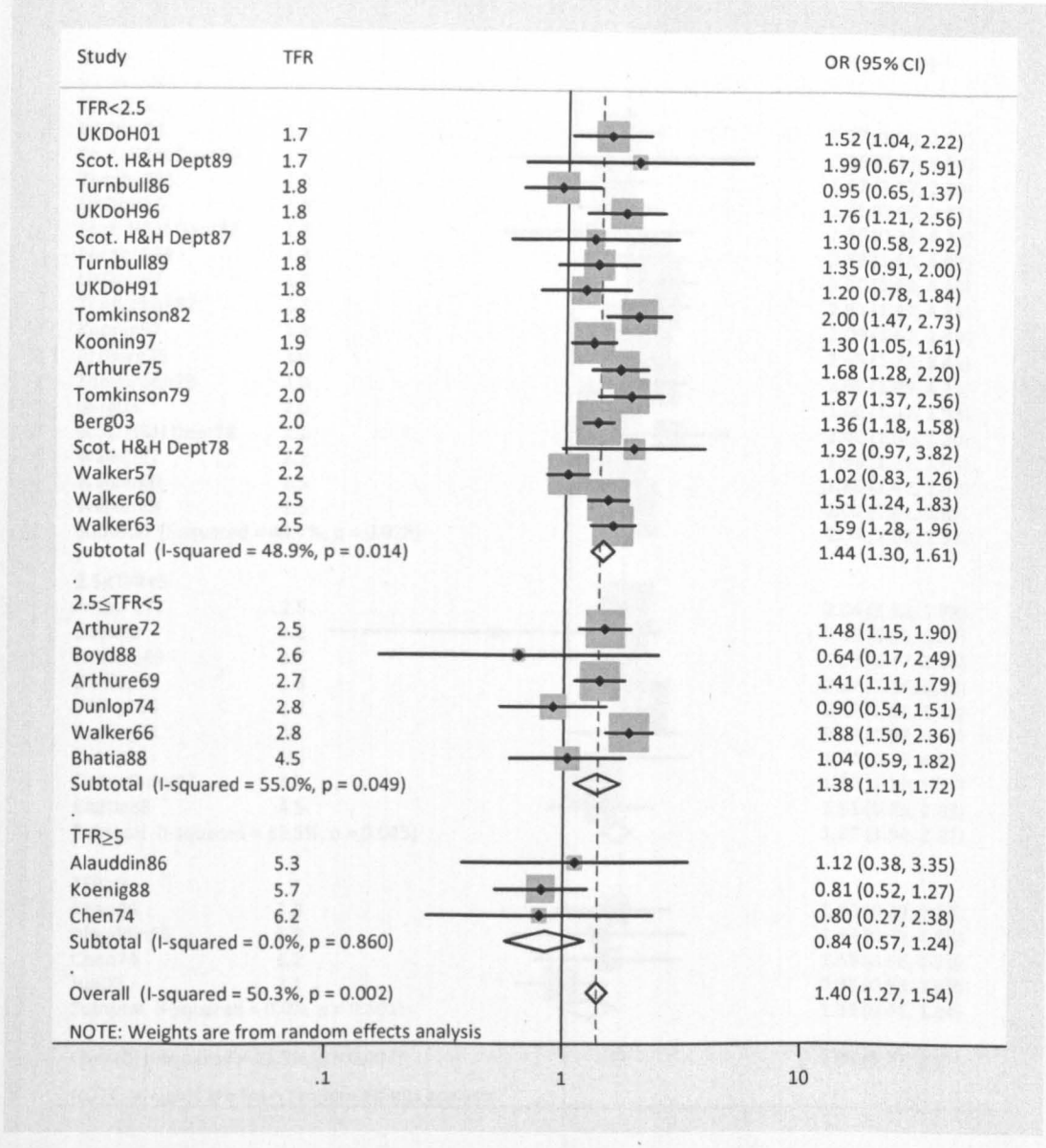

Figure 3.14: Crude odds ratios of maternal deaths comparing women with two previous pregnancies to women with one previous pregnancy in 25 studies, by fertility levels. The overall odds ratio was calculated using a random effects model.

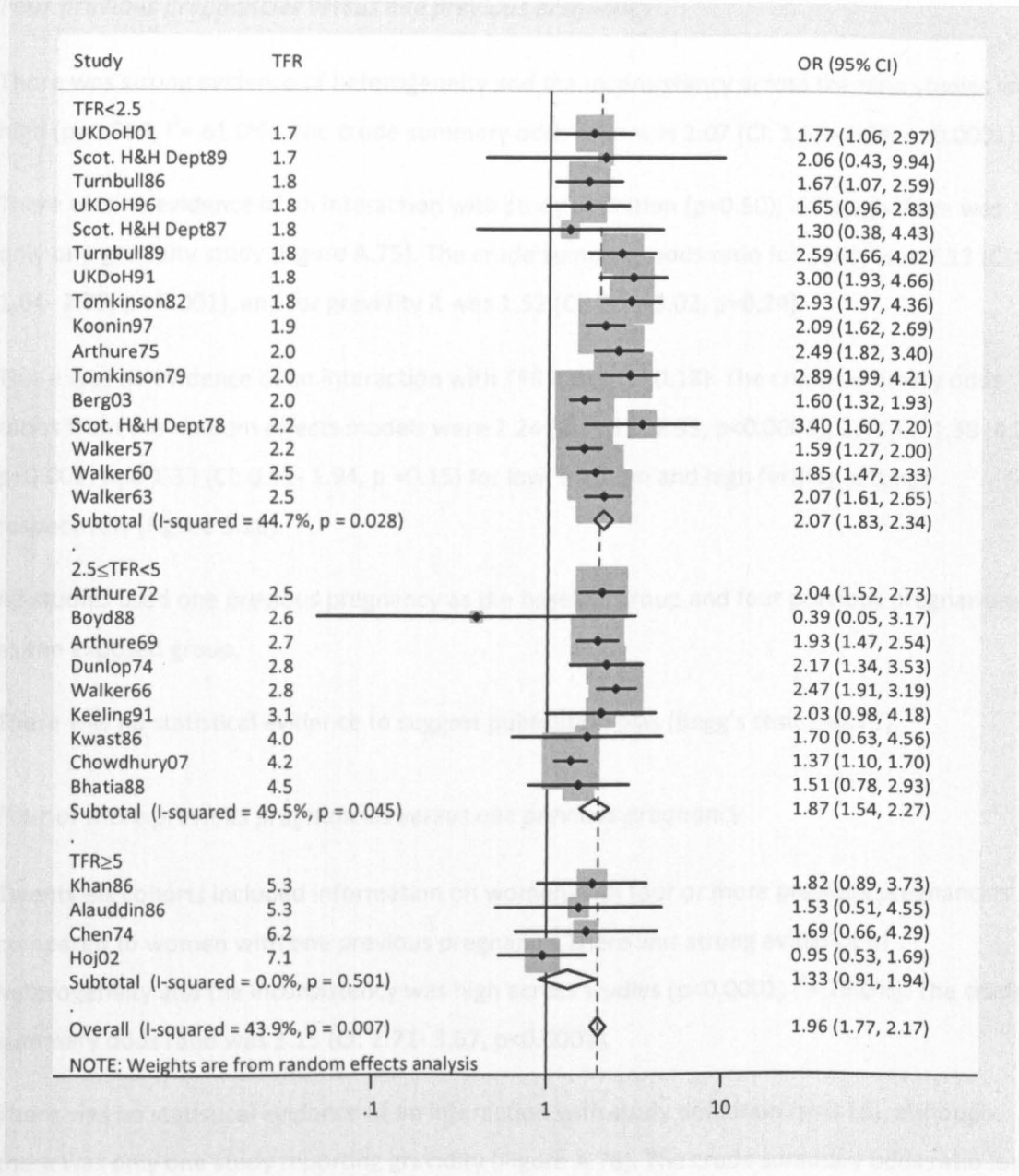

Figure 3.15: Crude odds ratios of maternal deaths comparing women with three previous pregnancies to women with one previous pregnancy in 29 studies, by fertility levels. The overall odds ratio was calculated using a random effects model.

Four and four or more previous pregnancies versus one previous pregnancy

Nine cohorts included information on women with four previous pregnancies compared with women with one previous pregnancy, and another seventeen studies grouping four or more pregnancies together. The meta-analysis consisted of two parts. Part one included the group of women with four previous pregnancies only. Part two included all studies reporting women with four or more previous pregnancies, combining exposure groups where necessary.

Four previous pregnancies versus one previous pregnancy

There was strong evidence of heterogeneity and the inconsistency across the nine studies was high (p=0.009, I^2= 61.0%). The crude summary odds ratio was 2.07 (CI: 1.62- 2.64, p<0.0001).

There was no evidence of an interaction with study definition (p=0.50), although there was only one gravidity study (Figure A.75). The crude summary odds ratio for parity was 2.13 (CI: 1.64- 2.75, p< 0.001), and for gravidity it was 1.52 (CI: 0.76-3.02, p=0.24).

There was no evidence of an interaction with TFR levels (p=0.18). The crude summary odds ratios from the random effects models were 2.24 (CI: 1.72- 2.93, p<0.0001), 2.41(CI: 1.38- 4.21, p=0.002) and 1.33 (CI: 0.91- 1.94, p =0.15) for low, medium and high fertility settings respectively (Figure 3.16).

All studies used one previous pregnancy as the baseline group and four previous pregnancies as the exposed group.

There was no statistical evidence to suggest publication bias (Begg's test: p=0.75).

Four or more previous pregnancies versus one previous pregnancy

Twenty-six cohorts included information on women with four or more previous pregnancies compared to women with one previous pregnancy. There was strong evidence of heterogeneity and the inconsistency was high across studies (p<0.0001, I^2= 78.0%). The crude summary odds ratio was 3.15 (CI: 2.71- 3.67, p<0.0001).

There was no statistical evidence of an interaction with study definition (p=0.18), although there was only one study reporting gravidity (Figure A.76). The crude summary odds ratio for parity was 3.22 (CI: 2.77- 3.76, p< 0.0001), and for gravidity it was 1.71 (CI: 1.00-2.91, p=0.05).

There was weak evidence of an interaction with TFR levels (p=0.10). After stratification, the crude summary odds ratios of maternal death appeared to be increasing with decreasing fertility levels. They were 3.47 (CI: 2.90- 4.14, p<0.0001), 3.06 (CI: 2.32- 4.03, p<0.0001) and 1.65 (CI: 1.24- 2.20, p=0.001) for low, medium and high fertility settings respectively (Figure 3.17).

All studies used one previous pregnancy as the baseline group, and four or more previous pregnancies as the exposure group.

There was no statistical evidence to suggest publication bias (Begg's test: p=0.54).

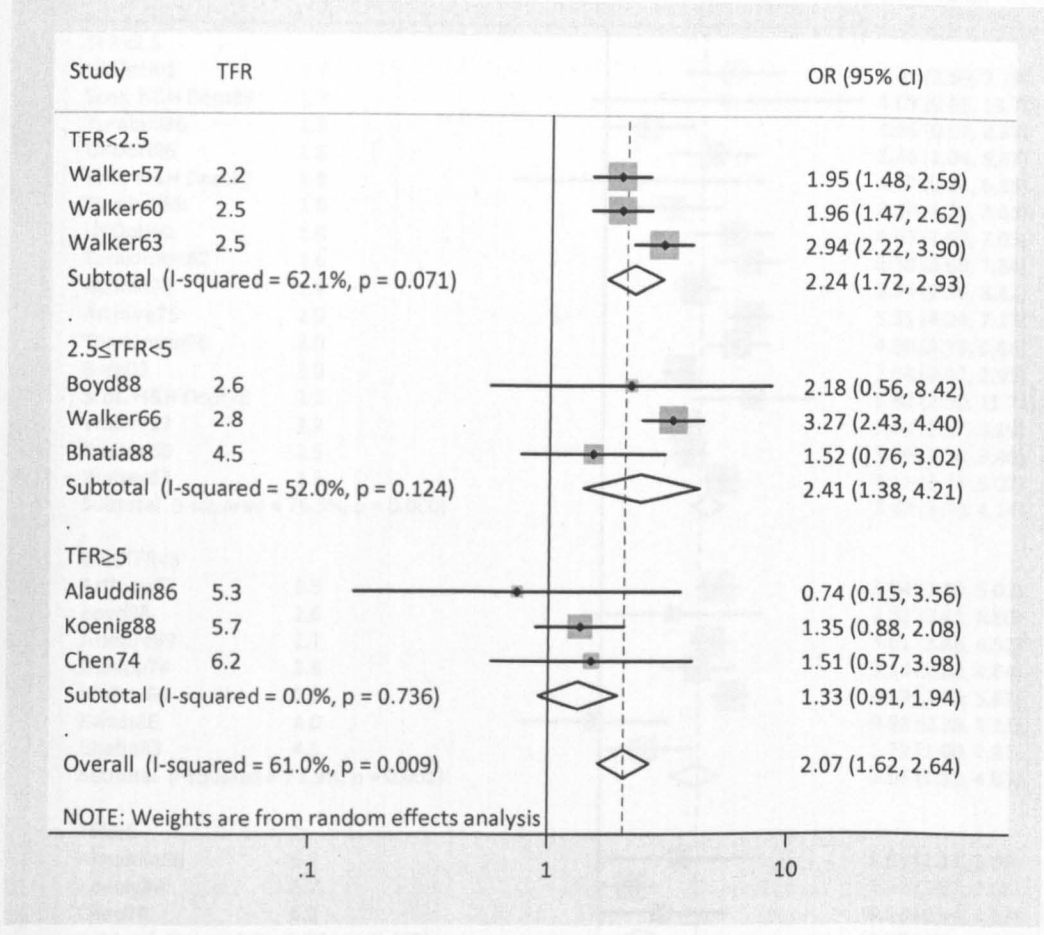

Figure 3.16: Crude odds ratios of maternal deaths comparing women with four previous pregnancies to women with one previous pregnancy in nine studies, by fertility levels. The overall odds ratio was calculated using a random effects model.

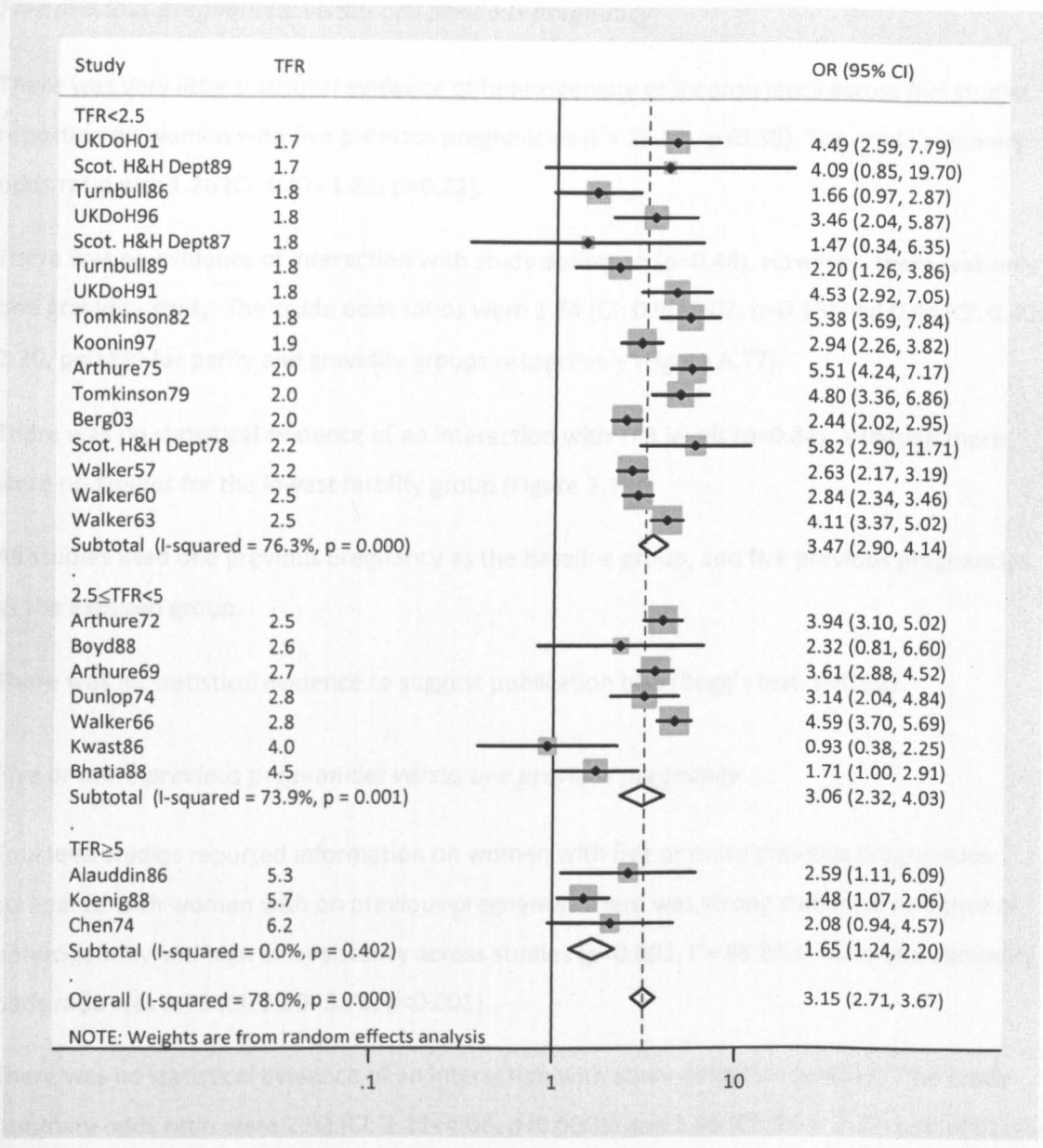

Figure 3.17: Crude odds ratios of maternal deaths comparing women with four or more previous pregnancies to women with one previous pregnancy in 26 studies, by fertility levels. The overall odds ratio was calculated using a random effects model.

Five and five or more previous pregnancies versus one previous pregnancy

Five cohorts included information on women with five previous pregnancies, with another eleven studies grouping five or more pregnancies together. The meta-analysis consisted of two parts. Part one included the group of women with five previous pregnancies. Part two included all studies reporting women with five or more previous pregnancies, combining exposure groups where necessary.

Five previous pregnancies versus one previous pregnancy

There was very little statistical evidence of heterogeneity or inconsistency across five studies reporting on women with five previous pregnancies (I^2= 17.9%, p=0.30). The crude summary odds ratio was 1.26 (CI: 0.87- 1.81, p=0.22).

There was no evidence of interaction with study definition (p=0.48). However, there was only one gravidity study. The crude odds ratios were 1.34 (CI: 0.90-2.02, p=0.15) and 0.94 (CI: 0.40-2.20, p=0.89) for parity and gravidity groups respectively (Figure A.77).

There was no statistical evidence of an interaction with TFR levels (p=0.84), although there were no studies for the lowest fertility group (Figure 3.18).

All studies used one previous pregnancy as the baseline group, and five previous pregnancies as the exposed group.

There was no statistical evidence to suggest publication bias (Begg's test: p=0.22).

Five or more previous pregnancies versus one previous pregnancy

Fourteen studies reported information on women with five or more previous pregnancies compared with women with on previous pregnancy. There was strong statistical evidence of heterogeneity and high inconsistency across studies (p<0.001, I^2= 88.8%). The crude summary odds ratio was 2.73 (CI: 2.00- 3.72, p<0.001).

There was no statistical evidence of an interaction with study definition (p=0.41). The crude summary odds ratio were 2.92 (CI: 2.11- 4.06, p<0.0001) and 1.95 (CI: 1.61- 2.37, p<0.0001) for parity and gravidity respectively (Figure A.78).

There was no statistical evidence of an interaction with TFR levels (p=0.46). After stratification, the crude summary odds ratios of maternal death were 3.91 (CI: 2.98- 5.14, p<0.0001), 2.21 (CI: 1.16 – 4.22, p=0.16) and 2.66 (CI: 1.35-5.22, p=0.005) for low, medium and high fertility settings respectively (Figure 3.19).

All studies used five or more previous pregnancies as the exposure group. Restricting to studies that used one previous pregnancy as the baseline group did not alter the conclusions of the overall or subgroup findings.

There was no statistical evidence to suggest publication bias (Begg's test: p=0.58).

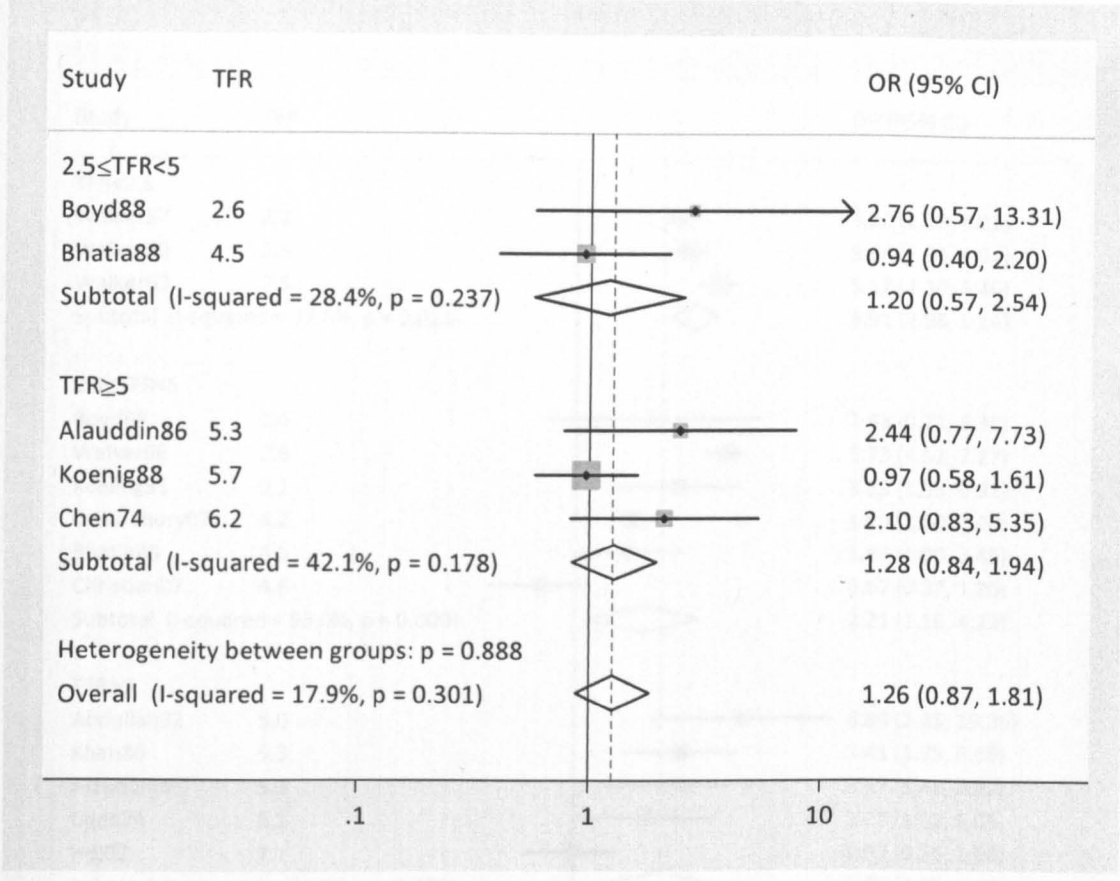

Figure 3.18: Crude odds ratios of maternal deaths comparing women with five previous pregnancies to women with one previous pregnancy in five studies, by fertility levels. The overall odds ratio was calculated using a fixed effect model.

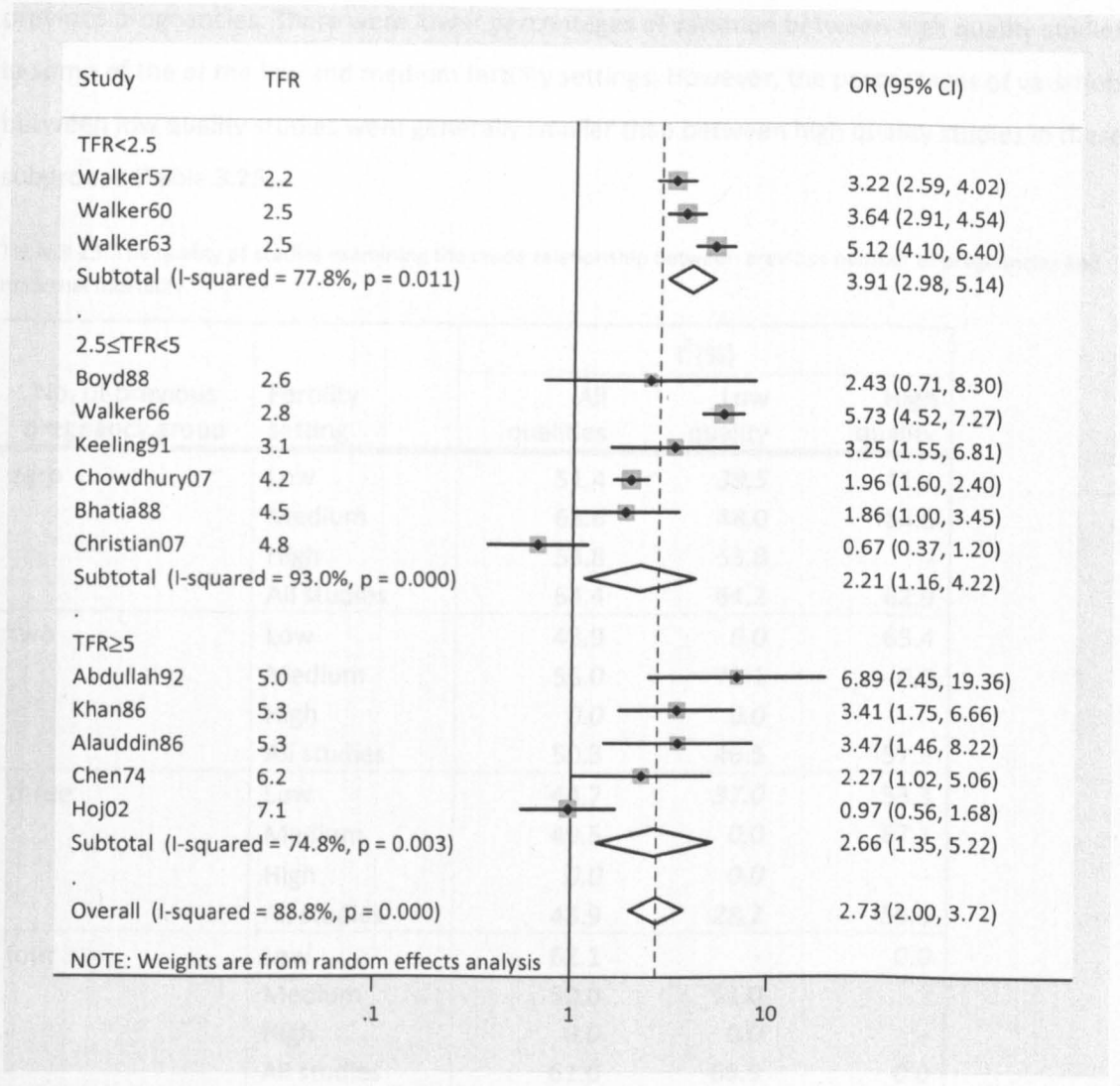

Figure 3.19: Crude odds ratios of maternal deaths comparing women with five or more previous pregnancies to women with one previous pregnancy in 14 studies, by fertility levels. The overall odds ratio was calculated using a random effects model.

Six or six or more previous pregnancies versus one previous pregnancy

There were fewer studies with higher number of previous pregnancies. For results please see Appendix A.9.

Quality of the studies

There was no consistent pattern in the relationship between study quality and heterogeneity between studies (Table 3.25). Please see Figure A.48 to Figure A.71 in Appendix A.7 for forest plots of study odds ratios by study quality.

The percentage of variation (I^2) between high quality studies was high for all numbers of previous pregnancies. There were lower percentages of variation between high quality studies in some of the of the low and medium fertility settings. However, the percentages of variation between low quality studies were generally smaller than between high quality studies in these subgroups (Table 3.25).

Table 3.25: The quality of studies examining the crude relationship between previous number of pregnancies and maternal mortality.

No. of previous pregnancy group	Fertility setting	I^2 (%)		
		All qualities	Low quality	High quality
zero	Low	51.4	*39.5*	41.4
	Medium	63.6	48.0	84.6
	High	53.8	53.8	-
	All studies	64.4	64.2	62.9
two	Low	48.9	*0.0*	65.4
	Medium	55.0	72.1	*0.0*
	High	*0.0*	*0.0*	-
	All studies	50.3	46.5	57.5
three	Low	44.7	*37.0*	53.3
	Medium	49.5	*0.0*	67.3
	High	*0.0*	*0.0*	-
	All studies	43.9	*28.2*	59.9
four	Low	62.1	-	*0.0*
	Medium	52.0	52.0	-
	High	*0.0*	*0.0*	-
	All studies	61.0	65.9	*0.0*
four or more	Low	76.3	81.5	71.4
	Medium	73.9	82.3	*0.0*
	High	*0.0*	*0.0*	-
	All studies	78.0	82.8	69.0
five or more	Low	77.8	-	*0.0*
	Medium	93.0	92.2	-
	High	74.8	74.8	-
	All studies	88.8	88.2	89.3

Text in italic indicates low inconsistency and heterogeneity between studies.
- where there were no or only one study in this category.

Summary

There was consistent evidence that women with first pregnancy were at increased risk of maternal death across all TFR groups (Figure 3.20). On average they were at 1.3 times higher odds of maternal death compared with women with one previous pregnancy (Table 3.26).

The effect of higher number of previous pregnancies was not consistent across all TFR groups. Women with two or more previous pregnancies were found to be at increased risk of maternal death in the two lowest fertility groups, but only women with five or more previous pregnancies were at increased risk of death in the high fertility setting. However, there was inconsistent statistical evidence of an interaction between TFR levels and higher previous pregnancies numbers.

The study quality did not consistently explain the heterogeneity between the studies.

Table 3.26: Summary odds ratios of maternal deaths comparing different number of previous pregnancies to women with one previous pregnancy, using random effects models.

No. of previous pregnancies	Number of cohorts	Crude odds ratio (95% CI)	p-value for OR=1
0	33	1.40 (1.28- 1.54)	<0.0001
1	-	1	-
2	25	1.40 (1.27- 1.54)	<0.0001
3	29	1.96 (1.77- 2.17)	<0.0001
4	9	2.07 (1.62- 2.64)	<0.0001
5+	14	2.73 (2.00- 3.72)	<0.0001

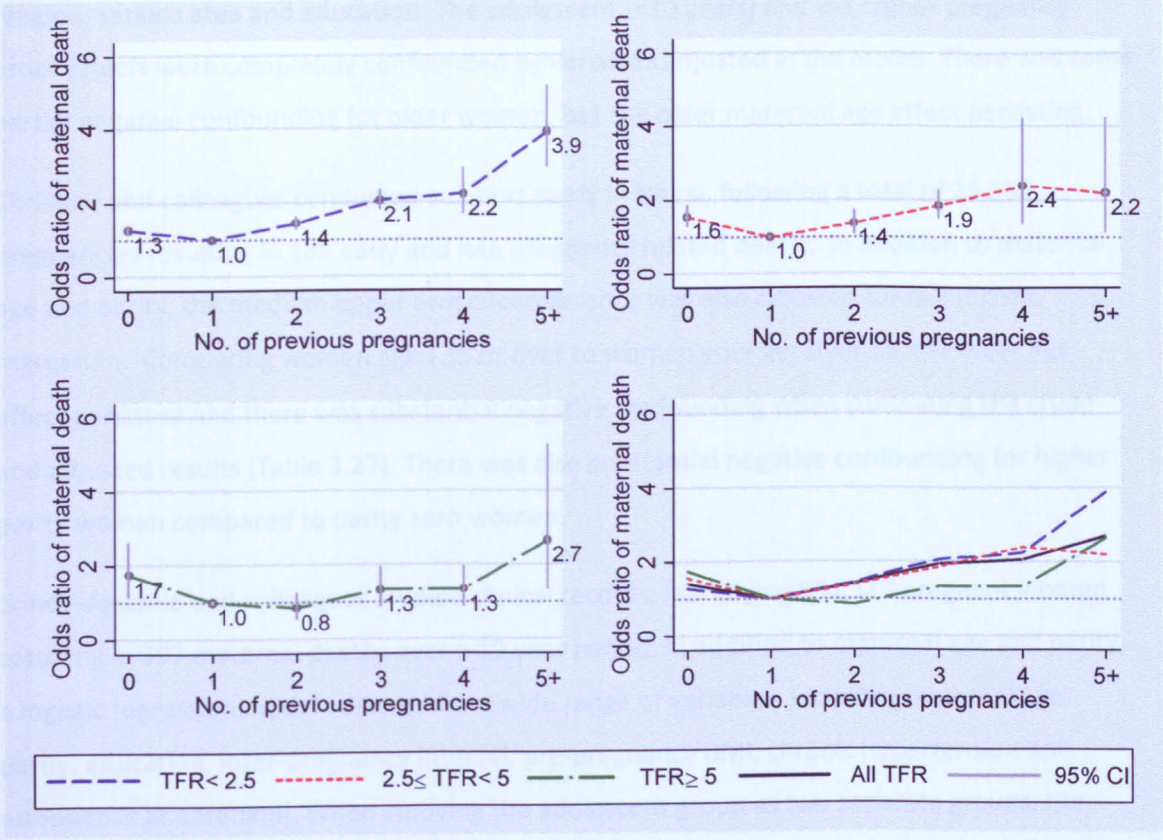

Figure 3.20: Crude meta-analyses summary odds ratio of maternal deaths for five exposure groups compared to the baseline group of one previous pregnancy, in different fertility settings.

3.2.4 Relationship between maternal age/number of previous pregnancies and maternal mortality adjusted for confounders

Only eight studies reported any adjusted estimates when investigating the relationships between maternal age/number of previous pregnancies and maternal mortality (Table 3.27 to Table 3.29)[9, 116 , 193-194, 197, 204, 269, 274].

Adjustment for maternal age and number of previous pregnancies

Five studies, including six populations, reported adjusted estimates controlling for the confounding effect of maternal age and number of previous pregnancies simultaneously (Table 3.27 and Table 3.28).

Chowdhury and colleagues conducted a cohort study in Matlab, Bangladesh following a total of 215,779 pregnancies resulting in 769 maternal deaths over a 30 year period. In addition to maternal age and pregnancy order, they used a logistic regression to adjust for asset quintiles,

religion, service area and education. The adolescent (<20 years) and the higher pregnancy order effects were completely confounded by variables adjusted in the model. There was some partial negative confounding for older women, but the older maternal age effect persisting.

Christian and colleagues conducted a cohort study in Nepal, following a total of 25,580 pregnancies resulting in 185 early and late pregnancy related deaths. In addition to maternal age and parity, the medium upper arm circumference was also adjusted for in a logistic regression. Comparing women aged 35 or over to women younger than 35, the older age effect persisted and there was substantial negative confounding when comparing the crude and adjusted results (Table 3.27). There was also substantial negative confounding for higher parity women compared to parity zero women.

Conde-Agudelo and colleagues studied clinical records, identifying 854,377 pregnant women resulting in 397 maternal deaths over a 19 year period. In addition to maternal age and parity, a logistic regression model adjusted for a wide range of variables, including maternal age, parity, education, inter-pregnancy interval, pre-pregnancy BMI, chronic hypertension and attendance at antenatal. When studying the adolescent group as two separate groups, the very young adolescent effect (≤15 years) persisted and there was minor positive confounding for this group. There was no association between older adolescence and maternal age in the crude or adjusted results and there was no confounding. Combining all adolescents (<20 years) and comparing to women aged 20 to 24 years, the adolescent effect completely disappeared after adjustment for confounders and the odds ratio reduced from 1.32 to 1.12.

Kwast and Liff only investigated non-abortion related maternal deaths in their nested case control study in Ethiopia. There were a total of 32 maternal deaths and 8,898 controls. In addition to maternal age and parity, a logistic regression adjusted for antenatal care use, occupation, income, education and marital status. There was no association between maternal age/parity and non abortion related maternal death in the crude or adjusted results.

Mbizvo and colleagues conducted a case control study in rural and urban regions of Zimbabwe, matching on the level of care for one set of controls, and matched additionally on age for another set of controls (Table 3.28). There were 97 cases and 194 controls from rural areas, 50 cases and 98 controls from urban areas. There were no associations between maternal age and maternal death in either region. It wasn't possible to assess the confounding effects due to the lack of crude results for comparison. In rural areas, higher parity women were had an increased risk of maternal death, even after taking account of the level of care. The direction of this association changed after taking account of age, suggesting strong confounding by

maternal age for this relationship. However, this was not observed in the urban areas, where there was no association between parity and maternal death after controlling for care and age.

Adjustment for other confounders

There were three further studies which controlled for other confounders but not for maternal age and previous pregnancies simultaneously (Table 3.29). Abdullah and colleagues conducted a study in Egypt identifying 8,656 pregnant women, resulting in 29 maternal deaths. The nulli and higher parity effect persisted after adjustment for residence, and there was minimal confounding by residence.

There were two matched case control studies, one conducted in India and one in China. Both studies matched on residence, and the study conducted in China also matched on the calendar month of maternal death (within three months). Both studies found an adolescent and older age effect even after controlling for residence (and calendar month of death). The nulligravidity and higher gravidity effect persisted after controlling for residence in India. However, in China, the first pregnancy was at the lowest risk of death after controlling for residence and calendar month of death. It was not possible to comment on whether residence (and calendar month of death) confounded the relationship between maternal age/gravidity and maternal death since there were no appropriate crude estimates to compare the matched estimates against.

Table 3.27: Summary of studies that reported estimates adjusting for both maternal age and number of previous pregnancies.

First author (year of publication)	Study design (year of study)	Model variables	Maternal age group (years)	Crude OR of maternal age effect (CI)	Adjusted/Matched OR of maternal age effect (CI)	Parity or gravidity group	Crude OR of parity or gravidity effect (CI)	Adjusted/Matched OR of parity or gravidity effect (CI)
Adjustment for both age and number of previous pregnancies								
Chowdhury 07 [24] (Bangladesh)	Cohort (1976-05)	age, pregnancy order, year, asset quintiles, religion, service area, education	≤ 19	1.53 (1.25- 1.86)	0.92 (0.73- 1.15)	1	2.03 (1.67- 2.46)	2.37 (1.91- 2.93)
			20-29	1	1	2-3	1	1
			30-39	1.52 (1.29- 1.80)	1.78 (1.43- 2.22)	4-5	1.37 (1.10- 1.70)	1.03 (0.82- 1.29)
			≥40	2.72 (2.03- 3.67)	2.99 (2.11- 4.24)	6+	1.96 (1.60- 2.40)	0.93 (0.73- 1.21)
Christian 07 [204] (Nepal)	Cohort (1993-01)	age, parity, medium upper arm circumference	<35	1	1	0	1	1
			≥35	1.91 (1.14- 3.20)	4.03 (2.02- 8.03)	1-4	0.66 (0.46- 0.96)	0.52 (0.35- 0.76)
						≥5	0.44 (0.22- 0.82)	0.15 (0.07- 0.35)
Conde - Agudelo 05 [57] (Latin American countries)	Survey of health facility records (1985-03) (3.2)	age, parity, education, marital status, cigarette smoking, inter-pregnancy interval, pre-pregnancy BMI, weight gain during pregnancy, history of miscarriage, LBW, perinatal death, chronic hypertension, gestational age at first attendance of ANC, no. of ANC visits, area, hospital type, year of delivery	≤ 15	4.67 (3.34- 6.51)	4.09 (3.86- 4.34)	not reported		
			16-17	1.01 (0.70- 1.45)	0.98 (0.66- 1.32)			
			18-19	1	1			
			<20	1.32 (1.08- 1.60)	1.12 (0.87- 1.37)			
			20-24	1	1			
Kwast 88 [26] (Ethiopia)	Nested Case Control (1982-83)	Maternal age, parity, ANC, occupation, income, education, marital status	14-19	2.5	2.0 (0.4- 10.3)	1	1.5	0.6 (0.2- 2.4)
			20-24	1.6	1.7 (0.5- 5.2)	2-3	1	1
			25-29	1	1	4-5	1.1	1.6 (0.5- 4.9)
			≥30	1.0	0.9 (0.3- 2.7)	≥6	2.0	1.5 (0.4- 5.6)

Table 3.28: Summary of studies that reported estimates adjusting for both maternal age and number of previous pregnancies in some parts of the study.

First author (year of publication)	Study design (year of study)	Model variables	Maternal age group (years)	Crude OR of maternal age effect (CI)	Adjusted/Matched OR of maternal age effect (CI)	Parity or gravidity group	Crude OR of parity or gravidity effect (CI)	Adjusted/Matched OR of parity or gravidity effect (CI)
Adjustment for both age and number of previous pregnancies in some parts of the study								
Mbizvo 93 [274] (rural area, Zimbabwe)	Matched Case Control (1989-90)	Rural area: matched on level of care. For gravidity - one set of controls matched on level care, another set matched on level of care and maternal age (within 5 years)	≤19		0.8 (0.4- 1.9)	0		1.4 (0.8- 2.6)
			20-24		1	1-3		1
			25-29		0.6 (0.3- 1.6)	4-6		1.2 (0.6- 2.3)
			30-34		0.7 (0.4- 1.7)	7+		3.0 (1.4- 6.5)
			35-39		4.2 (1.7- 10.3)			
			≥40		2.3 (0.8- 6.3)			adjusted for age
						0		1.8 (p=0.13)
						1-3		1
						4-6		0.7 (p=0.37)
						7+		0.43 (p=0.43)
Mbizvo 93 [274] (urban area, Zimbabwe)	Matched Case Control (1989-90)	Urban area: matched on level of care. For gravidity - one set of controls matched on level care, another set matched on level of care and maternal age (within 5 years)	≤19		1.3 (0.5-3.5)	0		0.6 (0.3- 1.4)
			20-24		1	1-3		1
			25-29		0.8 (0.3- 2.0)	4-6		1.1 (0.4- 3.2)
			30-34		1.1 (0.4- 3.0)	7+		1.1 (0.2- 7.3)
			35-39		2.0 (0.4- 9.0)			
			≥40		-			adjusted for age
						0		0.5 (p=0.09)
						1-3		1
						4-6		0.94(p=0.88)
						7+		-

Table 3.29: Summary of studies that reported estimates for maternal age or number of previous pregnancies adjusting for other confounders.

First author (year of publication)	Study design (year of study)	Model variables	Maternal age group (years)	Crude OR of maternal age effect (CI)	Adjusted/Matched OR of maternal age effect (CI)	Parity or gravidity group	Crude OR of parity or gravidity effect (CI)	Adjusted/Matched OR of parity or gravidity effect (CI)
Adjustment for other potential confounders								
Abdullah 92 [69] (Egypt)	Cohort and survey (1987)	parity, residence				0	5.45 (1.89, 15.70)	5.8
						1-4	1	1
						5+	6.89 (2.45, 19.4)	6.2
Ganatra 98 [60] (India)	Matched Case Control (1993- 95)	matched on village of residence	<20		1.61 (1.1- 2.3)	1		1.68 (1.1- 2.66)
			20-29		1	2		1
			30-35		2.2 (1.3- 3.7)	3-4		not reported
			>35		2.67 (1.2- 5.3)	≥5		1.58 (1.1- 2.61)
Ni 94 [194] (China)	Matched Case Control (1989-91)	matched on town of residence and month of death (within 3 months)	17-19		4.6 (1.8- 12.4)	0		1
			20-24		1	1		1.6 (1.21- 2.1)
			25-29		1.8 (1.3- 2.4)	2		2.7 (1.9 - 4.0)
			30-34		4.4 (2.7- 7.3)	3		2.0 (4.2- 15.1)
			35-46		23.6 (10.2- 57.5)	≥4		28.7 (13.0- 65.7)

Summary

It is difficult to summarise the findings for studies reporting adjusted estimates since very few studies adjusted for the same confounders. In addition, the three matched case control studies do not provide a suitable comparison to allow comments on the effect of the confounders on the association between age/parity and maternal mortality.

There was minimal or partial confounding for the effects of very young adolescents (≤15 years) and older maternal ages on maternal death. In the majority of studies the effects of very young adolescents and older maternal ages persisted after adjustment for confounders including parity. One (out of three) study did not find an old age effect after adjusting for at least number of previous pregnancies.

Three studies investigated the risk of maternal death for the combined adolescent group (<20) adjusting for number of previous pregnancies. The adolescent effect was completely confounded by parity/pregnancy order, education and other factors in studies in Bangladesh and Latin America [9, 269].There was partial confounding by parity, socio-economic status and other factors in the remaining study in Ethiopia [116], which found no adolescent effect.

There was no or minimal confounding by other variables such maternal age for the relationship between no previous pregnancy and maternal mortality [9, 116, 274]. There was no first pregnancy effect in three of out four populations after adjusting for at least maternal age.

There was at least partial positive confounding by maternal age and other variables in three out of four populations investigating the relationship between higher number of previous pregnancies and maternal mortality. In one population, the effect of higher parity was completely confounded by maternal age and socio-economic factors. For the remaining three populations, there was no higher parity/gravidity effect in the crude, matched or adjusted analyses.

3.3 Discussion

3.3.1 Main findings

This review suggests that at the crude level, the risk of maternal death is higher for very young adolescents, older women, and women experiencing their first pregnancy.

Very young adolescents have a 3.94 (CI: 3.18-4.88) times higher odds of maternal death compared to women aged 20-24 years and this effect was consistent across fertility levels. The odds ratio of maternal death increased with age, from 1.84 (CI: 1.68-2.02) for women aged 30-35 years to 6.15 (CI: 5.36- 7.07) for women aged 40 years or older. The magnitude of the odds ratio was generally inversely related to the fertility levels, with the odds ratio for the effect of older age higher in lower fertility populations.

Women experiencing their first pregnancies were at 1.40 (CI: 1.28-1.54) higher odds of maternal death compared to gravidity one women, and this effect was consistent across fertility settings. The risk of maternal death increased with increasing number of pregnancies, but the parity level at which this increase was seen varied between fertility levels. However, there was inconsistent statistical evidence for an interaction between TFR level and higher number of previous pregnancies.

Too few studies adjusted for maternal age and number of previous pregnancies together or for the potential confounding effects of socio-economic factors to be able to draw firm conclusions about the causality of the associations. The studies that did report adjusted results reported inconsistent evidence, with results varying between no, positive and negative confounding depending on context and variables adjusted for. I was unable to disentangle the independent effects of maternal age and number of previous pregnancies.

For the studies which reported adjusted results, there appears to be minimal confounding for the effects of first pregnancy and girls aged ≤15 on maternal mortality. Only the effect of very young adolescent (≤15) and older maternal ages persisted in the majority of the studies.

Three out of four cohorts did not find a nulliparity effect after controlling for maternal age. However, the number of studies was small, three or four populations for each age/previous pregnancy category. In addition, one study only reported non-abortion related deaths in a setting where 30% of maternal deaths identified were abortion related [116, 201]. There were only 29 non abortion related maternal deaths included in the adjusted analysis. Another study

including two populations, matched on the level of care, which is considered to be an effect modifier. Good quality of care could mitigate some of the risk of pregnancy and so this study may be less likely to report significant results.

3.3.2 Methodological limitations

In this section I discuss the completeness in the ascertainment of maternal deaths, maternal age and number of previous pregnancies status of pregnant women. In addition, I explore the suitability of the population at risk used to calculate the risk of maternal death.

The confounding effects of other variables within the crude relationship between maternal age/number of previous pregnancies and maternal mortality were discussed in detail previously in the Introduction (section 2.4). Therefore, the role of confounders will not be discussed further in this section.

Completeness in the ascertainment of maternal deaths

Maternal deaths are notoriously easy to misclassify due to difficulties in ascertaining pregnancy status at the time of death. This is true even in more developed countries where good civil registration systems exist. In France, for example, the under-reporting was found to be as high as 56-63% [284]. Studies from countries with relatively complete death registrations have found higher rates of maternal death misclassified at the extreme ages and at higher live birth orders [285-286]. However, other studies found higher rates of misclassification for women aged 20 to 24 years [287]. This suggests possible differential misclassification by maternal age or number of previous pregnancies. However, studies do not report consistent findings on the groups most likely to experience misclassification and therefore it is difficult to comment on the effect of this misclassification on the odds of maternal death. In countries with low coverage and completeness of death registration data, it is often hard to assess misclassification of maternal deaths due to a lack of comparable data sources or studies.

In cohort studies, loss to follow up or non participation was rarely discussed. Mortality and exposure status of excluded women were often unknown. Thus it is difficult to comment on whether there may be differences in the age/number of previous pregnancies of the women lost to follow up compared to women included in the study, and the subsequent bias that may result.

Induced abortion may be higher in older women and women with higher number of previous pregnancies [159]. In countries where abortion is illegal these deaths are more likely to be misclassified. For the five studies with abortion information, most abortion related deaths occurred among adolescents. This suggests some abortion related deaths among older women may have been missed in the studies, leading to an underestimation of the odds of maternal death for older women. The patterns by different number of previous pregnancies were less clear.

The definitions of maternal death differed between studies. Some studies included early maternal deaths, accidental/incidental deaths, whilst others did not. Some studies only followed up women until delivery and others included deaths up to 42 days, 60 days, 90 days or 365 days postpartum. However, within each study, there was no differential information bias for different maternal age or number of previous pregnancy groups and thus this should have limited impact on the relative risk across various exposure groups.

Completeness in the ascertainment of maternal age and number of previous pregnancies

The interpretation of the results for number of previous pregnancies was complicated by the lack of consistent and explicit exposure definitions, coupled with the ambiguity of including the index pregnancy in the exposure definition. When restricted to studies with an explicit definition of parity, the overall conclusions were unchanged. However, 80% of these studies were from the UK and most included the index pregnancy in the study definition.

Selection bias due to missing exposure status in maternal deaths should be minimised since studies with more than 20% exposure information missing were excluded. However the proportion of missing information was not always reported in the studies. Even for studies that reported on missing exposure information, it is often hard to speculate the maternal age or previous pregnancy distribution of the missing values. For example, in the United States, pregnancy related deaths by live birth order were reported for women who had live births only. Between 1991 and 1997, there were 3,201 pregnancy related deaths [118]. Reporting on pregnancy related deaths associated with a live birth delivery and known live birth order, only 49.5% of the original 3,201 pregnancy related deaths contributed to the analysis. Some of the deaths were excluded legitimately since they were to women who did not have live births. However, an unknown number of women who die after delivering a live birth were excluded

either because their pregnancy outcome status was unknown and/or the live birth order of the infant was unknown. It is difficult to speculate how this affects the risk of maternal death estimates.

The possibility of selection bias due to missing exposure information in the population at risk is even harder to assess since the number of live births or stillbirths with unreported mothers' age and/or number of previous pregnancies was rarely discussed in studies. If the maternal age/parity status of women who survived their pregnancies was missing at random, then this would have limited impact on the odds ratios of maternal death.

For household surveys, the exposure information for women who were alive may be more accurate than information for deceased women since information was self reported for women alive at the time of the interview. Men have been found to underestimate the past reproductive history of their partners [288]. This may result in the misclassification of deceased women at higher parities to a lower parity by their husbands/partners in studies based on household death surveys. This would lead to an underestimation of the risk of maternal death for women of higher number of previous pregnancies. However, concurrently, in less developed countries, older women were also found to under-report the number of past pregnancies especially if a child has died or left the family home [289]. This does not seem to be the case in the West [290-291]. This would result in the underestimation of the population at risk for women with a higher number of previous pregnancies, which would result in an overestimation of the risk of maternal death these women.

Past studies have found digit preference at 0 and 5 occurs for self and kinship reported age, and age heaping tends to increase with increasing age in surveys [292-293]. There was also evidence of age transfers at boundary age groups, for example, from 15-19 years to 10-14 years and from 45-49 years to 50 years or older. These types of age misclassification should only affect studies in less developed countries based on surveys, and given the similarity of the patterns seen for the association between maternal age and maternal death across all fertility groups, they are unlikely to affect the conclusions of the review.

Ascertainment of the population at risk

To calculate the risk of maternal death, the population at risk should be all pregnant women during the study period in the study population. To overcome the impossible task of identifying all pregnancies, studies often used the number of live births or live births and stillbirths as proxies. However, the use of live births/stillbirths as proxies to pregnancies may potentially underestimate the population at risk differently for different maternal age and parity groups because of differential risk of foetal losses.

Women with no previous pregnancies and older women have been found to have higher risk of having stillbirths [294-296]. The risk of miscarriages and ectopic pregnancies increases with maternal age, especially for those over the age of 35 years [297-300]. Other studies increased risk of miscarriage for adolescents aged younger than 15 compared to 18-19 years [301]. Therefore the use of live births (and stillbirth) may underestimate the population at risk for maternal death for women at extreme ages, and women having their first pregnancy. This could lead to an overestimate of the crude risk of maternal death for pregnancies to women in these groups.

Comprehensiveness of the review

The exclusion of non-English and non-Chinese studies resulted in a very limited number of studies from Latin American, where most publications are in Spanish or Portuguese. Middle income countries with a lower medium TFR were not readily included in the review. Therefore it is possible that some patterns relating to these countries were missed.

The search strategy searched for key terms in the abstracts and titles of the citations, without searching the full texts. Therefore articles with maternal age, number of previous pregnancies or maternal death mentioned in the full text only may have been missed.

Quality of the meta-analysis

The meta-analyses combined some odds ratios with slightly different exposure groupings that could lead to biased results. However, this bias should be minimal as restricting the analyses to women of the same age or number of previous pregnancies group had limited impact on the conclusions of the findings

Only subgroup analyses by TFR were carried out because maternal mortality levels and level of economic development were assumed to be correlated with fertility levels. For low and high fertility settings, there was high correspondence between fertility levels and the maternal mortality ratio levels. Of all cohorts which were classified in the low fertility setting, 97% also had a low maternal mortality ratio. The corresponding proportion was 83% for cohorts in the high fertility setting.

Only 27% of cohorts from the medium fertility setting were also from medium maternal mortality ratio level areas. The medium fertility group includes studies from more, less and least developed countries which generally have different maternal mortality ratio levels. The studies conducted in more developed countries were typically from the 1950s to 1970s during periods of medium fertility, with low maternal mortality levels. There were also more contemporary studies conducted in least developed countries after fertility has declined considerably, but the maternal mortality levels were still high compared to the global average. The mix of these three types of studies from different periods may partly explain the high degree of heterogeneity between studies. Thus, care should be taken not to interpret the magnitude of the summary odds ratio as the measurement of effect for any population with a medium fertility.

3.3.3 Interpretation of the findings

Consistency with other reviews

The findings of my study are consistent with those found by Nortman [6]. Nortman used civil registration statistics reported to the WHO in 41 countries for 1964-1966 to examine the relationship between maternal age and maternal mortality. Using age as a continuous variable, she found the minimum risk of maternal death at around 22 or 23 years old, and the risk increased with increasing age with the highest risk to women aged 40- 44 years. In addition, by looking at countries at different maternal mortality levels, Nortman found that the age differentials for maternal death widened as the level of maternal mortality decreased. For the age group, ten years plus or minus the age at minimal risk (22/23 ± 10 years), the excess risk was 85% for the high mortality countries (>100 maternal deaths per 100,000 live births) and this increased to 216% for low mortality countries (<35 maternal deaths per 100,000 live births).

In this review similar patterns of association were found for the relationship between maternal age and maternal mortality to the Norman study. In addition, as fertility levels decreased, the magnitude of the odds ratios increased. Since low fertility levels are associated with lower maternal mortality levels, this finding is consistent with the Norman study.

The general direction of the associations between maternal age and maternal mortality were similar for Nortman's and my review. However, Nortman reported higher relative risks compared to this review, in particular for countries with higher maternal mortality. For example, for the higher mortality countries, Nortman reported a relative risk of around seven for women aged 40- 44 years compared to women aged 20- 24 years. I found an odds ratio of 3.3 for the corresponding comparison for high fertility settings. The differences observed may be due to several different factors. There may be higher rates of under-reporting, of maternal death and live births, in the civil registration statistics reported to the WHO for 1964-1966 than the population studies included in this review. The temporal changes between the studies included in the two reviews may contribute to some of the differences. In addition, the use of fertility levels and maternal mortality levels do not correspond exactly as demonstrated previously.

A recent review published by the WHO in 2004 [5] included seven studies when investigating the effect of maternal age on maternal mortality. In most studies, the results were similar to those found in this review: adolescence and older age at pregnancy were associated with increased risk of maternal death when studying the crude relationship. No meta-analysis was carried in the WHO review. The WHO review also included two studies investigating the crude relationship between parity and maternal mortality. Both studies were included in this review, and they found increased risk of maternal death for parity zero women and women of higher parities.

Heterogeneity and generalisability

There was indication of significant heterogeneity between the studies for most maternal age and number of previous pregnancy groups. This is not surprising, since I would expect the crude effects of different maternal ages and number of pregnancies on maternal mortality to be different in different settings due to differences in the prevalence of chronic diseases, use of health care, quality of health care services and the standard of living in different countries.

China is unique in the method of reaching lower fertility due to the introduction of the one child policy in 1979. Inclusion of a large number of studies conducted in China could partially explain the heterogeneity between studies, and limit the generalisability of the low fertility setting results. However, only one matched case control study based in China was found in the review, and this was not included in the meta-analysis which included only studies reporting crude analysis. So the inclusion of Chinese language studies has limited impact on the heterogeneity/generalisability of the results in this review.

Heterogeneity between the studies was associated with the TFR levels in some groups. Generally the magnitude of the odds ratios was lower in high fertility countries. Lower national fertility levels are typically associated with higher wealth and standards of a living of its citizens, suggesting that better health systems and infrastructure exist in lower fertility countries. Thus, the general lower odds ratios observed in high fertility settings could suggest that the overriding factor was poverty which masks any age or parity effects, decreasing the magnitudes of the odds ratios.

There was still substantial heterogeneity between studies within the same TFR group for some maternal age/higher numbers of previous pregnancy groups. This may be in part due to

misclassification of the total fertility rates of the study population since it was not always possible to find fertility information relating to the specific study region at the time of the study period. Given the wide variations of fertility between regions of the same country, the use of national TFR levels may lead to misclassifications.

The quality of studies did not consistently explain the heterogeneity between studies investigating the effect of number of previous pregnancies on maternal mortality. However, since confounders were not adjusted for in these studies, I would not expect the quality of studies alone to explain all the variation between studies. Due to the high heterogeneity between studies, it is worth noting again that the random effects model assumes a different underlying effect for each study and the resulting summary odds ratio should be interpreted as an average of these underlying effects.

For age groups <20, 25-29 and 45 or over, the inconsistency (I^2) between high quality studies was low/medium, while the inconsistency between all studies of the relevant age groups was high. For the other age groups, the inconsistency between studies was high between high quality studies and between all studies.

A host of other variables may confound the relationship between maternal age, number of previous pregnancies and maternal mortality which may explain the heterogeneity between studies reporting only crude results. For example, care seeking behaviour differs between younger and older women, but there may also be variations in behaviour of young women from different study regions leading to heterogeneity between studies. Changes in medical practices, improvements in medical technology and better understanding/adaptations to new phenomena such as delayed childbearing over time, may also affect the magnitude of crude odds ratios, even between populations with the same overall fertility level. Please see chapter 1, section 2.4 for a detailed discussion of possible confounders.

I was unable to tease out the separate effects of maternal age and the number of previous pregnancies since most studies do not adjust for confounders. Thus the crude summary odds ratio presented here cannot be generalised as the magnitude of the independent effects of maternal age or number of previous pregnancies.

Biological plausibility

Many hypothesised biological pathways for the associations between maternal mortality, and maternal age and parity exist. Many of these pathways were explored in the Introduction, section2.4. A summary is given below.

Younger maternal age

Younger maternal age has been hypothesised to be a marker for a host of biological and physical immaturity that may individually or collectively compromise maternal adaption to the physiological demands of pregnancy [51]. For example, pregnancy may lead to nutritional competition between the growing mother and foetus [52]. Young girls may also have immature immunity leading to higher rates of infections [51, 61].

Older maternal age

Older mothers are more likely to have pre-existing conditions, including diabetes and chronic hypertension [120-121]. Gestational diabetes increases with age, and may be the result of decreased pancreatic cell B function and increased insulin resistance as women age [120, 302-303]. Obesity and diabetes prevalence increases with age, and may increase insulin resistance further in pregnant women. Diabetes was found to be associated with pre-eclampsia, increased insulin resistance and it may also cause other maternal metabolic changes that could lead to increased nutrients to the foetus resulting in macrosomia [302].

Age related deterioration of myometrial functions could lead to higher rates of uterine atony, a major risk factor for postpartum haemorrhage in older women [302]. Uterine fibroids increase with age, and have been shown to increase the risk of placental abruption, dysfunctional labour, foetal malpresentation, and caesarean delivery [64-65].

Nulliparity

Pregnancy and childbirth requires profound physiological adaptation in almost every system in the body [18], and the lack of previous experience may explain the increased risks for nulliparas compared to women with one previous pregnancy. Possible mechanisms put forward for the increased pre-eclampsia prevalence in women with no previous pregnancies

include maternal immunity naivety to paternal antigens [73] or less favourable angiogenic factor profile and/or greater reactivity to insulin resistance in early pregnancy [71-72].

In malaria endemic regions, a combination of immunological and hormonal changes during pregnancy may be responsible for increased susceptibility to malaria in nulliparas [146]. Having malaria could lead to anaemia, which may result in higher case fatality of haemorrhage [145].

Higher parities

Higher parity has been linked with increased risk of complications such as malpresentation, placenta praevia, postpartum haemorrhage and uterine rupture. However, most studies do not adjust for the confounding effects of maternal age. Of those that did adjust for maternal age, increased incidence of diabetes mellitus disappeared after adjustment when comparing multiparas to nulliparas [85, 304]. Gestational diabetes was also found to be related to maternal age rather than parity [84]. One study found increased risk of placenta praevia and placental abruption among higher parity women aged 20–25 years only, and the authors suggested short birth spacing or other confounders may be responsible [83]. A major risk factor for uterine rupture is previously scarred uterus, often from previous caesarean sections, which is obviously linked to parity [305-306].

4 COHORT STUDY

The objective of this chapter was to report on the retrospective cohort study conducted to investigate the relationship between maternal age, gravidity and pregnancy related death. This study used pregnancy information occurring between 1 January 1983 and 31 December 2005 recorded by the Health and Demographic Surveillance System in Matlab, Bangladesh.

4.1 Introduction

A number of factors were found to be associated with maternal age, number of previous pregnancies and maternal mortality, which may potentially confound the relationships between these variables. The systematic review in Chapter 3 identified a number of gaps with studies reporting the association between maternal age/previous pregnancies and maternal mortality. First, few studies adjusted for confounders, and the independent effects of age and previous pregnancies could not be ascertained. Second, some investigations did not focus on maternal age and previous pregnancies as the main exposures of interest and some statistical results such confidence intervals were omitted from the final report. Third, in some studies the definition of the number of previous pregnancies was unclear, or no definition was provided.

The objective of this chapter was to address the shortcomings in previous research.

In the Matlab dataset, a number of possible confounders are available, including maternal age, gravidity, year of pregnancy outcome, residing service area of the woman, years of formal education the woman's husband received, household asset quintile, years of formal education the woman received, religion of the woman and the birth to conception interval. The dataset also allows clear definition of the number of previous pregnancies (see section 4.2.3 below) and to carry out appropriate statistical tests.

I reported on the crude association between maternal age/gravidity and pregnancy related death, including odds ratios and their corresponding 95% confidence intervals in section 4.3.3. In addition, I reported on the multivariable analysis (section 4.3.4) adjusting for individual confounders, one at a time, and also collectively. Again odds ratios and confidence intervals for all variables were reported.

4.2 Methods

4.2.1 Health and Demographic Surveillance System in Matlab, Bangladesh

Description of study area

The Health and Demographic Surveillance System (HDSS) in Matlab, Bangladesh is maintained by the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B).

The Matlab Upazila is located 55km southeast of the capital, Dhaka (Figure 4.1). There were 224,750 people living in 142 villages in Matlab in 2005. Almost 90% of the population are Muslims with most of the remainder Hindus. The main sources of income are rice growing or fishing.

This area is a typical rural, riverine delta area of Bangladesh, and is flooded for part of the year. Travelling within the area is usually by foot, rickshaw or country boats, especially during the monsoon season.

In 1966, the Demographic Surveillance System started registering births, deaths and migration in 132 villages covering a population of 112,000. Enumerations of other vital registration events, such as household dissolutions were included in later years. The surveillance covers all households in the surveillance site, and data were collected from individuals who have resided in the area permanently or continuously for at least six months.

Major restructuring of the field operations took place in October 1977. This resulted in the inclusion of 149 villages, and the introduction of the Maternal and Child Health and Family Planning Programme (MCH-FP) in 70 villages covering a population of nearly 89,000 people [307]. This area became known as the treatment area, and more recently the ICDDR,B service area. The remaining 79 villages served as a comparison area with standard government services (84,500 people). This latter area is known as the government service area.

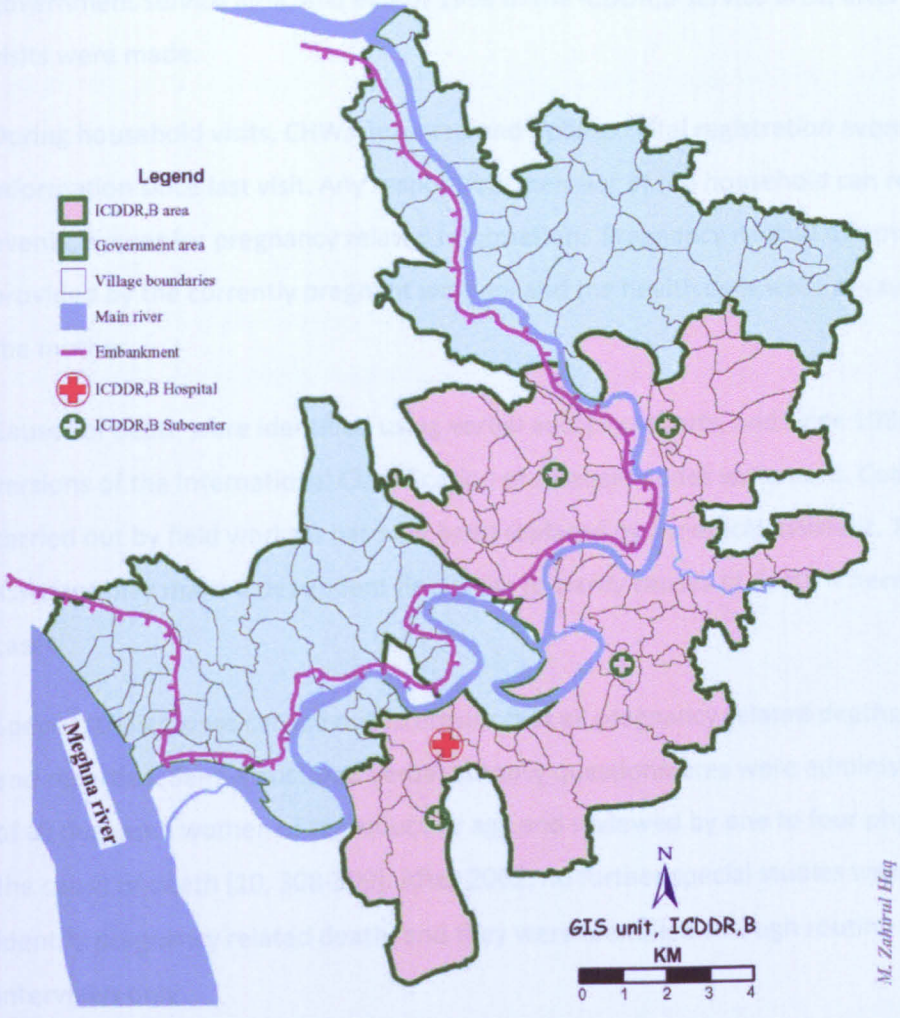

Figure 4.1: Map of the study area in Matlab, Bangladesh.
Source: Matlab Demographic Workbook, version July-2009-v2.

Field procedures

Originally dais (traditional birth attendants), mostly elderly women who were illiterate were responsible for detecting vital registration events at weekly household visits. Every six weeks, health assistants accompanied dais to record demographic events on registration sheets. Health assistants were supervised by senior health assistants.

With the introduction of the MCH-FP programme dais were replaced by female community health workers (CHWs) with at least secondary education. CHWs also started collecting data on child and reproductive health. Fortnightly household visits were made until end of 1998 in the

government service area, and end of 1999 in the ICDDR,B service area, after which monthly visits were made.

During household visits, CHWs enquired and updated vital registration events and health information since last visit. Any responsible member of the household can report demographic events, except for pregnancy related information. Pregnancy related information can only be provided by the currently pregnant woman, and the health data were always collected from the mother.

Causes of death were identified using verbal autopsy reports, and since 1986 the modified versions of the International Classification of Diseases codes were used. Coding which was carried out by field workers has now been replaced by a medical assistant. The medical assistant may make independent field visits to clarify causes of death if necessary (10-15% of cases).

Special studies were carried out to ensure that all pregnancy related deaths were identified and recorded. Semi-structured verbal autopsy questionnaires were administered to relatives of all deceased women of reproductive age and reviewed by one to four physicians to identify the cause of death [10, 308-309]. After 2002, no further special studies were commissioned to identify pregnancy related death, and they were identified through routine verbal autopsy interviews only.

Socio-economic information was collected in censuses in 1974, 1982, 1996 and 2005. Two types of structured questionnaire were used: individual-level (demographic data, education, occupation, woman's clothes) and household-level (sources of household income, possessions of household assets, construction materials used for roof, wall and floor of the main dwelling, possession of homestead and agricultural land, type of water use and latrine use). In addition, information on the membership of micro-credit societies and prevailing food shortage in the households throughout the year were also included in the questionnaire.

Unique identifiers of all residents in the surveillance area, including women and children, can link the information from various sources to obtain all the socio-demographic and pregnancy related data necessary for this analysis.

Family planning and fertility in Matlab

In October 1975 an intensive door to door distribution programme of conceptions began in 150 villages, while another 84 villages with standard government services served as a comparison group.

Within three months, the contraception use rate increased from a baseline of 1.1 percent to 17.9 percent amongst married women aged 15-44 years. However, longer assessment revealed that contraception use gradually declined to 11 percent over the next two years. This was partly due to the poor training and supervision of the lady village workers who delivered contraception to clients, and also due to the lack of method choice available to women [307, 310].

The introduction of the MCH-FP programme aimed to improve the family planning services by offering a wider range of contraceptive methods, and providing better trained and supervision of the health workers. The contraceptive prevalence in the two service areas has diverged since the implementation of the MCH-FP programme. The contraceptive prevalence rate was 30% in the ICDDR,B service area in 1979, and the rate was 16% in the government service area. By 1996 there was a 20% difference between the two areas – 68% for the ICDDR,B service area and 48% for the government service area [311] .

The total fertility rate in Matlab has decreased from an average of just under six live births per woman in the early 80s to just under three live births per woman in 2005 (Figure 4.2). It is clear from the total fertility rate and the age specific fertility rates that the greatest drop in fertility occurred between the early 80s and mid 90s (Figure 4.3). During this period, there were steady decreases in the age specific fertility rates for women of all ages, although they are most noticeable for women aged 20-35. Figure 4.2 shows that the total fertility rate was lower in the ICDDR,B service area compared to the government service area. However, this fertility gap has been narrowing over time, and there was only a difference of 0.1 children per woman in 2005.

Past studies observed that fertility decline in Bangladesh has stalled since the mid-1990s [312]. Since then the total fertility rate in Matlab has remained around three, despite an increase in the proportion of women using contraceptives. The contraceptive prevalence were 50% in the government service area and 70% in the ICDDR,B service area in 2000 [311].

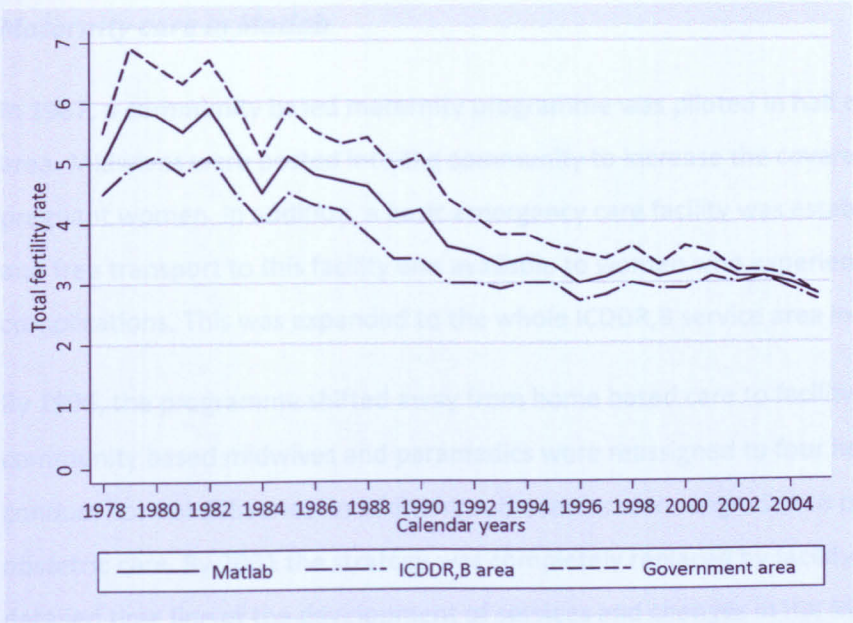

Figure 4.2: Trends in the total fertility rate in Matlab, by service areas (1978-2005).
Source: HDSS annual reports and Matlab Demographic Workbook, version July-2009-v2.

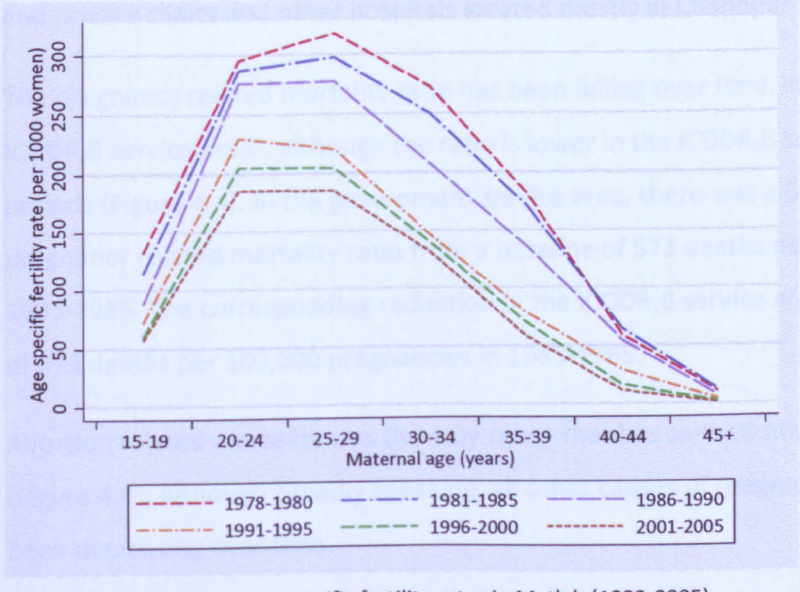

Figure 4.3: Trends in the age specific fertility rates in Matlab (1982-2005).
Source: HDSS annual reports and Matlab Demographic Workbook, version July-2009-v2.

Maternity care in Matlab

In 1987, a community based maternity programme was piloted in half of the ICDDR,B service area. Midwives were posted into the community to increase the coverage of home care to pregnant women. In addition, a basic emergency care facility was established in Matlab town, and free transport to this facility was available to women who experienced obstetric complications. This was expanded to the whole ICDDR,B service area in 1990.

By 1996, the programme shifted away from home based care to facility based care. The community based midwives and paramedics were reassigned to four health sub-centres to conduct normal deliveries. In addition, sub-centres were upgraded to provide basic emergency obstetric care. By 2001 the strategy was completely replaced by facility based care. For a more detailed time line of the development of services and changes in the Matlab HDSS, see Appendix B.1

In addition to the services provided by ICDDR,B, maternity services were available from the government thana health complex in Matlab, the government district hospital at Chandpur, and private clinics and other hospitals located mostly in Chandpur town.

The pregnancy related mortality ratio has been falling over time, in both the government and ICDDR,B service areas, although the ratio is lower in the ICDDR,B service area for most time periods (Figure 4.4). In the government service area, there was a 61% reduction in the pregnancy related mortality ratio from a baseline of 573 deaths per 100,000 pregnancies in 1983-1985. The corresponding reduction in the ICDDR,B service area was 68% from a baseline of 473 deaths per 100,000 pregnancies in 1983-1985.

Abortion related mortality was the only cause that has consistently decreased in both areas (Figure 4.4). Although broadly speaking, all other causes of pregnancy related deaths have been decreasing over time.

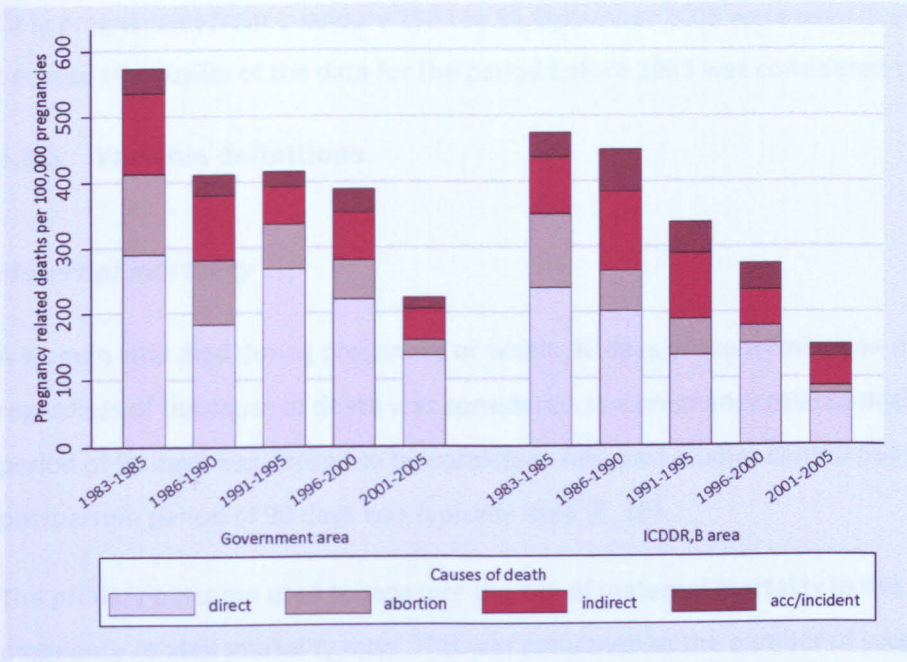

Figure 4.4: Trends in the pregnancy related mortality ratio by cause and areas in Matlab (1983-2005)

4.2.2 Description of the data

I used a pregnancy dataset provided by ICDDR,B, and this dataset linked information from several sources. Information on pregnancy outcome (live birth, stillbirth, miscarriage or induced abortion), date of outcome, pregnancy duration and number of infants born was collected at the time of pregnancy outcome and included in the birth records. The information from the birth records was linked with 1) the women's dataset to identify the mother's date of birth, and her past reproductive history; 2) the mortality dataset to identify women who died due to pregnancy related or other causes; 3) the censuses which included information such as the household asset quintiles, maternal education and husband's education. The most recent socio-economic status information available was linked to each pregnancy.

I checked the data for duplicates and possible entry errors by checking inconsistencies in the combined dataset. The checks included consistencies of the maternal dates of birth for all her pregnancies, plausibility of the maternal ages, and plausibility of the time between two consecutive pregnancy outcomes to the same woman. In addition, I checked for impossible events such as births after the supposed death of the woman. For further details of the datasets and data checking/cleaning see Appendix B.2.

Only pregnancies from 1 January 1983 to 31 December 2005 were used in this analysis because the quality of the data for the period before 1983 was considered to be poor.

4.2.3 Variable definitions

Maternal mortality

A woman who died during pregnancy or within 90 days of the termination of pregnancy regardless of the cause of death was considered as a pregnancy related death. A postpartum period of 90 days was chosen to be consistent with past studies carried out in Matlab, where a postpartum period of 90 days was typically used [8, 10].

The primary outcome used to measure the risk of maternal mortality in this study was the pregnancy related mortality ratio. This was calculated as the number of pregnancy related deaths divided by the number of pregnancies over the study period of 1983-2005. The use of number of pregnancies as the denominator provided a more accurate representation of the true population at risk. Multiple gestations were treated as single pregnancies.

Pregnancy related death was used rather than maternal death because this minimised misclassification of deaths. In addition, past studies have observed pregnant women were at higher risks of intended and possibly unintended injury, particularly to young women [313-315]. Therefore excluding injuries was not deemed appropriate. Injuries accounted for 9.6% of pregnancy related deaths.

Maternal age

The maternal age of a woman was defined to be her age at last birthday at the time of the pregnancy outcome.

All pregnancies to women of any age were included in the analysis. Women were grouped into five year age categories between the ages of 10 to 44. Women 45 or older were grouped together.

Number of previous pregnancies

Gravidity was used as the study measurement of the number or previous pregnancies. Gravidity was defined as the number of previous pregnancies a woman has had, excluding the index pregnancy and its postpartum period (regardless of its duration or infant/ maternal outcome). With this definition, if a woman dies due to her index pregnancy, her gravidity status stays the same whether she dies before, during or after the index delivery. It avoids confusion when a woman dies undelivered, an issue found in the systematic review.

Gravidity was grouped into single, consecutive pregnancies, starting from no previous pregnancies. Women with nine or more previous pregnancies were grouped together. Multiple gestations counted as a single gravid event, irrespective of how many infants were born.

In the Matlab dataset, most multiple gestations had been counted as multiple gravid events. For example, a woman who had twins in her first pregnancy would often be recorded as gravidity two after the postpartum period, suggesting she has had two previous pregnancies. I corrected multiple gestation pregnancies as single gravid events to reflect the gravidity definition. For the example above, this woman would be corrected to gravidity one.

Gravidity rather than parity was investigated as one of the main exposures of interest because women's parity status (i.e. number of previous live or stillbirths) was not readily available in the data. In the Matlab data, the previous number of stillbirths and abortions (spontaneous and induced) had been grouped together, and so it was impossible to obtain the number of stillbirths a woman has had previously.

Consistency in gravidity order was checked for each woman to ensure the order was ascending. Certain rules were applied to correct the gravidity order if descending gravidity order appeared. For example, if gravidity levels of all pregnancies to the same woman were in ascending order except for one, the odd one out was assumed to be an entry error, and corrected accordingly.

Confounders

Variables that may confound the two relationships of interest were also available in the data set. Maternal age was considered an a priori confounder for the relationship between gravidity

and pregnancy related death. Gravidity was considered an a priori confounder for the relationship between maternal age and pregnancy related death.

In the Matlab dataset, possible confounders in the relationship between maternal age/gravidity and pregnancy related mortality included year of pregnancy outcome, residing service area of the woman at the time of pregnancy outcome, number of years of formal education the woman's husband received, household asset quintile, number of years of formal education the woman received, religion of the woman and the birth to conception interval.

The year of the pregnancy outcome, from 1983 to 2005, was grouped into five year categories except for 1983-1985.

An existing household asset quintile variable in the Matlab dataset was used to represent the household assets in the analysis. The methods used to compute the asset quintile have been described previously [9]. The authors used all families with a pregnancy outcome between 1976 and 2005. Since asset ownership may change for each pregnancy, they used pregnancy as the unit of analysis, and used the asset information from the most recently available census for each pregnancy. Common asset variables to the 1974, 1982, 1996 and 2005 socio-economic census were used in their analysis. The assets included were source of drinking water; type of latrine; principal material of floor, wall, and roof; electricity supply; ownership of quilt, hurricane, watch, radio, television, bicycle, boat, cow, telephone or remittance. The asset quintiles were derived from the first principal component using principal components analysis in SPSS version 10.

Years of education were grouped into categories to reflect the schooling system in Bangladesh; no formal education (including madrasah education), 1-5 years of formal education (primary education), 6-8 years of formal education (junior secondary education), 9-12 years of formal education (secondary education including the secondary school certificate examination) and 13 or more years of formal education (higher secondary education or above). If any pregnancies had missing values for maternal or partner education, education information from any previous or subsequent pregnancies to the same woman/husband was used, assuming education levels stayed consistent in these instances. If this was not possible, dummy variables were used to indicate missing education information to ensure all pregnancies could be included in the analysis.

Maternal religion was categorised into Islam, Hinduism and other religions.

Birth to conception interval was considered the most relevant measurement of birth interval for the investigation of pregnancy related death because it does not include the gestation period of the index pregnancy which may have an independent effect on pregnancy related mortality. Shorter gestations may include more abortions, and a higher proportion of women who die undelivered. Both of these factors may be associated with an increased risk of pregnancy related death.

I used the inter-outcome intervals, i.e. the interval between two pregnancy outcomes, in addition to the birth to conception intervals when investigating birth interval trends in Matlab. The inter-outcome interval is the interval between two pregnancy outcomes for which there were less missing values. So the inter-outcome interval was also used to keep missing values to a minimum.

The birth to conception/inter-outcome interval was grouped into intervals of less than six months, between 6 to 14 months, 15 to 26 months, 27 to 50 months, 51-62 months, and 75 months or longer. One month was assumed to have 28 days. Women who have never had a pregnancy were grouped separately. A dummy variable was used to indicate missing interval information to ensure all pregnancies could be included in the analysis.

The conception date of the index pregnancy was estimated by subtracting the gestational age of the index pregnancy from the date of outcome. The HDSS records the date of the last menstrual period as soon as women miss a period, so the recorded gestational ages are relatively accurate. The pregnancy duration or gestational age of each pregnancy was recorded in the dataset in months (one month was assumed to be 28 days). Gestational age was unknown in 38.7% of pregnancies. Two different assumptions as suggested by Ronsmans and Campbell were used to estimate the missing gestational age base on the pregnancy outcome [104]. The first model utilised the known information on gestational age, and imputed information for pregnancies with unknown gestational age. The second model imputed information for all pregnancies regardless of whether the gestational age was known or not. Analyses were carried out using each assumption separately. The assumptions for the two models were as follows:

1) Pregnancy duration known

Estimated gestational age = observed pregnancy duration x 28 days

Pregnancy duration unknown

Estimated gestational age = 280 days for live births

= 252 days for stillbirths

= 84 days for abortions

= 280 days for unknown pregnancy outcomes

2) Pregnancy duration whether known or unknown

Estimated gestational age = 280 days for live births

= 252 days for stillbirths

= 84 days for abortions

= 280 days for unknown pregnancy outcomes

Effect modifiers

Women with first pregnancies were at increased risk of maternal death compared to women with one previous pregnancy in the systematic review (chapter 3). The strain of first pregnancies (gravidity 0) could be modified by the effect of older maternal age (≥35 years old). I hypothesised that the effect of first pregnancy would be greater in older maternal age groups.

No consensus exists in the literature on whether the often observed (crude) relationship between nulligravidity/multigravidity and higher risk of pregnancy related death is due to biological or social mechanisms. If biological mechanisms exist, the risk could potentially be mitigated by good antenatal, intra-partum and postnatal care to women. In Matlab, better provision of care existed in the later years and so I tested for a potential interaction between calendar years (<1991, ≥1991) and gravidity (0, 1-5, ≥6).

4.2.4 Statistical analysis

Associations with pregnancy related death

Associations between maternal age, gravidity and pregnancy related death were investigated using the chi^2 test for association. Categories were combined if there were no outcomes in a particular group.

Logistic regression was used to model the effect of maternal age on pregnancy related death and the effect of gravidity on pregnancy related death. Many women had more than one pregnancy during the 24 year study period. However, I did not use a random effects model designed for correlated data because pregnancy related death only occurs once per woman.

The selection of confounders was carried out in two stages. A possible confounder was considered to be a variable associated with maternal age/gravidity, an independent risk factor for maternal age, and not on the casual pathway between the two variables. Possible confounders identified during the crude analysis were adjusted individually to determine whether they were a confounder of the association between the exposure (maternal age/gravidity) and pregnancy related death.

A possible confounder was considered to be a confounders if after its adjustment, there was more than 5% change (compared to the crude estimates) in at least one strata-specific:

i) odds ratio and at least one of its confidence limits, or

ii) lower and upper confidence limits [316]

Stage two involved selection into the final multivariable model using the forward selection strategy. All confounders, in either relationship between maternal age and pregnancy related death or between gravidity and pregnancy related death, were eligible for inclusion in the final multivariable model.

Variables were fitted in groups according to a hierarchical framework as recommended by Victora and colleagues [317]. Pregnancy outcome year and area were grouped as community level variables and were fitted one by one first. Household level variables were fitted next, including husband's formal education years and asset quintiles. Finally women level variables were fitted, including her years of formal education and birth to conception interval. Confounder selection into the final model was carried out in a similar fashion as in step one. So a possible confounder was selected into the multivariable model if there was more than five percent difference between the model estimates with and without adjustment for that variable, in at least one strata-specific:

i) odds ratio and at least one of its confidence limits, or

ii) lower and upper confidence limits [316]

Likelihood ratio tests were used to test for associations between exposures of interest and pregnancy related deaths after adjustment for confounders.

Investigation of interactions was left as the last step to avoid multiple use of a test that is known to lack power [318]. The likelihood ratio test was used to test for the goodness of fit of the model including an interaction term.

Sensitivity analysis

Sensitivity analysis was carried out using alternative definitions of pregnancy related death:

1) Pregnancy related death, including deaths up to 42 days postpartum.
2) Maternal death (pregnancy related deaths excluding intentional or unintentional injuries), up to 90 days postpartum.

4.3 Results

4.3.1 Pregnancy and women characteristics

There were 159,210 pregnancies to 62,401 women between 1 January 1983 and 31 December 2005. The vast majority of the pregnancies ended in at least one live birth (87.3%). Multiple gestations comprised of just under 1% of all pregnancies. Of the 62,401 women in the study, just over 30% emigrated out of Matlab at least once.

The majority of pregnancies ended in a live birth (87%,Table 4.1). The pregnancy outcome was unknown for only 193 (0.12%) pregnancies. However, all unknown outcomes were to women who died due to pregnancy related causes; representing 33.2% of all pregnancy related deaths. This is likely to be due, in part, to the fact that women who die undelivered (before or during labour) will not have a recorded pregnancy outcome.

Table 4.1: Outcomes of pregnancies in Matlab, 1983-2005

Pregnancy outcome	No. of pregnancies	Percentage
Live birth	138,937	87.27
Spontaneous abortion	9,499	5.97
Induced abortion	5,752	3.61
Stillbirth	4,829	3.03
Not recorded	193	0.12
Total pregnancies	159,210	100.00

4.3.2 Childbearing composition

Maternal age distribution

The maternal age at pregnancy outcome ranged from 11 to 61 years, with just under 60% of all pregnancies occurring to women aged 20-29. Pregnancies to the extreme age groups of 10-14 and 45 or older contributed a trivial amount to the overall pregnancy numbers (Table 4.2 and Figure 4.5).

The overall change in the age distribution of the pregnancies over the 23 year period has shifted slightly away from childbearing in the traditional "high risk" groups ($p<0.001$). Broadly speaking, the largest reduction to the proportion of pregnancies to women younger than 20 or 40 and older occurred in the mid eighties to early nineties, and there has been little change since. There has been a small shift towards a higher proportion of pregnancies to women aged 30-39 years, and a concurrent decrease in the proportion of pregnancies to women aged 20-29 years.

The mean age at first pregnancy outcome has increased over time (Table 4.3).

The childbearing trends in the government and ICDDR,B service areas follow the same general patterns as Matlab as a whole. There were consistently lower proportions of women falling pregnant at 40 years or older in the ICDDR,B service area compared to the government area (data not shown).

Table 4.2: Trends in maternal age distribution of pregnancies in Matlab, Bangladesh (1983-2005)

Maternal age (years)	1983-1985 n=23,672 (%)	1986-1990 n=38,805(%)	1991-1995 n=32,400 (%)	1996-2000 n=31,290 (%)	2001-2005 n=33,043 (%)
10-14	42 (0.2)	23 (0.1)	28 (0.1)	30 (0.1)	36 (0.1)
15-19	4,134 (17.5)	4,939 (12.7)	3,767 (11.6)	3,554 (11.4)	4,326 (13.1)
20-24	8,134 (34.4)	13,632 (35.1)	10,653 (32.9)	9,592 (30.7)	9,950 (30.1)
25-29	5,300 (22.4)	10,499 (27.1)	9,613 (29.7)	8,647 (27.6)	8,499 (25.7)
30-34	3,137 (13.3)	5,510 (14.2)	5,434 (16.8)	6,194 (19.8)	6,064 (18.4)
35-39	2,059 (8.7)	2,773 (7.1)	2,112 (6.5)	2,635 (8.4)	3,246 (9.8)
40-44	757 (3.2)	1,213 (3.1)	658 (2.0)	532 (1.7)	811 (2.5)
≥45	109 (0.5)	216 (0.6)	135 (0.4)	106 (0.3)	111 (0.3)

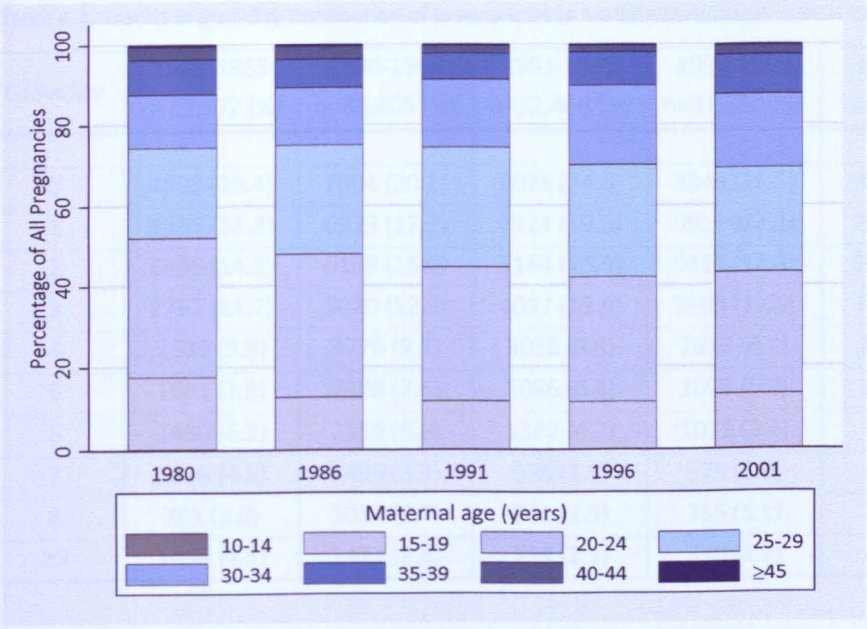

Figure 4.5: Trends in maternal age distribution of pregnancies in Matlab, Bangladesh (1982-2005).

Table 4.3: The mean age of outcome of the first three pregnancies.

Calendar period	Mean age in years (standard deviation)		
	First pregnancy	Second pregnancy	Third pregnancy
1983-1985	19.3 (±2.6)	21.2 (±2.7)	23.5 (±3.1)
1986-1990	20.0 (±2.7)	22.2 (±2.9)	24.3 (±3.1)
1991-1995	20.6 (±3.0)	23.3 (±3.1)	25.7 (±3.4)
1996-2000	20.9 (±3.3)	24.1 (±3.5)	27.2 (±3.7)
2001-2005	21.0 (±3.5)	24.4 (±3.9)	27.9 (±4.2)

Gravidity distribution

Gravidity at pregnancy ranged from zero to twenty-one. There were clear and consistent reductions in the proportion of high gravidity pregnancies over time, with a concurrent increase in the proportion of first pregnancies (Table 4.4 and Figure 4.6). Gravidity and calendar year of pregnancy was statistically associated ($p<0.001$).

This pattern of decrease in higher gravidity order pregnancies was seen in both the government and ICDDR,B service areas of Matlab (data not shown).

Table 4.4: Trends in gravidity distribution of pregnancies in Matlab, Bangladesh (1983-2005)

Gravidity	1983-1985 n=23,672 (%)	1986-1990 n=38,805 (%)	1991-1995 n=32,400 (%)	1996-2000 n=31,290 (%)	2001-2005 n=33,043 (%)
0	4603 (19.4)	7804 (20.1)	8025 (24.8)	8345 (26.7)	9612 (29.1)
1	4335 (18.3)	6929 (17.9)	6324 (19.5)	6911 (22.1)	7931 (24.0)
2	3496 (14.8)	6198 (16.0)	5164 (15.9)	5421 (17.3)	5923 (17.9)
3	2762 (11.7)	5020 (12.9)	4097 (12.6)	3903 (12.5)	4029 (12.2)
4	2332 (9.9)	3775 (9.7)	3036 (9.4)	2617 (8.4)	2486 (7.5)
5	1861 (7.9)	2908 (7.5)	2086 (6.4)	1697 (5.4)	1390 (4.2)
6	1460 (6.2)	2169 (5.6)	1362 (4.2)	1072 (3.4)	792 (2.4)
7	1066 (4.5)	1499 (3.9)	936 (2.9)	579 (1.9)	453 (1.4)
8	701 (3.0)	1032 (2.7)	611 (1.9)	355 (1.1)	213 (0.6)
≥9	1056 (4.5)	1471 (3.8)	759 (2.3)	390 (1.2)	214 (0.6)

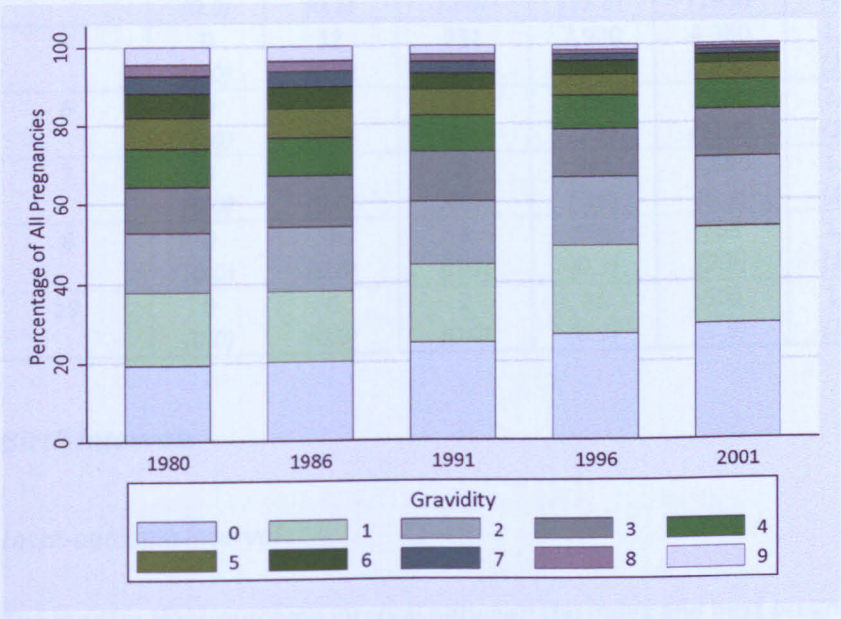

Figure 4.6: Trends in gravidity distribution of pregnancies in Matlab, Bangladesh (1983-2005)

Age- gravidity distribution

Maternal age and gravidity were associated as expected ($p<0.001$). Adolescent childbearing (<20 years old) was dominated by first pregnancies – 79% of all pregnancies to adolescents younger than 20 were first pregnancies. The proportion of higher gravidity pregnancies increased as women aged (Table 4.5). Around 45% of pregnancies to women aged 45 or older were gravidity nine pregnancies.

Between 1983 and 2005, pregnancies to gravidity one women, aged 20-24 accounted for the highest proportion of all pregnancies - 11.9%. Gravidity zero pregnancies to women aged 20-24 also accounted for a high proportion of all pregnancies (11.5%).

Table 4.5: Number of pregnancies by maternal age and gravidity for pregnancies in Matlab (1983-2005)

Gravidity group	Maternal age groups (years)							
	10-14 (%)	15-19 (%)	20-24 (%)	25-29 (%)	30-34 (%)	35-39 (%)	40-44 (%)	≥45 (%)
0	138 (86.8)	16,261 (78.5)	18,289 (35.2)	3,074 (7.2)	507 (1.9)	94 (0.7)	16 (0.4)	10 (1.5)
1	17 (10.7)	3,655 (17.6)	18,975 (36.5)	8,094 (19.0)	1,429 (5.4)	223 (1.7)	32 (0.8)	5 (0.7)
2	3 (1.9)	643 (3.1)	9,789 (18.8)	11,453 (26.9)	3,585 (13.6)	643 (5.0)	72 (1.8)	14 (2.1)
3	1 (0.6)	119 (0.6)	3,535 (6.8)	9,602 (22.6)	5,141 (19.5)	1,247 (9.7)	154 (3.9)	12 (1.8)
4	0 (0.0)	27 (0.1)	1,049 (2.0)	5,893 (13.8)	5,238 (19.9)	1,762 (13.7)	246 (6.2)	31 (4.6)
5	0 (0.0)	12 (0.1)	231 (0.4)	2,900 (6.8)	4,380 (16.6)	1,990 (15.5)	393 (9.9)	36 (5.3)
6	0 (0.0)	2 (0.0)	68 (0.1)	1,058 (2.5)	3,095 (11.8)	2,089 (16.3)	473 (11.9)	70 (10.3)
7	0 (0.0)	0 (0.0)	20 (0.0)	341 (0.8)	1,690 (6.4)	1,786 (13.9)	604 (15.2)	92 (13.6)
8	0 (0.0)	1 (0.0)	3 (0.0)	109 (0.3)	768 (2.9)	1,335 (10.4)	592 (14.9)	104 (15.4)
≥9	0 (0.0)	0 (0.0)	2 (0.0)	34 (0.1)	506 (1.9)	1,656 (12.9)	1,389 (35.0)	303 (44.8)

Birth intervals

Inter-outcome interval

The median inter-outcome interval between the index and next pregnancy outcome was 36.5 months, with an inter-quartile range of 25.2 months and 52.7 months, for pregnancy outcomes in Matlab, 1983-2005.

The median inter-outcome interval lengthened from 33 months in 1983-1995 to 42 months for pregnancies occurring in 1991-1995, and has remained stable until 2000. After 2000, selection bias of pregnancies with shorter inter-outcome intervals has artificially decreased the median inter-outcome intervals for pregnancies occurring in 2001-2005.

The inter-quartile ranges of intervals have lengthened between 1983 and 2000, suggesting a wider range of birth intervals over time. The percentage of pregnancies followed by another

pregnancy within 36/60 months has decreased over time, which could be due to lengthening intervals or decreased fertility where the current pregnancy was not followed by another pregnancy.

Table 4.6: Inter-outcome interval summaries by calendar period for pregnancies in Matlab (1983-2005).

Calendar period	Inter-outcome interval (months)		% intervals closed by	
	Median	IQR*	36 months	60 months
1983-1985	33.3	25.0-44.1	47.2	75.0
1986-1990	35.6	25.6-51.3	39.8	66.0
1991-1995	42.0	27.7-62.5	29.5	55.9
1996-2000	41.2	26.7-57.5	27.0	52.7
2001-2005	24.9	15.6-36.4	25.0	48.2

IQR* inter-quartile range

Birth to conception interval

The gestational age information was missing for 38.7% of pregnancies, and was more likely to be unknown for women who had died due to pregnancy related causes. It was unknown for 38.6% of pregnancies to women who survived their pregnancies and to 60.9% of pregnancies to women who died due to pregnancy related causes.

There were only very minor differences in the distribution of the birth to conception intervals using the two different assumptions to estimate the gestational age of the pregnancies (Table 4.7). The birth to conception interval was between 15 to 50 months for 36% of all pregnancies or 44% of known interval length.

Table 4.7: Birth to conception interval estimates for pregnancies occurring in Matlab, Bangladesh between 1983 and 2005.

Birth to conception interval (months)	Model 1 n=159,210 (%)	Model 2 n=159,210 (%)
First pregnancy	38389 (24.1)	38389 (24.1)
<6	4537 (2.8)	4751 (3)
6-14	10076 (6.3)	10268 (6.4)
15-26	24884 (15.6)	24876 (15.6)
27-50	32395 (20.3)	32088 (20.2)
51-62	7836 (4.9)	7808 (4.9)
63-74	4677 (2.9)	4642 (2.9)
≥75	6760 (4.2)	6732 (4.2)
unknown	29656 (18.6)	29656 (18.6)

4.3.3 Crude associations with pregnancy related mortality

There were 581 pregnancy related deaths, of which 56 were deaths due to intentional/unintentional injuries (Table 4.8). 51% of all pregnancy related deaths were due to direct causes. This gave an overall pregnancy related mortality ratio of 365 (95% confidence interval (CI) 335-395) deaths per 100,000 pregnancies.

Table 4.8: Causes of pregnancy related deaths in Matlab, Bangladesh (1983-2005)

Causes of pregnancy related death	No. of deaths	Percentage
Direct obstetric	298	51.3
Abortion related	100	17.2
Indirect	127	21.9
Accidental/Incidental	56	9.6
Total deaths	581	100.0

Maternal age and gravidity

There was strong evidence of an association between maternal age and pregnancy related death ($p<0.0001$). Very young girls aged 10-14 had nearly six times higher odds of maternal death compared to women aged 20-24 years (crude odds ratio(COR) =6.32, CI 1.97-19.72). Adolescents aged 15 to 19 years were also at increased risk of pregnancy related death (COR=1.37, 95% CI 1.05-1.77).

The increased risk of pregnancy related death rose steadily from 30 years onwards with women aged 45 or older having a 3.87 (CI 1.90-7.91) times higher odds of pregnancy related death compared to women aged 20-24 (Table 4.9).

There was strong evidence of an association between gravidity and pregnancy related death ($p<0.0001$). Women with no prior pregnancies or more than four prior pregnancies had higher odds of maternal death compared to women with only one previous pregnancy (Table 4.9). Women having their first pregnancy had a 1.59 times (CI 1.23-2.05) higher odds of pregnancy related death compared to women with one previous pregnancy.

After adjusting for gravidity, there was still a very strong association between maternal age and pregnancy related death ($p<0.001$). Girls aged 10-14 years remained at increased odds of maternal death (adjusted odds ratio (AOR) =4.96, 95%CI: 1.6-15.8), but older adolescents aged

15-19 years were no longer at increased odds of pregnancy related death (AOR=1.12, CI: 0.85-1.48). Older women remained at increased odds of pregnancy related death (Table 4.9).

After adjusting for maternal age, only nulligravidas and women with six or more previous pregnancies remained at increased risk of pregnancy related death (Table 4.9).

Table 4.9: Association between maternal age, gravidity and the pregnancy related death for 159,210 pregnancies in Matlab, 1983-2005.

	Number of pregnancies (n=159,210)	PRMRatio (per 100,000 pregnancies)	Crude OR (CI)	Adjusted OR* (CI)
Maternal age (years)			p< 0.001	p< 0.001
10-14	159	1886.8	6.23 (1.97-19.72)	4.96 (1.56-15.80)
15-19	20,720	419.9	1.37 (1.05-1.77)	1.12 (0.85-1.48)
20-24	51,961	307.9	1.00	1.00
25-29	42,558	298.4	0.97 (0.77-1.22)	1.03 (0.79-1.35)
30-34	26,339	368.3	1.20 (0.93-1.54)	1.12 (0.81-1.57)
35-39	12,825	491.2	1.60 (1.19-2.14)	1.37 (0.92-2.05)
40-44	3,971	906.6	2.96 (2.06-4.26)	2.45 (1.49-4.01)
≥45	677	1181.7	3.87 (1.90-7.91)	3.16 (1.42-7.03)
Gravidity			p< 0.001	p= 0.002
0	38,389	435.0	1.59 (1.23-2.05)	1.53 (1.16-2.02)
1	32,430	274.4	1.00	1.00
2	26,202	213.7	0.78 (0.56-1.09)	0.77 (0.54-1.08)
3	19,811	333.1	1.21 (0.88-1.67)	1.16 (0.82-1.64)
4	14,246	379.1	1.38 (0.99-1.94)	1.26 (0.86-1.85)
5	9,942	402.3	1.47 (1.01-2.13)	1.26 (0.82-1.94)
≥6	18,190	599.2	2.19 (1.65-2.90)	1.55 (1.04-2.30)
6	*6,855*	*598.1*	*2.19 (1.51-3.17)*	*1.75 (1.12-2.72)*
7	*4,533*	*529.5*	*1.93 (1.23-3.04)*	*1.40 (0.82-2.37)*
8	*2,912*	*549.5*	*2.01 (1.18-3.42)*	*1.32 (0.71-2.44)*
≥9	*3,890*	*719.8*	*2.63 (1.72-4.03)*	*1.47 (0.85-2.54)*

PRMRatio = pregnancy related mortality ratio; OR= odds ratio; 95% CI = confidence interval
* maternal age was adjusted for gravidity; gravidity was adjusted for maternal age.

Other exposures

There was strong evidence of associations between pregnancy related deaths and, calendar period of pregnancy outcome, service area, household asset quintiles, husband's formal years of education, maternal formal years of education and birth to conception interval (Table 4.10).

The risk of pregnancy related death has been decreasing over time. Women experiencing a pregnancy in 2001-2005 were at 65% lower odds of pregnancy related death compared to women experiencing a pregnancy in 1983-1985 (Table 4.10).

Living in the ICDDR,B service area was associated with a 17% (COR=0.83, 95% CI: 0.71-0.98) lower odds of pregnancy related death compared to residing in the government service area.

The household asset quintile was missing for 8.3% of pregnancies. The odds of pregnancy related death was just over two times lower in the least poor group compared to the poorest group (COR= 0.47, 95% CI: 0.35-0.62).

There were very few pregnancies and pregnancy related deaths in the top education category of 13 years or more, and thus the top two categories were combined. The husband's number of formal education years was missing for 9.8% of pregnancies. Women who died due to pregnancy related causes were more likely to have missing information.

Women whose husbands had any years of education were generally found to have decreased odds of pregnancy related death compared to women whose husband had no formal education. However, there was no overall association between husband's education and pregnancy related death of their wives (Table 4.10).

There was missing information for maternal education for 4% of pregnancies. Women with one to five years of formal education had a 37% (COR=0.63, 95%CI: 0.51-0.77) lower odds of pregnancy related death compared to women with no formal education. This increased to 80% (COR=0.20, 95%CI: 0.12-0.33) lower odds for women with nine or more years of formal education (Table 4.10). There was a dose response relationship between increasing years of education and decreasing odds of maternal death ($p<0.001$)

The majority of pregnancies were to women who were Muslims (88.3%). There was one pregnancy with missing religion information, and this pregnancy was excluded from this part of the analysis. There was no statistical evidence of an association between pregnancy related deaths and the woman's religion (COR=1.09, 95%CI: 0.85-1.39; Table 4.10).

The birth to conception interval information was missing for 37% of pregnancies. Women with missing birth to conception interval information had a higher risk of pregnancy related death ($p<0.001$).

Women with no previous pregnancies were at approximately 1.6 times higher odds of pregnancy related death compared to women with a birth to conception interval of 27-50 months (Table 4.10). Women who had an interval shorter than 15 months or 75 months or longer had increased odds of pregnancy related death when compared to women with a of birth to conception interval of 27-50 months. This pattern was observed for both models used to estimate birth to conception intervals (Table 4.10).

Table 4.10: Crude association between various exposure variables and pregnancy related death in 159,210 pregnancies in Matlab, Bangladesh (1983-2005).

Exposure variables	No. of pregnancies (n=159,210)	PRMRatio [1]	Crude Odds Ratio (CI)	p-value
Calendar period				
1983-1985	23,672	528.1	1.00	<0.0001
1986-1990	38,805	427.8	0.81 (0.64-1.02)	
1991-1995	32,400	379.6	0.72 (0.56-0.92)	
1996-2000	31,290	335.6	0.63 (0.49-0.82)	
2001-2005	33,043	187.6	0.35 (0.26-0.48)	
Service area				
ICCDR,B	85,772	395.2	1.00	0.03
government	73,438	329.5	0.83 (0.71-0.98)	
Asset quintile				
poorest	21,616	499.6	1.00	0.01
poorer	28,259	421.1	0.84 (0.65-1.09)	
poor	26,488	434.2	0.87 (0.67-1.13)	
less poor	31,748	343.3	0.69 (0.53-0.90)	
least poor	37,859	235.1	0.47 (0.35-0.62)	
unknown	13,240	309.7	0.62 (0.43-0.89)	
Husband's education (years)				
none	64,950	358.7	1.00	0.01
1-5	41,582	279.0	0.78 (0.62-0.97)	
6-8	13,490	296.5	0.83 (0.59-1.16)	
≥9	23,566	246.1	0.69 (0.51-0.91)	
unknown	15,622	857.8	2.40 (1.94-2.97)	
Maternal education (years)				
none	80,334	485.5	1.00	0.01
1-5	39,960	305.3	0.63 (0.51-0.77)	
6-8	16,863	213.5	0.44 (0.31-0.62)	
≥9	15,767	95.1	0.20 (0.12-0.33)	
unknown	6,286	286.4	0.59 (0.37-0.94)	
Religion				
Islam	140,650	361.2	1.00	0.5
other	18,559	393.3	1.09* (0.85-1.39)	
unknown	1			
Birth to conception interval (months)[2]				
gravidity zero	38,389	435.0	1.62 (1.25-2.10)	p<0.001
<6	4,537	529.0	1.97 (1.26-3.11)	
6-14	10,076	496.2	1.85 (1.31-2.62)	
15-26	24,884	305.4	1.14 (0.84-1.55)	
27-50	32,395	268.6	1.00	
51-62	7,836	216.9	0.81 (0.48-1.36)	
63-74	4,677	299.3	1.11 (0.63-1.96)	
≥75	6,760	562.1	2.10 (1.43-3.08)	
unknown	29,656	364.2	1.36 (1.02-1.80)	

1- per 100,000 pregnancies; * pregnancy with unknown religion excluded;

2- results from model 1 and model 2 were virtually identical, only results from model 1 presented here.

4.3.4 Multivariable analysis

Controlling for single confounders

Adjusting for each potential confounder individually, husband's education, maternal education gravidity and birth to conception interval were found to confound the relationship between maternal age and pregnancy related mortality (Table 4.11). The very young adolescent (<15 years) and older maternal age effects persisted after adjustment. The older adolescent effect (15-19 years) disappeared after adjustment for gravidity or for the birth to conception interval (Table 4.11).

There were only slight changes to the odds ratios for the very young and older maternal ages after adjustment for confounders. Thus there was only very minor confounding by other variables in the relationship between maternal age and pregnancy related mortality. The confounding effect of birth to conception interval observed appears to be mainly due to the effect of gravidity, as both gravidity and birth to conception have a category for first pregnancies. Also, the gravidity adjusted and birth to conception interval adjusted odds ratios for younger adolescents were virtually identical. Finally, the gravidity and birth to conception adjusted odds ratios for all age groups were very similar to the gravidity adjusted only odds ratios (data not shown). The results using the second model to estimate the birth to conception intervals were very similar to the first model (data not shown).

Confounders for the relationship between gravidity and pregnancy related death include maternal age, calendar year, asset quintiles, husband's and maternal education. The effect of first pregnancies persisted after adjustment for confounders. It weakened slightly after adjustment for husband's or maternal education. The effect of having higher gravidity pregnancies weakened after adjustment for all confounder except for husband's education.

Husband's education as a negative confounder in the relationship between higher gravidities and pregnancy related mortality was surprising. It may be due to missing values in the husband's education (9.81%) - women whose husband's education status was missing were at higher odds of pregnancy related death compared to women with a value for husband's education. Thus the latter relationship may be the main driver of the negative confounding found, rather than the husband's education per se causing the negative confounding.

Controlling for multiple confounders

Variables included for forward selection into the multivariable analysis included maternal age, gravidity, calendar period, asset quintiles, husband's education, maternal education and birth to conception interval (Table 4.11 and Table 4.12).

The final multivariable model included maternal age, gravidity, calendar period, husband's education and maternal education. After adjusting for these variables, maternal age was still strongly associated with pregnancy related death (p=0.001). Very young adolescents aged 10-14 had four times higher odds of pregnancy related death compared to women aged 20-24 (AOR=4.00, CI: 1.25-12.82, Table 4.13). The magnitude of the odds ratio has decreased compared with the crude odds ratio of 6.23 (CI: 1.97-19.72), suggesting partial confounding by the variables included in the model.

The effect of older maternal age (≥35 years old) increased after adjusting for confounders (Table 4.13). From age 35 years onward, the magnitude of the adjusted odds ratio increases steadily with women aged 45 years or older at nearly four (AOR=3.92, CI:1.75-8.77) times higher odds of pregnancy related death compared to women aged 20-24 (Table 4.13).

After adjusting for all confounders including maternal age, pregnancy outcome period husband's years of education and maternal years of education, gravidity was still strongly associated with pregnancy related death (p<0.001). Women who have zero previous pregnancies were the only group at increased odds of maternal death compared with gravida one women (AOR=1.63, 95%CI: 1.24-2.16).

There was some evidence that women with two previous pregnancies were at decreased odds of pregnancy related death after adjustment for confounders (AOR=0.70, 95%CI 0.50-0.99). The higher gravidity (≥3) effects were completely confounded by variables included in the model (Table 4.13).

Other exposures:

The final multivariable model included maternal age, gravidity, calendar period, husband's education and maternal formal years of education. Variables including calendar period (p<0.001), husband's (p<0.001) and maternal education (p<0.001) were all strongly associated with pregnancy related death after adjusting for the other variables in the model.

Women having pregnancies in later calendar periods were less likely to die due to pregnancy related causes, e.g. women having a pregnancy in 2001-2005 were at 56% lower odds of pregnancy related death compared to women having a pregnancy in 1983-1985, after adjustment for confounders (Table 4.13).

Women with 9 years or more of formal education were at 86% lower odds (AOR=0.14, CI: 0.08-0.24) of pregnancy related death compared to women with no formal education after adjusting for maternal age, gravidity, calendar year of pregnancy outcome and husband's education (Table 4.13).

Women who had missing values for husband's education were at the highest risk of pregnancy related death (AOR=4.15, CI: 3.30-5.22). Surprisingly after adjustment for confounders, women whose husband had nine or more years of formal education were at increased risk of pregnancy related death compared to women whose husband had no formal education (Table 4.13).

Table 4.11: Adjusting for potential confounders separately for the association between maternal age and pregnancy related death in 159,210 pregnancies in Matlab, Bangladesh (1983-2005)

Maternal age (years)	Crude OR (CI)	OR adjusted for (CI)						
		gravidity	calendar period	service area	asset quintiles	husband's education	maternal education	birth to conception interval model
10-14	6.23 (1.97-19.72)	4.96 (1.56-15.8)	6.21 (1.96-19.69)	6.24 (1.97-19.77)	6.50 (2.05-20.61)	5.69 (1.79-18.08)	6.11 (1.93-19.39)	4.95 (1.56-15.76)
15-19	1.37 (1.05-1.77)	1.12 (0.85-1.48)	1.36 (1.05-1.77)	1.37 (1.05-1.77)	1.36 (1.05-1.77)	1.33 (1.02-1.72)	1.39 (1.07-1.81)	1.11 (0.84-1.47)
20-24	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
25-29	0.97 (0.77-1.22)	1.03 (0.79-1.35)	0.99 (0.78-1.25)	0.97 (0.77-1.22)	0.97 (0.76-1.22)	1.00 (0.79-1.27)	0.91 (0.72-1.15)	1.18 (0.92-1.52)
30-34	1.20 (0.93-1.54)	1.12 (0.81-1.57)	1.26 (0.97-1.62)	1.19 (0.93-1.54)	1.19 (0.93-1.53)	1.27 (0.98-1.63)	1.06 (0.82-1.36)	1.50 (1.14-1.98)
35-39	1.60 (1.19-2.14)	1.37 (0.92-2.05)	1.67 (1.24-2.23)	1.59 (1.18-2.13)	1.57 (1.17-2.11)	1.71 (1.27-2.29)	1.34 (1.00-1.80)	1.97 (1.43-2.71)
40-44	2.96 (2.06-4.26)	2.45 (1.49-4.01)	2.92 (2.03-4.19)	2.92 (2.03-4.20)	2.84 (1.98-4.09)	3.23 (2.24-4.65)	2.38 (1.65-3.44)	3.65 (2.48-5.38)
≥45	3.87 (1.90-7.91)	3.16 (1.42-7.03)	3.77 (1.85-7.71)	3.83 (1.87-7.82)	3.80 (1.86-7.75)	4.20 (2.05-8.59)	3.07 (1.50-6.27)	4.71 (2.27-9.77)

Table 4.12 Adjusting for potential confounders separately for the association between gravidity and pregnancy related death in 159,210 pregnancies in Matlab, Bangladesh (1983-2005)

Gravidity	Crude OR (CI)	OR adjusted for (CI)					
		maternal age	calendar period	service area	asset quintiles	husband's education	maternal education
0	1.59 (1.23-2.05)	1.53 (1.16-2.02)	1.60 (1.24-2.08)	1.59 (1.23-2.06)	1.61 (1.25-2.09)	1.46 (1.13-1.89)	1.13 (1.89-1.76)
1	1.00	1.00	1.00	1.00	1.00	1.00	1.00
2	0.78 (0.56-1.09)	0.77 (0.54-1.08)	0.77 (0.55-1.07)	0.78 (0.56-1.09)	0.76 (0.54-1.06)	0.81 (0.58-1.13)	0.58 (1.13-0.71)
3	1.21 (0.88-1.67)	1.16 (0.82-1.64)	1.18 (0.86-1.62)	1.21 (0.88-1.66)	1.16 (0.85-1.6)	1.29 (0.94-1.78)	0.94 (1.78-1.05)
4	1.38 (0.99-1.94)	1.26 (0.86-1.85)	1.31 (0.93-1.84)	1.37 (0.97-1.92)	1.30 (0.93-1.83)	1.48 (1.05-2.08)	1.05 (2.08-1.15)
5	1.47 (1.01-2.13)	1.26 (0.82-1.94)	1.35 (0.93-1.96)	1.45 (0.99-2.10)	1.36 (0.94-1.98)	1.59 (1.09-2.31)	1.09 (2.31-1.19)
6	2.19 (1.51-3.17)	1.75 (1.12-2.72)	1.96 (1.35-2.85)	2.14 (1.48-3.11)	2.01 (1.38-2.91)	2.39 (1.65-3.47)	1.65 (3.47-1.74)
7	1.93 (1.23-3.04)	1.40 (0.82-2.37)	1.70 (1.08-2.68)	1.89 (1.20-2.97)	1.76 (1.12-2.77)	2.13 (1.35-3.35)	1.35 (3.35-1.52)
8	2.01 (1.18-3.42)	1.32 (0.71-2.44)	1.74 (1.02-2.97)	1.96 (1.15-3.34)	1.81 (1.06-3.10)	2.20 (1.29-3.76)	1.29 (3.76-1.56)
≥9	2.63 (1.72-4.03)	1.47 (0.85-2.54)	2.23 (1.45-3.42)	2.56 (1.67-3.92)	2.39 (1.56-3.66)	2.95 (1.92-4.54)	1.92 (4.54-2.02)

Table 4.13: Crude and adjusted odds ratios of the effect of various exposures on pregnancy related death in Matlab, Bangladesh, 1983-2005.

Exposure variables	Number of pregnancies (n=159,210)	PRMRatio (per 100,000 pregnancies)	Crude OR	Adjusted OR*
Maternal age (years)				
10-14	159	1886.8	6.23 (1.97-19.72)	4.00 (1.25-12.82)
15-19	20,720	419.9	1.37 (1.05-1.77)	1.04 (0.79-1.38)
20-24	51,961	307.9	1.00	1.00
25-29	42,558	298.4	0.97 (0.77-1.22)	1.16 (0.88-1.52)
30-34	26,339	368.3	1.20 (0.93-1.54)	1.38 (0.98-1.95)
35-39	12,825	491.2	1.60 (1.19-2.14)	1.74 (1.15-2.64)
40-44	3,971	906.6	2.96 (2.06-4.26)	3.13 (1.89-5.20)
≥45	677	1181.7	3.87 (1.90-7.91)	3.92 (1.75-8.77)
Gravidity				
0	38,389	435.0	1.59 (1.23-2.05)	1.63 (1.24-2.16)
1	32,430	274.4	1.00	1.00
2	26,202	213.7	0.78 (0.56-1.09)	0.70 (0.50-0.99)
3	19,811	333.1	1.21 (0.88-1.67)	0.97 (0.68-1.38)
4	14,246	379.1	1.38 (0.99-1.94)	0.98 (0.66-1.44)
5	9,942	402.3	1.47 (1.01-2.13)	0.93 (0.60-1.44)
6	6,855	598.1	2.19 (1.51-3.17)	1.22 (0.77-1.94)
7	4,533	529.5	1.93 (1.23-3.04)	0.95 (0.55-1.64)
8	2,912	549.5	2.01 (1.18-3.42)	0.88 (0.47-1.64)
≥9	3,890	719.8	2.63 (1.72-4.03)	0.97 (0.55-1.71)
Calendar Period				
1983-1985	23,672	528.1	1.00	1.00
1986-1990	38,805	427.8	0.81 (0.64-1.02)	0.83 (0.66-1.05)
1991-1995	32,400	379.6	0.72 (0.56-0.92)	0.78 (0.61-1.01)
1996-2000	31,290	335.6	0.63 (0.49-0.82)	0.75 (0.57-0.98)
2001-2005	33,043	187.6	0.35 (0.26-0.48)	0.44 (0.32-0.61)
Maternal education (years)				
none	80,334	485.5	1.00	1.00
1-5	39,960	305.3	0.63 (0.51-0.77)	0.58 (0.47-0.73)
6-8	16,863	213.5	0.44 (0.31-0.62)	0.37 (0.26-0.54)
≥9	15,767	95.1	0.20 (0.12-0.33)	0.14 (0.08-0.24)
unknown	6,286	286.4	0.59 (0.37-0.94)	0.37 (0.23-0.61)
Husband's education (years)				
none	64,950	358.7	1.00	1.00
1-5	41,582	279.0	0.78 (0.62-0.97)	0.95 (0.76-1.2)
6-8	13,490	296.5	0.83 (0.59-1.16)	1.23 (0.87-1.73)
≥9	23,566	246.1	0.69 (0.51-0.91)	1.57 (1.14-2.15)
unknown	15,622	857.8	2.40 (1.94-2.97)	4.15 (3.30-5.22)

PRMRatio = pregnancy related mortality ratio; OR= odds ratio; 95% CI = confidence interval
* adjusted for maternal age, gravidity, calendar period, husband's and woman's formal years of education.

Interactions

Gravidity zero and older maternal age:

The effect of first pregnancy was modified by older maternal ages (p=0.03) in the crude analysis, with higher odds ratios observed for women aged 35 years or over. For women younger than 35, the odds of pregnancy related death was 1.46 (CI: 1.21-1.76) times higher for gravida zero women compared with women with one or more previous pregnancies. The corresponding odds ratio was 5.78 (CI: 2.09-15.94) for women aged 35 years or older.

After adjusting for calendar period, maternal and husband's years of education, there was still evidence of an interaction (p=0.03). The effect of nulligravidity was 1.56 (CI: 1.29-1.90) for women younger than 35 years old, and this rose to 6.21(CI: 2.22-17.43) for women aged 35 or older. The nulligravidity effect was 3.98 (CI: 1.40-11.3) times higher for older women (≥35 years old) than younger women.

Gravidity order and calendar period:

There was statistical evidence of an interaction between the effects of gravidity and calendar period in the crude analysis (p=0.003; Table 4.14). Gravida zero women were at increased risk of pregnancy related death compared to women of gravidity one or higher in the earlier calendar period, but the effect disappeared in the later period when access to maternal care improved (Table 4.14). The odds ratio for the higher gravidity effect increased in the later calendar period as the total fertility rate decreased, in line with the findings of the systematic review.

After adjusting for maternal age, husband's and maternal education, however, there was only marginal statistical evidence for an interaction between gravidity and calendar period (p=0.12).

Table 4.14: The effect of gravidity on pregnancy related death stratified by calendar years in Matlab, Bangladesh, 1983-2005.

Stratified by calendar period	Gravidity*	Crude OR	95% CI
1983-1990	0	1.98	1.51-2.58
	1-5	1.00	
	≥6	1.70	1.26-2.29
1991-2005	0	1.18	0.91-1.55
	1-5	1.00	
	≥6	2.29	1.65-3.18

OR= odds ratio; CI = 95% confidence interval
*p-value for interaction = 0.003

4.3.5 Sensitivity analysis

There were 581 pregnancy related deaths using the definition of death due to any cause, up to 90 days postpartum. There were 528 pregnancy related deaths when restricting to deaths up to 42 days postpartum. There were no changes to the conclusions of the findings in the crude analysis when using this definition. There were very little changes to the adjusted results. However, gravidity two women were no longer at decreased odds of pregnancy related death compared to gravidity one women. Very young girls, nulligravidas and women aged 35 years or older remained at increased odds of pregnancy related death.

There were 525 pregnancy related death excluding intentional (suicide and homicides) and unintentional (e.g. snake bite, burns and drowning) injuries within 90 days postpartum. Using this definition, there was no statistical evidence that very young adolescents (<15 years old) were at increased risk of maternal death (pregnancy related death excluding injuries). However, the sample size was small and thus may lack the power to detect any effect - number of deaths in the very young adolescent group reduced from three deaths to one. Women aged 30 years or older had increased odds of maternal death – five years earlier compared to pregnancy related death (Table 4.15). Nulligravidity women and higher gravidity women remained at increased risk of maternal death in the crude analysis (Table 4.15).

After adjusting for confounders, women aged 30 or older were at increased risk of pregnancy related death excluding injuries but neither adolescent group was at increased risk (Table 4.15). Women with no previous pregnancies were at increased risk of pregnancy related death excluding injuries after adjusting for confounders (Table 4.15).

Table 4.15: Results of the sensitivity analysis using maternal death (pregnancy related death excluding injuries) as the outcome.

	Number of pregnancies (n=159,210)	MMRatio (per 100,000 pregnancies)	Crude OR (CI)	Adjusted*OR (CI)
Maternal age (years)				
10-14	159	628.9	2.43 (0.34-17.48)	1.54 (0.21-11.16)
15-19	20,720	347.5	1.34 (1.01-1.78)	1.02 (0.75-1.38)
20-24	51,961	259.8	1.00	1.00
25-29	42,558	282.0	1.09 (0.85-1.39)	1.30 (0.97-1.74)
30-34	26,339	360.7	1.39 (1.07-1.81)	1.61 (1.12-2.31)
35-39	12,825	467.8	1.80 (1.33-2.45)	1.97 (1.28-3.04)
40-44	3,971	856.2	3.32 (2.27-4.84)	3.47 (2.05-5.87)
≥45	677	1181.7	4.59 (2.24-9.41)	4.63 (2.05-10.46)
Gravidity				
0	38,389	364.7	1.56 (1.18-2.06)	1.67 (1.23-2.25)
1	32,430	234.4	1.00	1.00
2	26,202	202.3	0.86 (0.61-1.23)	0.75 (0.52-1.07)
3	19,811	302.9	1.29 (0.92-1.82)	0.97 (0.67-1.41)
4	14,246	358.0	1.53 (1.07-2.18)	1.00 (0.66-1.50)
5	9,942	402.3	1.72 (1.17-2.52)	0.99 (0.63-1.56)
6	6,855	568.9	2.44 (1.65-3.59)	1.24 (0.77-2.00)
7	4,533	507.4	2.17 (1.36-3.46)	0.97 (0.55-1.70)
8	2,912	515.1	2.20 (1.27-3.84)	0.88 (0.46-1.69)
≥9	3,890	719.8	3.09 (2.00-4.77)	1.03 (0.58-1.85)

MMRatio = Maternal mortality ratio;
OR= odds ratio; 95% CI = confidence interval;
* adjusted for maternal age/gravidity, calendar period, husband's and woman's formal years of education.

4.4 Discussion

4.4.1 Main findings

Adolescents younger than 20 and women aged 35 years or older were at increased risk of pregnancy related death compared to women aged 20-24 years in Matlab, Bangladesh. The effects persisted after adjustment for confounders for adolescents younger than 15 years and older women, but the increased risk of death among girls aged 15-19 was entirely confounded by gravidity.

First pregnancies were at increased risk of pregnancy related death and this effect persisted after adjustment for confounders. The higher risk of pregnancy related death in the higher

gravidity groups completely disappeared after adjusting for maternal age, calendar period, husband's and maternal education. The higher risk in first pregnancies was much stronger in women aged 35 years or older compared to younger women, even after adjustment for confounders. In the crude analysis, the higher risk of firs pregnancies disappeared after 1990 when maternity services improved.

4.4.2 Interpretation of the findings

Effect of maternal age

The patterns of the crude association between age and pregnancy related mortality found is consistent to that found for the systematic review. However, the magnitude of the odds ratios differed. In addition, women aged 20-25 were not observed to be at increased risk of pregnancy related death, but older adolescents (15-19 year olds) were in contrast to the systematic review. While there was partial confounding, the very young age and older age effect persisted, consistent with the findings of the systematic review.

Comparing with specific studies, only one Latin American study reported adjusted results for girls younger than 15 and the findings of this analysis was consistent with the Latin American study. They found very young adolescents were at a fourfold increased risk of maternal death compared to women aged 18-19 after adjustment for various confounders including parity and education [269].

Christian and colleagues found increased older age effects after adjusting for parity and upper arm circumference in Nepal [204]. However, a study among non-abortion deaths in Ethiopia did not find an older age effect after adjustment for confounders including parity, antenatal care, occupation, income, education and marital status [116]. The authors only included non-abortion related maternal deaths, which constituted only 70% of all maternal deaths. In addition, this was a small study with 29 non abortion related deaths.

The higher risk of pregnancy related death in very young women in Matlab appears to be partly related to the higher number of intentional/unintentional injury related deaths in this age group. This confirms findings from previous studies which suggest that young unmarried girls are at increased risk of injury death when they fall pregnant [110, 313, 315]. Pregnancies outside of marriages are social taboos in rural Bangladesh, including Matlab, and girls falling pregnant may resort to induced abortion or suicide [110].

Interestingly, the dramatic decline in fertility in Matlab was not accompanied by major changes to the proportion of pregnancies at different ages. This may be partially due to increased induced abortion rates, especially to older women of higher parities [161]. In addition, there was evidence that the inter-pregnancy outcome intervals have increased over time, and thus reduced fertility may be achieved through greater spacing of pregnancies.

Effect of gravidity

The patterns of the crude association between gravidity and pregnancy related death found is consistent with that of the findings in the systematic review (chapter 3). In contrast to the systematic review, gravidity two women were not associated with increased risk of death in this study. There was minimal confounding for the relationship between gravidity zero and pregnancy related mortality, and positive confounding for the higher gravidity effect, consistent with the systematic review.

After adjustment for confounders such as maternal age and socio-economic status, only the nulligravidity effect persisted. This study suggests that high gravidity is not causally related to maternal mortality. Rather, high order pregnancies are at higher risk because these women tend to be older or poorer. This finding will have major implications for the effect of reducing the total number of births on maternal mortality.

Effect modification:

The excess risk of nulligravidity was higher in older women compared to younger women, even after adjusting for confounders. This is consistent with studies which found older nulliparous women at increased risk of operative deliveries compared to younger nulliparous women [303, 319]. The authors concluded that this *"may be explained largely by the increase in other complications of pregnancy"* in older nulliparous women. However, this observed effect may be due to the selection of women who have trouble conceiving due to poor health, and it is this health status that drives the higher risk of maternal death rather that nulligravidity per se. This may be especially applicable to women in rural Bangladesh since children are highly valued, and all married women are expected to have children if possible.

The use of delivery care may be an effect modifier in the relationship between maternal age/gravidity and pregnancy related death as discussion in the Introduction, section 2.4. While

it was not possible to explicitly adjust for delivery in this study, I used a calendar period as a proxy for improved care in Matlab. There was evidence that the increased risk of first pregnancies disappeared after 1990, suggesting that better maternity care may mitigate the higher risk in first pregnancies. However, there was only very weak evidence of an interaction once confounders were adjusted. Further work, with complete information on delivery attendant and place of delivery, should be carried out to elucidate the role of delivery care.

Effect of other factors

The higher risks of pregnancy related death found in the crude relationships for the earlier calendar period, the government service area, lower asset quintiles, and lower maternal education confirm findings of earlier studies [10, 193-194].

After adjustment for maternal age, gravidity, and maternal and husband's education, women who had pregnancies during later calendar periods still had a decreased risk of pregnancy related death. This may be due to a variety of time related changes such as improved maternity and other health services and better access to such facilities. Other societal changes such as improved standards of living, schemes such as micro-credit for the poor may have helped to raise women's status, increasing their autonomy and decision making powers.

There were striking differences in the pregnancy related mortality ratios by women's formal years of education, even after adjusting for confounders such as maternal age, gravidity, calendar year of pregnancy outcome and husband's education. This may be because women with higher educational attainment are more knowledgeable about the benefits of using skilled birth attendants, and are better able to negotiate the public health system to access health care. Continuing to educate girls and ensure they stay longer in education could help reduce pregnancy related mortality.

Both shorter (≤ 14 months) and longer (≥75 months) birth to conception intervals were found to have higher risk of pregnancy related death in the crude analysis. This is in contrast to two previous studies conducted in Matlab, neither study found an association between shorter birth interval and maternal mortality in the crude analysis [102, 320].

The differences between this study and the study by DaVanzo may be due to differences in the definition of birth interval. This research investigated the birth to conception interval, and DaVanzo and colleagues used the outcome to conception interval. In addition, DaVanzo and

colleagues restricted their analysis to singleton pregnancies only, whereas this research included all pregnancies.

4.4.3 Strengths and limitations

The data from the HDSS are unique in that the prospective surveillance carefully records all demographic events, but an assessment of data quality and its implications on the findings is nevertheless warranted. Issues addressed below include information bias (i.e. the ascertainment of outcome and exposure), selection bias (i.e. loss to follow-up) and the modelling approach.

Information bias

Outcome assessment

The ascertainment of adult mortality is likely to be complete in Matlab, but some pregnancy related deaths may have been missed. As in all studies of maternal mortality, pregnancy related mortality may have been underestimated. This will only affect the results if this misclassification is also related to exposure (i.e. maternal age or gravidity). Deaths in very young girls, if related to the unwantedness of a pregnancy, may not be reported as pregnancy related by the family. Menstrual regulation has facilitated the debate around induced abortion in Bangladesh, but acknowledging that a young girl died as a result of abortion is very difficult. The magnitude of effect of young age on maternal mortality may thus have been underestimated.

Exposure assessment

The classification of maternal age is likely to be correct, at least for women born after the surveillance was established in 1966 and for whom a date of birth is known with accuracy. For women born before the surveillance started the date of birth was reported by the family. Most women included in the analysis would have been very young at that time and misclassification of age is unlikely to have been a major problem.

The classification of gravidity, on the other hand, was not straightforward. Adjustments were made for multiple gestations, which were traditionally counted as more than one pregnancy, and for consecutive pregnancies with inconsistent pregnancy order. Such inconsistencies are

largely due to migration, where pregnancy orders have to be updated once women re-enter the area. There were few inconsistencies, whether related to multiple gestation or incorrect pregnancy order and so the results are likely to be valid.

The adjustments for socio-economic factors were more complete than those reported in other studies, but some misclassification may have affected the findings. The methods used to estimate the asset quintiles may have been inadequate, particularly since pooling assets over the 30 year period does not take account of the changing values of assets over this time. However, Chowdhury and colleagues reported no changes in their analyses when using the alternative period specific asset quintiles [9], and thus it would be unlikely to change the results of this analysis.

There may be residual confounding or unmeasured confounders that may affect the results. For example, from the literature review, current health status of women may confound the relationship between maternal/gravidity and pregnancy related death. However, no information regarding women's health status was readily available to assess its confounding effects. So it is possible that the observed higher risks were due to uncontrolled confounders.

The missing values in the maternal and husband's years of formal education could have biased the results. The results restricting to pregnancies with no missing values were similar for older maternal age, and higher gravidity orders. However, there were insufficient numbers for gravidity zero and pregnancies to younger women to make any firm conclusions.

The gestational age used to estimate the birth to conception interval was missing for 38.7% of pregnancies. In addition, women with missing gestational age were at nearly 2.5 times higher odds of pregnancy related death compared to women with gestational age information. If women who die due to pregnancy related causes were assumed to have shorter birth to conception intervals, then the risk of pregnancy related death for women with shorter birth intervals may be overestimated.

Selection bias

All households of the DSS villages were regularly visited (fortnightly until 1997, and every month since) by trusted female community health workers. Thus follow up of women, who continue to live in Matlab at the time of pregnancy outcome should be 100%. However, like any data collection a very small percent may be missed due to various administrative errors.

It is possible that loss to follow up of pregnant women may be due to migration out of Matlab. The proportion lost to follow up through migration is not available in the dataset used for this analysis since only data for women who had pregnancy outcomes in Matlab were linked back to women's information. Between 1983 and 2005, the out migration rate for women aged 15-49 years ranged from 88 to 135 per 1,000 women [321]. The age ranges with the highest rates were among 15-19 year olds and 20-24 year olds (accounting for around 65-76% of all women aged 15-49 who migrated out of Matlab). If the majority of women aged 15-24 migrated out to get married, then they are unlikely to be lost to follow up in the context of this study as pregnancy outside of marriage is a social taboo in Matlab. This may be especially true during the 1980s when the peak out migration rate was for 15-19 year olds.

Subjectivity of model building

Model selection represents a series of steps during which a combination of statistical diagnostic criteria and subjective personal opinion come into play. This is especially true in model selection for exposure-outcome relationships, where most assessments were associated with confounding and thus subjective. This means that despite the use of explicit criteria, both statistical and pre-defined cut offs, the final determination of which variables were confounders to include in the model may vary from one investigator to the next. I have sought the most parsimonious model using a pre-defined set of criteria that would enable replication of the model selection by others.

Generalisability

ICCDR,B has worked in Matlab for over four decades to improve public health. It may be argued that the population of Matlab is now so different from other populations that any Matlab based research findings, such as this one, may not be generalisable to other less developed countries. This may be true in some respects, for example, the proportion of births with a skilled birth attendant was 53% in the ICDDR,B area in 2005 [9] compared to a national average of 12% over a similar period [202].

However, Matlab is still a typical rural area of Bangladesh and is culturally similar to the rest of Bangladesh. This is particularly true for the Government service area, which has demographic trends that match those for rural Bangladesh. The special status of Matlab as being the only demographic surveillance site in a less developed country has been lost. There are now nearly

70 such sites in less developed countries. The population of these other sites may also benefit from public health messages and improved access to better quality of care. In addition, this study included pregnancies from the 1980s and 1990s when access and quality of maternity services have greater similarities with contemporary least developed countries. So there are still many similarities between Matlab and many parts of the less developed countries that would suggest the results from this research would be generalisable.

5 FERTILITY CHANGES AND MATERNAL MORTALITY

This chapter describes the compartmental model developed to assess the impact of changes in the age and gravidity distribution of pregnancies, as a result of fertility changes, on the pregnancy related mortality indicators. I start with the framework of the compartmental model and methods used to parameterise the model. I explore both observed and theoretical changes in age-gravidity pregnancy rates and their impact on the pregnancy related mortality indicators. Finally, I discuss some of the strengths and limitations of the model.

5.1 Methods

5.1.1 Model and assumptions

Individuals in a population can be categorised into broad subgroups or "compartments", e.g. by different age groups. A compartmental model aims to model what happens on average in the population as individuals pass through different subdivisions in the population or different compartments. The compartmental model describes the transition between subgroups by applying average transition rates. Individuals within each compartment are assumed to be homogeneous.

A compartmental model (Figure 5.1) was used to describe the flow of a cohort of women through their reproductive lives. The model tracked women from age 10 to age 49, recording any pregnancies during this period. The model included eleven gravidity compartments, i=0...10, where gravidity was defined as the number of previous pregnancies, excluding the index pregnancy if a woman was currently pregnant or within the postpartum period.

The number of pregnancies rather than live births was used in the numerator to calculate the fertility rates, and they will be referred to as pregnancy rates for the rest of the analysis. As a result the total fertility rate calculations were based on pregnancies rather than live births, and will be referred to as the total pregnancy rates for the rest of this chapter.

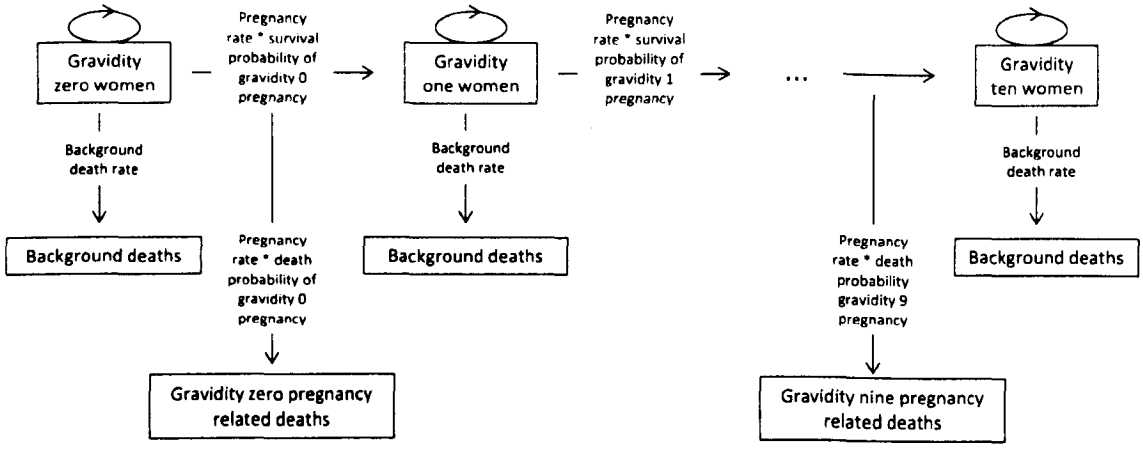

Figure 5.1: Structure of the fertility model following a cohort of women through their reproductive lives (10-49 years).

Women aged as they were followed through the model, thus time was modelled as age, and i.e. age and time were interchangeable for this model. Women aged a, gravidity i were denoted by W_a[i] and they may die due to non pregnancy related causes according to defined age specific background death rates, μ_a. The background deaths were tracked for separate gravidities and the cumulative gravidity i background deaths by age a was denoted by D_a^b[i] in the model.

Women may fall pregnant at defined age-gravidity specific pregnancy rates, $f_a[i]$. I assumed that women can have at most one pregnancy per year, and therefore women can move at most one gravidity compartment from age a and $a + 1$. Pregnancies were modelled as instantaneous events. The intermediate step of the number of pregnancies were also tracked in the model, and denoted by PW_a[i].

Once pregnant, women may die due to pregnancy related causes according to defined age-gravidity specific pregnancy related mortality ratios, $prmr_a[i]$. Women who die due to pregnancy related causes were tracked in the model and $D_a^p[i]$ represented the cumulative gravidity i pregnancy related deaths by age a. Figure 5.2 shows the schematic of possible movements between compartments in a single year.

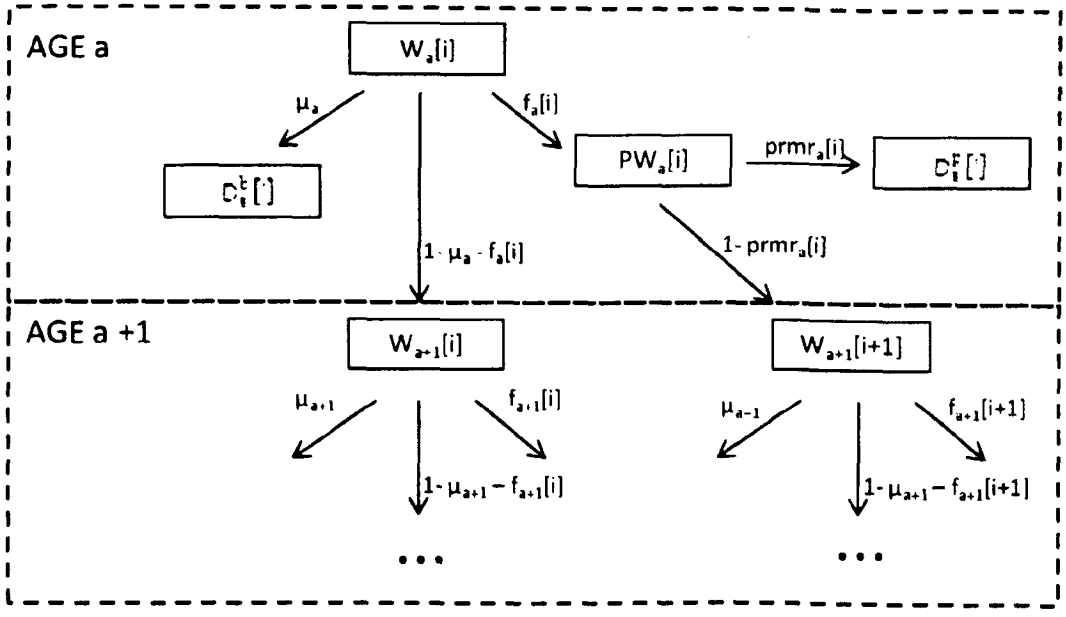

Figure 5.2: Possible movements in the compartmental model over a one year period. Women aged a, gravidity i are denoted by $W_a[i]$. Pregnant women aged a, gravidity i are denoted by $PW_a[i]$. $D_a^b[i]$ and $D_a^p[i]$ denote the cumulative gravidity i deaths due to background and pregnancy related causes by age a respectively. The age-gravidity specific pregnancy rates are represented by $f_a[i]$. The age-gravidity specific pregnancy related mortality ratios are represented by $prmr_a[i]$. The age specific background death rates are represented by μ_a.

The following difference equations can be used to describe the model:

$$W_{a+1}[0] = W_a[0](1-\mu_a-f_a[0]) \quad (1)$$

$$W_{a+1}[i+1] = W_a[i+1](1-\mu_a-f_a[i+1]) + W_a[i]f_a[i](1-prmr_a[i]) \quad (2)$$

$$D_{a+1}^b[i] = D_a^b[i] + W_a[i]\mu_a \quad (3)$$

$$D_{a+1}^p[i] = D_a^p[i] + W_a[i]f_a[i]prmr_a[i] \quad (4)$$

Equation (1) represents the number of gravidity zero women at age a + 1, i.e. the number of women who was gravidity zero at age a, and did not die a background death or fall pregnant by age a + 1.

Equation (2) is an extension of equation (1) and represents the number of gravidity i + 1 women at age a + 1. They are women who were gravidity i + 1 at age a, and did not die a background death or fall pregnant by age a + 1, plus the women who were gravidity i at age a but subsequently fell pregnant and survived that pregnancy by age a + 1.

Equation (3) represents the cumulative number of background deaths to gravidity i women by age a + 1. This includes all gravidity i women who died due to background causes by age a, plus the number of gravidity i women who died due to background causes between age a and age a + 1.

Equation (4) represents the cumulative number of pregnancy related deaths to gravidity i women by age a + 1. This includes all gravidity i women who died due to pregnancy related causes by age a, plus the number of gravidity i women who died due pregnancy related causes between age a and age a + 1.

The main model output parameters of interest were the number of pregnancy related deaths and overall pregnancy related mortality indicators including:

- pregnancy related mortality ratio (PRMRatio)= $\frac{\text{number of pregnancy related deaths}}{\text{number of pregnancies}}$ x 100,000
- pregnancy related mortality rate (PRMRate) = $\frac{\text{number of pregnancy related deaths}}{\text{number of women aged 10-49 years}}$ x 1,000
- lifetime risk of pregnancy related death= $\sum_{a=10}^{49}(\text{PRMRate}_a \times 5)$, 5 for five year age categories, it is possible for this to include other age intervals.
- proportionate mortality ratio= $\frac{\text{number of pregnancy related deaths}}{\text{number of all cause death to women aged 10-49 years}}$

Other model output parameters calculated were the overall, age specific and gravidity specific pregnancy rates, death rates and total pregnancy rate for women aged 10 to 49 years.

In addition the gravidity progression ratio was calculated among all women still alive at the end of age 49. The gravidity progression from gravidity j to gravidity j+1 was defined as the proportion of women who had a jth pregnancy and who went on to have another pregnancy.

An abridge life table was constructed using model outputs to estimate the parameters of interest. The number of women and the number of pregnancy related and non-pregnancy related deaths within each age interval were used to populate the life table.

5.1.2 Parameters

The model was parameterised to represent pregnancies experienced by women from Matlab, Bangladesh. Details of the study site and population in Matlab have been described previously

in the retrospective cohort study in chapter 4). In addition to the core pregnancy dataset, for the period 1 January 1983 and 31 December 2005 used in the retrospective cohort study I used a dataset of all women residing in Matlab between 1 January 1983 and 31 December 2001 which included information on the women's entry date into Matlab, their marital status at entry date and the date of their first pregnancy outcome (if any) in Matlab. This dataset was used to calculate the age specific rates of falling pregnant for the first time, $f_a[0]$. The pregnancy dataset described in the retrospective cohort study (chapter 4) was used to calculate other age-gravidity specific pregnancy rates.

The baseline parameters were calculated using observed vital event data including pregnancies, births and deaths from Matlab, Bangladesh between 1983 and 1993, the baseline period. This was a period of high fertility and relative high mortality in Matlab. References in this chapter to the baseline pregnancy rates or baseline maternal mortality ratios refer the pregnancy rates or maternal mortality ratios calculated using data from this baseline period in Matlab.

The model was initialised with a hypothetical cohort of 100,000 girls aged 10 years.

Pregnancy rates

The observed age-gravidity specific pregnancy rates were calculated using standard survival analysis methods of women years [322]. I used the conditional risk set (time from the previous event) to calculate the gravidity specific pregnancy parameters. This model measures the time between two events, resetting the clock to zero after each failure, i.e. the clock was reset after each pregnancy.

A Lexis expansion is a method to disaggregate an individual's follow up time in a study into distinct intervals based on certain characteristic or a set of characteristics [322]. Consider a woman who was followed up in the study from the day she turned 10 to the day before she turned 25 years, then her follow up time would be 15 years. Lexis expansion on age (based on 5 year categories) would split her follow up time into three distinct segments - 5 years followed up in the 10-14 age group, 5 years followed up in the 15-19 age group, and 5 years followed up in the 20-24 age group. These three segments may be divided into even smaller categories based on calendar year, gravidity or other characteristics.

Lexis expansions were performed to calculate the age-gravidity specific parameters. A There was insufficient data to calculate the pregnancy rates for single year age groups. Women were grouped into five year age groups from 15 to 49 years, and I assumed the pregnancy rates within five year age groups were constant. Girls aged 10 to 14 years were split into two groups, 10-12 and 13-14 year olds, to reflect different pregnancy rates within these age groups.

The age of a woman was defined to be her age at last birthday, at the time of failure or censored event.

The number of women years contributed by each individual was calculated using their entrance and exit dates into a particular gravidity risk set. Gravidity zero women were defined to enter into the risk group of falling pregnant for the first time on the earliest date out of the following events:

1. date of their tenth birthday if they were resident in Matlab and this date fell within the study period of 1 January 1983 and 31 December 2005;
2. start date of the study, 1 January 1983, if they were aged ten or older, having experienced no previous pregnancies prior to this date, were not currently pregnant and resided in Matlab;
3. date of entry into Matlab if they had no previous pregnancies, were not currently pregnant and were aged ten or older on entry date.

Women who were recorded as "never married" on entry into Matlab were assumed to have never been pregnant if no other information on their past pregnancy history was available. This is a reasonable assumption in the context of rural Bangladesh where there is a strong taboo against illegitimate births, which accounts for around 0.05% of all live births in Matlab [110]. Women with missing information on marriage status and previous pregnancy histories were excluded from the calculation of $f_{\alpha}[0]$ estimates.

After a gravidity i pregnancy outcome, women were defined to be at risk of falling pregnant again on the 91st day after the pregnancy outcome if they were still resident in Matlab and this date was within the study period of 1 January 1983 to 31 December 2005. Pregnancy related death was defined as a death of a woman during pregnancy or within 90 days of the termination of pregnancy regardless of the cause of death. Therefore prior to the 91st day after pregnancy outcome, women were at risk of a pregnancy related death.

Women exited the risk set of having a gravidity $i + 1$ pregnancy on the earliest date out of the following events:

1. conception date of the gravidity $i + 1$ pregnancy, if they still resided in Matlab;
2. migration date – censored date;
3. date of death - treated as censored date;
4. date of 50th birthday;
5. end of the study - 31 December 2005.

The conception dates were estimated by subtracting the gestational age of the index pregnancy from the outcome date of the index pregnancy. However, the gestational age was unknown for 38.7% of pregnancies. I estimated the conceptions dates by utilising known information on gestational age, and imputing plausible gestational ages for pregnancies with unknown durations, using the same assumptions as in the retrospective cohort study (chapter 4):

Pregnancy duration known:

Estimated gestational age = observed pregnancy duration (months) x 28 days

Pregnancy duration unknown:

Estimated gestational age = 280 days for live births
= 252 days for stillbirths
= 84 days for abortions
= 280 days for unknown pregnancy outcomes

Women who exited on the same date as their start date were assumed to contribute a day to the relevant risk set.

In Matlab, women were observed to have up to 21 previous pregnancies excluding the index pregnancy. However, women were only assumed to have up to nine previous pregnancies excluding the index one in the model. This was because there were insufficient numbers to model the pregnancy related mortality accurately. Unlike for the other age-gravidity pregnancy rates, I cannot estimate $f_a[9]$ using Lexis expansion due to clustering. To take account of clustering of gravidity nine or over conceptions within each woman, I modelled the pregnancy rates, $f_a[9]$, by using a random effects Poisson model including all gravidity nine or higher pregnancies.

The age-gravidity pregnancy rates were calculated only for age-gravidity subgroups where the pooled experience of all women, the total follow-up period, was 75 women years or longer. This was an arbitrary cut off. For subgroups of less than 75 follow up years, the age-gravidity pregnancy rates was assumed to be zero. A cut off point was used because for certain rare combinations of the age-gravidity groups the total follow period was small. This often resulted in unstable and impossibly large age-gravidity specific pregnancy rates due to the small denominators. For example, in the baseline period for gravidity one girls who were aged 10-12, there was one conception and a total follow up period of 0.92 years.

Using the Matlab data, the Lexis expansion was used to calculate the pregnancy rates for different calendar periods. The baseline pregnancy rates used for the model were the rates from Matlab during the period between 1 January 1983 and 31 December 1993 (Table 5.1). Some age-gravidity pregnancy rates were implausibly high because pregnancies instead of live births were used to calculate these rates and they may include women who experienced multiple miscarriages. In the compartmental model, these high rates only applied to very few individuals since women were assumed to have only one pregnancy per year. Therefore only a limited number of women reached the higher gravidities with high pregnancy rates.

Table 5.1: Baseline age-gravidity specific pregnancy rates per 1,000 women year, $f_a[i]$, estimated using information from Matlab Bangladesh (1983-1993).

$f_a[i]$, age- gravidity specific pregnancy rates (per 1,000 women year)										
Age interval in years (a)	Gravidity (i)									
	0	1	2	3	4	5	6	7	8	9+
10-12	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
13-14	2.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
15-19	85.2	356.8	408.0	423.9	634.9	0.0	0.0	0.0	0.0	0.0
20-24	217.2	399.2	355.5	346.2	374.9	383.3	456.0	0.0	0.0	0.0
25-29	165.3	358.0	320.9	292.9	289.7	320.2	335.2	380.8	405.3	254.0
30-34	77.2	244.4	210.0	191.2	187.6	210.7	241.7	269.8	285.8	238.6
35-39	13.8	148.6	124.3	113.3	108.3	108.2	127.7	149.4	179.3	174.2
40-44	1.2	0.0	47.9	72.3	62.7	63.8	59.2	65.2	85.8	85.9
45-49	0.7	0.0	0.0	0.0	0.0	29.2	27.9	20.8	22.7	25.9

Pregnancy related mortality ratios

I modelled the relationship between maternal age, gravidity and the pregnancy related mortality in the baseline period using a logistic regression restricting to the 82,832 pregnancies

that were recorded between 1 January 1983 and 31 December 1993 in Matlab. The method, using logistic regression, has been described in the retrospective cohort study (chapter 4).

The odds of pregnancy related death in the reference group (gravidity one women aged 20-24 years) was 3/1000 (95% CI: 2/1000 – 4/1000). The estimated odds ratio of pregnancy related deaths for Matlab (1983-1993) are shown in Table 5.2. Very young adolescents (10-14 years) and women aged 35 or older were at increased odds of pregnancy related death after adjusting for gravidity. In addition women with their first pregnancy were at increased risk of pregnancy related death after adjusting for maternal age.

Table 5.2: The estimated odds and odds ratios of pregnancy related death from a logistic regression model for the period 1983-1993 in Matlab.

	Gravidity adjusted odds ratio	95 % confidence interval			Age adjusted odds ratio	95 % confidence interval
Maternal age (years)				Gravidity		
10-14	5.27	1.27- 21.93		0	1.84	1.29- 2.64
15-19	1.16	0.83- 1.64		1	1.00	-
20-24	1.00	-		2	0.75	0.48- 1.18
25-29	1.40	0.98- 1.98		3	0.96	0.60- 1.52
30-34	1.29	0.80- 2.08		4	1.12	0.68- 1.83
35-39	2.30	1.32- 3.99		5	0.91	0.51- 1.61
40-44	3.60	1.85- 7.02		6	1.05	0.57- 1.92
≥45	3.84	1.26- 11.73		7	0.96	0.49- 1.90
				8	0.69	0.31- 1.56
				≥9	0.81	0.40- 1.67

Applying the odds ratios to the odds of pregnancy related death for gravidity one women aged 20-24, I was able to estimate the baseline age-gravidity specific pregnancy related mortality ratios (probabilities) by standard conversion between odds and probabilities, i.e. odds=probability/(1-probability). These are shown in Table 5.3.

The baseline age-gravidity pregnancy related mortality ratios were highest for pregnancies to very young adolescents (<15 year olds). They were also elevated for first pregnancies and pregnancies to women of older ages for each gravidity group. Some rare/impossible age-gravidity groups have estimates for the pregnancy related mortality ratio since these were modelled using a logistic regression.

Maternal age was grouped into five year age intervals from age 10 to 49, and thus constant pregnancy related mortality ratio was assumed within each five year age group. Women with pregnancies of gravidity nine or more were grouped together, assuming constant risk of pregnancy related death within this group.

Table 5.3: Baseline age-gravidity specific pregnancy related mortality ratios per 100,000 pregnancies, $prmr_a[i]$, modelled using logistic regression of pregnancy data from Matlab Bangladesh (1983-1993).

$prmr_a[i]$, age- gravidity pregnancy related mortality ratio (per 100,000 pregnancies)										
Age interval in years (a)	Gravidity (i)									
	0	1	2	3	4	5	6	7	8	9+
10-14	2820	1551	1169	0	0	0	0	0	0	0
15-19	636	346	260	332	387	315	0	0	0	0
20-24	547	298	224	285	333	271	312	287	0	0
25-29	762	415	312	398	464	378	434	400	288	338
30-34	706	385	289	368	430	350	402	370	266	314
35-39	1248	681	513	653	762	620	713	656	472	556
40-44	1944	1064	802	1020	1190	970	1113	1025	739	869
45-49	2068	1133	854	1086	1267	1032	1186	1092	787	926

Background death rates

The age specific, non-pregnancy related, background death rates, for women aged 10-49 years, were estimated using a combination of published data and the core dataset on pregnancies in Matlab (1983-2005) using the following formula:

$$\mu_a = \frac{\sum_{yr} \text{no. of non pregnancy related death}_{a\_yr}}{\sum_{yr} \text{mid} - \text{year population of women}_{a\_yr}}$$

The age specific mid-year population of women from different calendar years were obtained from published reports of the Matlab surveillance area by the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B) [323]. The number of non pregnancy related deaths was calculated by subtracting the number of pregnancy related deaths in the pregnancy dataset from the published number of all cause deaths for each age group and year. Women were grouped into five year age categories from ages 10 to 49 years. Therefore constant background death rate within the five year interval was assumed. The background death rates were assumed to be independent of gravidity status.

The baseline age specific background death rates estimated for 1983-1993 are shown in Table 5.4.

Table 5.4: Baseline age specific background death rates, μ_a, estimated using data from Matlab Bangladesh (1983-1993).

Age interval in years	μ_a, background death rates (per 1,000 women)
10-14	0.92
15-19	1.09
20-24	1.22
25-29	1.52
30-34	1.35
35-39	1.99
40-44	3.19
45-49	4.54

Parameter uncertainty

All estimated parameters have uncertainty associated with them expressed as the 95% confidence intervals. This model only accounted for the uncertainties associated with the estimation of the age-gravidity pregnancy related mortality ratios since the main outcomes of interest were pregnancy related mortality indicators. In addition, the rarity of pregnancy related deaths suggests higher levels of uncertainty associated with these parameters compared to the others.

The uncertainties of the pregnancy related mortality ratio estimates were propagated through the model by employing Monte Carlo simulation to select 1,000 values at random from the lognormal distribution, based on the pregnancy related odds or odds ratio estimates and their 95% confidence intervals (Table 5.2) [324]. I sampled from the lognormal distribution because the odds and odds ratios of pregnancy related death were estimated using a logistic regression. In addition, the variance-covariance matrix from the logistic regression was used to provide correlated parameter draws from the Monte Carlo simulation.

The variance-covariance matrix was obtained from standard post-estimation commands in Stata, version 11 [233, 325]. The Cholesky decomposition of the variance-covariance matrix, $\boldsymbol{T}$, was calculated and a vector of correlated variables, $\boldsymbol{x}$, were generated using the following formula [324]:

$$\boldsymbol{x} = \boldsymbol{y} + \boldsymbol{T}\boldsymbol{z},$$

where $\boldsymbol{z}$ represents a vector of independent standard normal variates, and $\boldsymbol{y}$ represented the parameter estimates from the logistic regression.

The average of the simulated model output parameters was used as the point estimate. The 95% uncertainty interval was calculated as the range of values between the 2.5th and 97.5th percentile of the simulated output values.

5.1.3 Model validation

Internal validity of the model was assessed by ensuring the number of women who entered the cohort was the same as the number of women in all compartments combined at any given age, i.e., there were 100,000 women at any give age.

To validate the model using external sources, the output parameter figures were compared to published parameter values from the Bangladesh Demographic and Health Surveys (DHS) conducted in 1996-1997 and 1999-2000 and the Bangladesh Maternal Health Services and Maternal Mortality Survey 2001 (BMMS) [202, 326-327].

I used three consecutive published surveys as the external validation source rather than just one because this enabled me to use information over a longer period of time (1994-2000), which allowed sufficient data to cumulate to calculate the pregnancy rates and pregnancy related mortality ratios more accurately.

The disadvantage of using information from three surveys over different calendar period is that the fertility and/or maternal mortality ratios may have changed over these periods. However, the reported fertility rates over the three surveys were relatively stable; the total fertility rates were 3.27 for the three year preceding the 1996-1997 DHS, 3.31 for the 1999-2000 DHS and 3.22 for the BMMS. There were some shifts in the age specific fertility rates over these surveys, but the differences were relative small. The input parameters calculated for the external validation were vital events data from Matlab for the period 1994-2000 (Table 5.5 and Table 5.6).

The Bangladesh DHS and BMMS were nationally representative surveys designed to collate a range of demographic and health outcomes including fertility rates. The BMMS also collected information on maternal mortality indicators. Household questionnaires collected information on household characteristics, selected socio-demographic information of household members, and all deaths within the household in the three years preceding the survey. Separate women's questionnaire was administered to ever married women (13-49 years) to collect information including socio-demographic characteristics and reproductive history. In addition to these two questionnaires, BMMS also conducted verbal autopsy questionnaires to identify

causes of all adult female deaths (13-49 years), including pregnancy related and maternal mortalities.

The DHS and BMMS reported on the age specific and overall fertility rates for the period 1994-1996, 1997-1999 and 1998-2000 using the birth history data from the women's questionnaire.

BMMS used two methods to estimate the age specific and overall pregnancy related mortality ratios/rates; directly from household deaths questionnaires and based on sibling histories. Estimates from the household deaths questionnaire were for the period of 1998-2001. The pregnancy related mortality ratios estimates based sibling histories were for the period 1991-1996, 1996-2001 and 1998-2001. All methods and time periods reported in the DHS and BMMS were used for comparisons with the model outputs.

The output parameters from my model were pregnancy rates in contrast to reported fertility rates (number of live births per 1,000 women) in the DHS and BMMS. To ensure comparability between model outputs and reported indicators, I estimated the age specific fertility rates by adjusting the pregnancy rates. This was done by multiplying the age specific pregnancy rates by the proportion of live births resulting from all pregnancies for that age group. The total fertility rates calculated from the model were based on these estimated age specific fertility rates.

When calculating the model total fertility and overall pregnancy related mortality indicators, the denominators used were women aged 15-49 years so that they were comparable to the published indicators.

Table 5.5: The age-gravidity specific pregnancy rates per 1,000 women years, $f_a[i]$ used for model validation, estimated using Matlab pregnancy data for 1994-2000.

$f_a[i]$, age- gravidity specific pregnancy rates (per 1,000 women year)										
Age interval in years (a)	Gravidity (i)									
	0	1	2	3	4	5	6	7	8	9+
10-12	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
13-14	2.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
15-19	75.0	257.9	264.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0
20-24	205.9	311.2	251.6	234.5	242.8	258.6	0.0	0.0	0.0	0.0
25-29	189.5	365.4	247.4	221.6	210.9	229.7	212.5	209.3	0.0	0.0
30-34	144.8	224.2	201.3	151.2	140.6	145.3	160.2	165.9	202.3	190.8
35-39	54.1	69.7	87.0	67.3	62.2	63.0	76.0	85.7	98.5	108.7
40-44	14.7	48.1	39.9	18.0	16.0	15.1	15.7	17.6	19.9	40.1
45-49	3.9	0.0	0.0	14.6	10.5	4.2	4.8	5.2	5.5	5.3

Table 5.6: Age specific background death rates, μ_a, estimated using data from Matlab Bangladesh (1994-2000) used for model validation.

Age interval in years	μ_a, background death rates (per 1,000 women years)
10-14	0.63
15-19	0.88
20-24	0.92
25-29	0.96
30-34	1.22
35-39	1.60
40-44	2.07
45-49	3.27

5.1.4 Sensitivity analysis

The age-gravidity pregnancy rates were calculated only for age-gravidity subgroup where the collective experience of all women in the subgroups had a total follow-up period of 75 women years or longer. For subgroups of less than 75 follow up years, the age-gravidity pregnancy rates was assumed to be zero. This 75 years cut off was set arbitrarily, and therefore I conducted sensitivity analyses assuming different cut offs, namely a minimum of 0, 25 or 50 years.

5.1.5 Analyses of fertility effect

I assessed the impact of fertility changes on pregnancy related mortality by comparing different childbearing composition assumptions to the baseline model, which was parameterised using 1983-1993 data from Matlab. I modelled two sets of scenarios: observed and theoretical. I modelled the actual changes in fertility observed in Matlab in 1983-93, 1994-99 and 2000-05. The theoretical changes are summarised in Table 5.7.

Table 5.7: Summary of the observed and theoretical fertility changes examined in this research.

	Description of assumed fertility schedules
Baseline model	1983-1993 parameter values for the model
Observed changes	
Scenario 1	1994-1999 pregnancy rates, other parameters at 1983-1993 levels.
Scenario 2	2000-2005 pregnancy rates, other parameters at 1983-1993 levels.
Theoretical changes	
Scenario 1	Assume women reached different maximum gravidities: a) $f_a[i]$=0 for $i \geq 9$ b) $f_a[i]$=0 for $i \geq 8$ ... i) $f_a[i]$=0 for $i \geq 1$. Other parameters at 1983-1993 levels.
Scenario 2	Assume no conceptions to women of older maternal ages: a) $f_a[i]$=0, for a=45-49 years b) $f_a[i]$=0, for a=40-49 years c) $f_a[i]$=0, for a=35-49 years Other parameters at 1983-1993 levels.
Scenario 3	No conceptions to girls aged 10 to 14 years, i.e. $f_{10-14}[i]$=0, other parameters at 1983-1993 levels.
Scenario 4	No conceptions to girls aged 10 to 19 years: a) $f_a^{new}[i]$ = 0, for a=10-19 years, where $f_a^{new}[i]$ assumed women waited until age 20 to conceive their first pregnancy, with subsequent pregnancies having the same inter-pregnancy interval. b) $f_a^{new\_adj}[i]$ =0, for a=10-19 years, where $f_a^{new\_adj}[i]$ have the same assumptions as $f_a^{new}[i]$, and are adjusted to take account of differential fecundity by age. Other parameters at 1983-1993 levels.
Scenario 5	Conceptions to women aged 20 or older, and assuming there were no conceptions to older women. a) $f_a^{new}[i]$=$f_a^{new\_adj}[i]$=0, for a=45-49 years b) $f_a^{new}[i]$=$f_a^{new\_adj}[i]$=0, for a=40-49 years c) $f_a^{new}[i]$=$f_a^{new\_adj}[i]$=0, for a=35-49 years Other parameters at 1983-1993 levels.
Scenario 6	Conceptions to women aged 20-39 years only, reaching different maximum gravidities: a) $f_a^{new}[i]$=$f_a^{new\_adj}[i]$=0 for all $i \geq 6$, a =40-49 years b) $f_a^{new}[i]$=$f_a^{new\_adj}[i]$=0 for all $i \geq 5$, a =40-49 years c) $f_a^{new}[i]$=$f_a^{new\_adj}[i]$=0 for all $i \geq 4$, a =40-49 years d) $f_a^{new}[i]$=$f_a^{new\_adj}[i]$=0 for all $i \geq 3$, a =40-49 years Other parameters at 1983-1993 levels.
Scenario 7	Conceptions to women aged 20-44 years only. Maximum gravidity = 6 a) Step one - 50% reduction in the baseline pregnancy rates of 40-44 year olds and gravidity 3 to 5 women. b) Step two – step one, and 20% reduction in the baseline pregnancy rates of 35-39 year olds and gravidity 2 women. Used both new fertility schedules Other parameters at 1983-1993 levels.

Observed fertility changes

To compare the effect of actual fertility changes in 1983-1993, 1994-1999 and 2000-2005, runs of the model were made using different period pregnancy rates, whilst keeping all other parameters at baseline level (1983-1993). The difference observed between the indicators as a result would be the change in the pregnancy related mortality attributable to actual fertility changes in Matlab between the calendar periods, 1994-99 and 2000-05 and the baseline calendar period of 1983-1993.

Theoretical fertility changes

The following seven scenarios in fertility changes were considered:

Scenario one: eliminate high gravidity conceptions.

This scenario assumed that women have a decreasing maximum number of total pregnancies. I started off assuming women reached a maximum of gravidity nine, i.e. $f_a[i]$=0 for all $i \geq 9$, then I assumed women reached a maximum of gravidity eight, i.e. $f_a[i]$=0 for all $i \geq 8$, etc, until women were assumed to have a maximum of one pregnancy each, $f_a[i]$=0 for all $i \geq 1$. All other parameters were kept at baseline levels.

Scenario two: eliminate conceptions to older women.

I assumed there were no conceptions to women of older maternal ages, starting from no conceptions to women aged 45 or older, i.e. $f_a[i]$=0, for a=45-49, followed by no conceptions to women aged 40-49, and finally assuming no conceptions to women aged 35 to 49. Other pregnancy rates, death rates and pregnancy related mortality ratios were kept at baseline levels.

Scenario three: eliminate conceptions to young adolescents (<15 years old)

I assumed there were no conceptions to girls aged 10 to 14, i.e. $f_{10-14}[i]$=0. In Matlab, only 0.1% of pregnancies were to girls aged 10 to 14. So the effect of preventing childbearing to this age group was assumed to have negligible impact on the fertility schedules of the other ages. Apart from $f_{10-14}[i]$, all other parameters, including other age-gravidity pregnancy rates were kept at baseline levels.

Scenario four: eliminate conceptions to all adolescents (<20 years old)

I assumed there were no conceptions to girls aged 10 to 19, i.e. $f_a[i]$=0 for a =10-14 and 15-19. All death rates and pregnancy related mortality ratios were kept constant at baseline levels.

In Matlab, 18% of all conceptions of any gravidity between 1983 and 1993 were to adolescents aged 10 to 19, and these adolescents went on to have a total of 26,808 (33%) conceptions between 1983 and 1993. In addition, of these 14,689 adolescents, 19% had more than one pregnancy during their adolescence. So if these adolescents had to wait until age 20 before falling pregnant for the first time, the fertility schedules of the other age groups would be expected to change as a result of these delays in childbearing. This is especially true for age 20, the age at which a high proportion of pregnancies to the 14,689 adolescents would now occur in this scenario.

The original baseline pregnancy schedules will not take account of the expected rise of conceptions at age 20 as a result of delayed childbearing. So using the baseline pregnancy schedule (Table 5.1) would underestimate the pregnancy rates, especially for the pregnancies to younger women of lower gravidities.

New age-gravidity pregnancy rates, $f_a^{new}[i]$, were estimated assuming all women with an estimated conception date between ages 10 and 19 waited until their 20th birthday to conceive their first pregnancy. Any subsequent conceptions to these women were also assumed to take place after age 20, and were assumed to follow with the same inter-pregnancy outcome interval as the observed intervals in the data. No changes were made to women who did not or were not known to have a conception between ages 10 to 19. The shifts proposed are illustrated in Table 5.8.

Women aged 10 to 19 can, in theory, be gravidity one or higher. However, during 1983-1993 in Matlab, the majority (91%) of women who had a conception between 10 and 19 had their first pregnancy outcome. Women who had higher gravidity conceptions between ages 10 and 19, and had missing information of their lower gravidity pregnancies were assumed to have their second conception at age 21, third conception at age 22, etc. Of the women who had a conception between ages 10 and 19 in Matlab in the baseline period, only 1.8% of women had a conception order higher than two.

Women who conceived pregnancies between ages 10 and 19 were artificially aged by assuming an earlier date of birth (Table 5.8). Here, I have implicitly assumed that all other events women experienced, such as subsequent pregnancies, migration or deaths were shifted to a later maternal age.

The pregnancy rates for the first two pregnancies to women aged 20 years, $f_{20}^{new}[i], i = 0,1,$ were expected to increase substantially due to the delayed childbearing. Thus separate gravidity specific pregnancy rates were calculated for women aged 20 years who were having their first or second pregnancies. The age groups used for the new pregnancy rates included: 20, 21-24, 25-29, 30-34, 35-39, 40-44 and 45-49 years.

Table 5.8: Illustration of the assumptions and method used to calculate the new age-gravidity pregnancy rates that shift conceptions to women aged 20 or older.

Observed events

Date of birth of woman	Year of conception	maternal age at conception (years)	pregnancy order
1977	1990	13	1
1977	1995	18=13+5	2
1977	1999	22=18+4	3
1977	2003	26=22+4	4

Assumed events

Date of birth of woman	Year of conception	maternal age at conception (years)	pregnancy order
1970	1990	20	1
1970	1995	25=20+5	2
1970	1999	29=25+4	3
1970	2003	33=29+4	4

The new fertility schedules, $f_a^{new}[i]$, do not take account of differential fecundity at different ages. On average if adolescents delayed childbearing until 20 year old, the pregnancy rate may be higher compared to the same women conceiving during adolescence due to sub-fecundity in the adolescent years. In contrast, if women waited until older maternal ages to conceive, the pregnancy rates may be lower due to sub-fecundity at older maternal ages. A second set of fertility schedules, $f_a^{new\_adj}[i]$, were calculated weighting pregnancies to women who have delayed their childbearing from adolescence according to the relative fecundity rates reported by Bongaarts and Potter [328]. The age specific fecundity rate estimated by Bongaarts and Potter are shown in Table 5.9. In addition to their estimates, I have assumed that the fecundity rates of 10 to 14 year olds were 75% of adolescents aged 15 to 19 years. Looking at the previous example (Table 5.8), the first conception at 13 years old, would be delayed until age 20, and this conception would be weighted 682/511=1.34 to take account sub-fecundity at age

13. Similarly the last conception, now at age 33 would be weighted 414/641=0.66 to take account of sub-fecundity at conceiving at age 33 compared to age 26.

Table 5.9: Age specific fecundity rates reported by Bongaarts and Potter [328] and I have assumed that the fecundity rate for 10-14 year olds were 75% of adolescents aged 15-19 years.

Age group (years)	Fecundity Rate (per 1,000 women)
10-14	384
15-19	511
20-24	682
25-29	641
30-34	549
35-39	414
40-44	205
45-49	59

The new fertility schedules assume women do not reduce their inter-pregnancy outcome intervals to "catch-up" on their missed childbearing opportunities.

Scenario five: eliminate conceptions to women of extreme ages

This scenario is a combination of scenarios two and four, limiting conceptions to women aged 20 or older and assuming older women do not fall pregnant, i.e. the new fertility schedules under scenario four, $f_a^{new}[i]=f_a^{new\_adj}[i]=0$ for a = 45-49 years, then a=40-49 years, and finally a=35-49 years. Other parameters were kept at baseline levels.

Scenario six: eliminate conceptions to women of extreme ages, and higher gravidities

This scenario is a combination of scenarios one and five. I assumed conceptions to women aged between 20-39 only using the new fertility schedules from scenario four and I assumed women have a decreasing number of pregnancies each, from a maximum of gravidity six down to three, i.e. $f_a^{new}[i]=f_a^{new\_adj}[i]=0$ for all a = 40-44, 45-49 years and i≥6, then i≥5, .., i≥3.

All other parameters at assumed to be at baseline levels.

Scenario seven: eliminate and reduce conceptions to women for a combination high risk groups

To assess a more realistic version of scenario six, women were assumed to confine their conceptions to ages 20-44 years, and reach a maximum of gravidity six. In addition, step one of

the fertility reduction assumed 50% reductions to the baseline pregnancy rates of women aged 40-44 years and gravidity three to five women. The baseline pregnancy rates of women who fell within both combinations, e.g. women aged 40-44 who were gravidity four were assumed to have their fertility reduce by 50% once only.

Step two of the fertility reduction assumed all reductions up to step one, i.e. conceptions to women aged 20-44, reaching a maximum of gravidity six only, 50% reduction to the baseline pregnancy rates of women aged 40-44 years and to women of gravidity three to five. In addition, a further 20% reduction to the pregnancy rates of women aged 35-39 and to gravidity two women who were not already affected by previous fertility reductions.

These reductions were explored using the new fertility schedules with and without adjusting for different fecundity by age. All other parameters were assumed to be at baseline levels.

5.2 Results

5.2.1 Model validation

The model was internally consistent; all 100,000 girls who started at age 10 were accounted for at each age.

The model predicted a total pregnancy rate of 3.9 pregnancies per woman for the period of 1994 to 2000. After taking account of pregnancy losses in different age groups, the total pregnancy rate was considered to be equivalent to 3.4 live births per woman, which is comparable to the average total fertility rate of 3.3 published in the DHS/BMMS reports over the same period.

Comparing in more detail, it is apparent that there were some discrepancies between the age specific fertility rates from the model and the published estimates in the DHS/BMMS. Women in my model have lower adolescent (15-19 year olds) fertility compared to the national average, and women aged between 25-34 years have higher fertility rates (Figure 5.3). However, this was mainly due to the differences in the fertility behaviour of women living in Matlab compared to the national average (Figure 5.3).

There were some small discrepancies between my model and ICDDR,B published age specific fertility rates since these two estimates were not directly comparable. The model estimates were based on the age of women at the conception of the live births. Whereas, the ICCDR,B

reports were the age of mother at the live birth event. For example, a considerable number of women who conceived age 20 would have their pregnancy outcome after age 20. Thus, the slightly higher fertility rates observed for younger ages and slightly lower rates for older maternal ages may be due in part to the delay between conception and live births.

The overall pregnancy related mortality ratio from my model was 382 (95% uncertainty interval (UCI): 318-462) deaths per 100,000 pregnancies for the period 1994-2000. For 1998-2001, BMMS reported a national pregnancy related mortality ratio of 382 per 100,000 live births from the household deaths and 400 (CI: 337-462) deaths per 100,000 live births estimated from sibling histories. For the period 1996-2001, BMMS reported a pregnancy related mortality ratio of 449 (CI: 400- 498) per 100,000 live births.

The overall model pregnancy related mortality rate was 0.43 (UCI: 0.29-0.44) pregnancy related deaths per 1,000 women for the period 1994-2000. This was compared to the pregnancy related mortality rate of 0.43 published in the BMMS from household deaths, and 0.46 pregnancy related deaths per 1,000 women published in the BMMS from sibling histories for the period 1998-2001. For the period of 1996-2001, BMMS reported a pregnancy related mortality rate of 0.55 deaths per 1,000 women, which was outside of the 95% uncertainty interval of my model estimate.

The overall pregnancy related mortality indicators were around 15%- 20% lower in my model for similar periods compared to published national estimates. However, Matlab has been noted previously as a region with better than national average maternal outcomes, including pregnancy related mortality [9, 329]. Thus it is reasonable to expect lower figures from my model which was parameterised using Matlab data.

There was more variation between the model and published national parameters when looking in more detail at the age specific pregnancy related mortality ratios and rates (Figure 5.4). The model age specific pregnancy related mortality ratios were lower for the higher maternal ages. The age specific pregnancy related mortality rates were higher for women aged 20-34 years, but this may be due to higher fertility in this group in Matlab compared to the national average (Figure 5.3)

Overall, the model output parameter estimates were within reasonable ranges of the published national parameters when taking account of differential fertility behaviour and health outcomes between Matlab and the national average in Bangladesh.

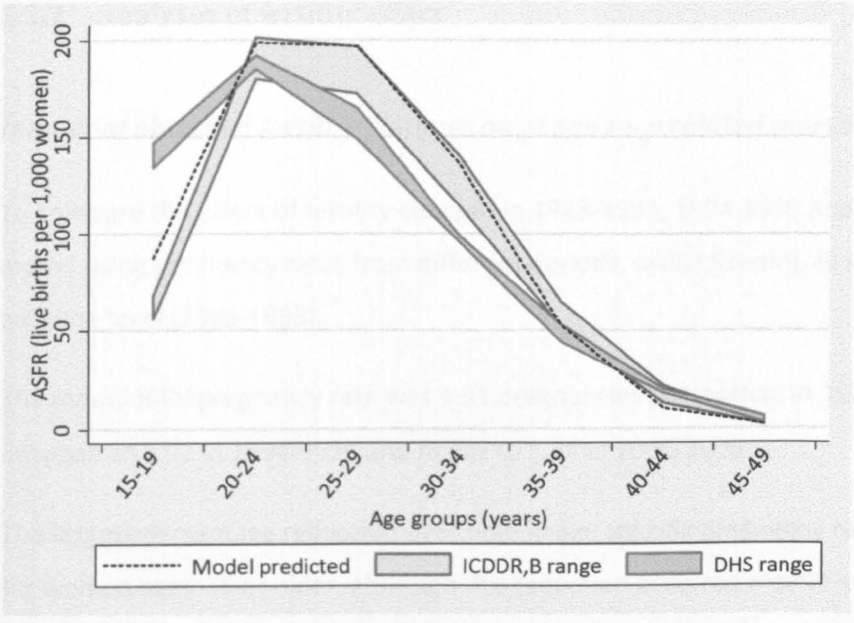

Figure 5.3: Model estimated age specific fertility rate (ASFR) for the period 1994-2000 compared to DHS/BMMS and ICDDR,B published estimates. The ranges represent the highest and lowest published age specific fertility rates in the external reports for the period 1994-2000.

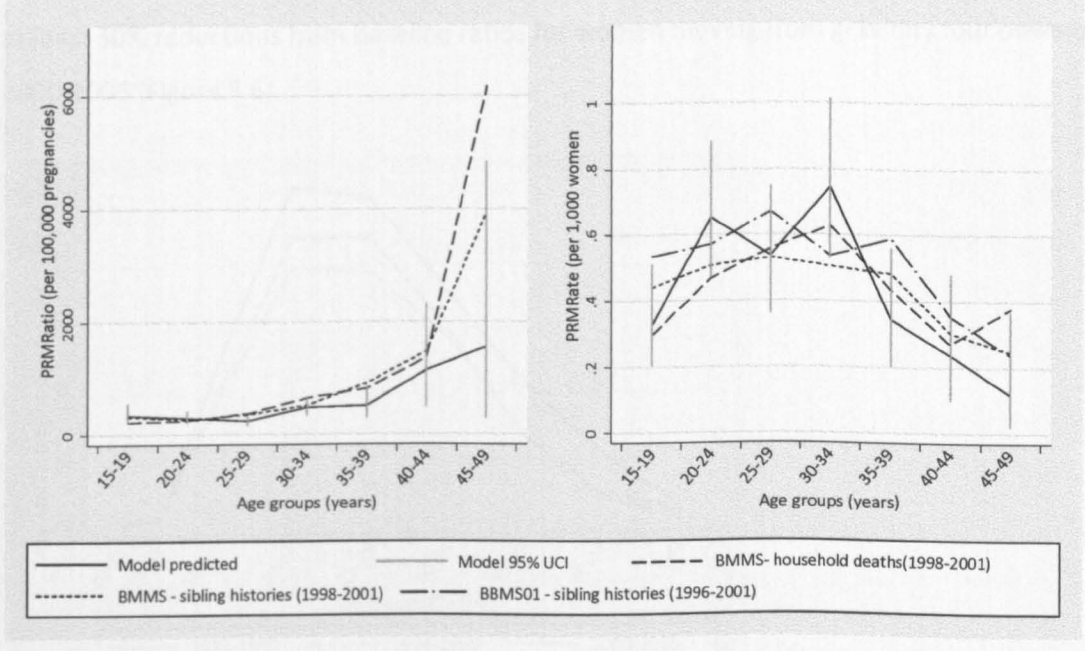

Figure 5.4: Model estimated pregnancy related mortality ratio and rate by different age groups compared to the BMMS reported indicators.

5.2.2 Analyses of fertility effect

Impact of observed fertility changes on pregnancy related mortality

To compare the effect of fertility changes in 1983-1993, 1994-1999 and 2000-2005, I ran the model using pregnancy rates from different periods, whilst keeping all other parameters at baseline level (1983-1993).

The model total pregnancy rate was 4.91 pregnancies per woman in 1983-1993, and this dropped to 3.92 in 1994-1999 and finally to 3.58 in 2000-2005.

The largest percentage reduction over time in age specific pregnancy rates in my model was for women aged 35 or older, although this reduction occurred mainly between 1983-1993 and 1994-1999. Steady reductions were also seen to the age specific pregnancy rates of younger women over the calendar periods (Figure 5.5).

Of all women who survived to the end of age 49 years old, the gravidity progression ratios reduced for all progressions except for progression to the first pregnancy (Figure 5.6). The percentage reductions were the highest for the higher gravidity progression ratios; there were at least 30% reductions from baseline ratios for women moving from gravidity four onwards by 2000-2005 (Figure 5.6).

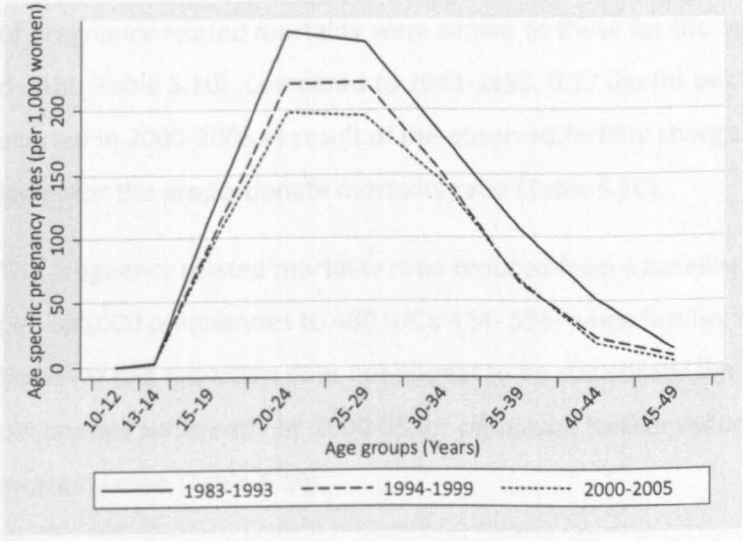

Figure 5.5: Model estimated age specific pregnancy rates for calendar periods 1983-1993, 1994-1999 and 2000-2005.

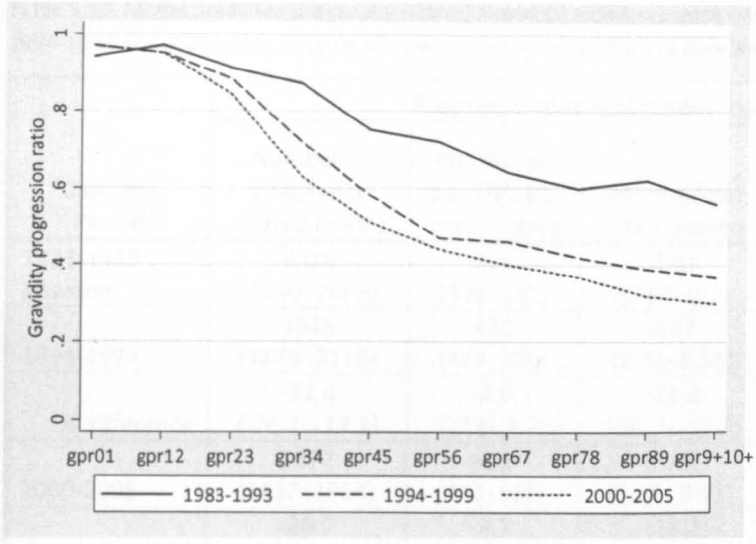

Figure 5.6: Model gravidity progression ratios for calendar periods 1983-1993, 1994-1999 and 2000-2005.

The model predicted 2328 (UCI: 2040- 2663) pregnancy related deaths using the baseline pregnancy rates from 1983 to 1993 (Table 5.10). The number of pregnancy related deaths reduced to 1825 (UCI: 1575- 2115) deaths by 1994-1999 and to 1677 (UCI: 1437-1964) deaths by 2000-2005 (Table 5.10). These changes were equivalent to a reduction of 21.6% (UCI: 17.1%-26.1%) in the number of pregnancy related deaths between 1983-1993 and 1994-1994, and 28.0% (UCI: 22.4%- 33.3%) reduction between 1983-1993 and 2000-2005.

The percentage reductions for both the pregnancy related mortality rate and the lifetime risk of pregnancy related mortality were similar to those for the number of pregnancy related deaths (Table 5.10). Compared to 1983-1993, 0.17 deaths per 1,000 women aged 10-49 were averted in 2000-2005 as result of the observed fertility changes. The reductions were slightly lower for the proportionate mortality ratio (Table 5.10).

The pregnancy related mortality ratio reduced from a baseline of 489 (UCI: 428- 561) deaths per 100,000 pregnancies to 480 (UCI: 414- 556) when fertility declined to 1994-1999 levels. However this reduction does not appear to be statistically significant. The fertility levels did not change sufficiently by 2000-05 for significant further reductions to the pregnancy related mortality ratio (Table 5.10).

Table 5.10: Model predicted pregnancy related mortality indicators using pregnancy rates from periods 1983-1993, 1994-1999 and 2000-2005, keeping all other parameters constant at baseline level.

Calendar Period	Pregnancy related mortality indicators (95% UCI)				
	Number of pregnancy related deaths	PRMRatio - per 100,000 pregnancies	PRMRate per 1000 women	Lifetime risk of pregnancy related death	Proportionate mortality ratio
1983-1983 baseline	2328 (2040- 2663)	489 (428- 561)	0.61 (0.53- 0.7)	0.02 (0.02- 0.03)	23.8 (21.4- 26.4)
1994-1999	1825 (1575- 2115)	480 (414- 556)	0.47 (0.41- 0.55)	0.02 (0.02- 0.02)	19.5 (17.3- 22.0)
% difference	*-21.6 (-26.1- -17.1)*	*-2.0 (-7.6- 3.7)*	*-21.8 (-26.3- -17.3)*	*-22.0 (-26.6- -17.5)*	*-17.6 (-21.6- -13.7)*
2000-2005	1677 (1437- 1964)	481 (412- 565)	0.44 (0.37- 0.51)	0.02 (0.01- 0.02)	18.2 (16.0- 20.7)
% difference	*-28.0 (-33.3- -22.4)*	*-1.7 (-8.9- 5.9)*	*-28.2 (-33.5- -22.6)*	*-28.4 (-34.0- -22.8)*	*-23.1 (-28.0- -18.2)*

Impact of theoretical fertility changes on pregnancy related mortality

Scenario one: eliminate high gravidity conceptions.

The total pregnancy rate dropped in an exponential fashion as women had a decreasing number of pregnancies (Figure 5.7). From a baseline rate of 4.91 pregnancies per woman, the total pregnancy rate fell to 4.36 if women reached a maximum of gravidity six. If all women were only to reach a maximum of gravidity three, the total pregnancy rate dropped to 2.69 and finally this dropped to 0.94 pregnancies if women reached a maximum of one pregnancy each (Figure 5.7). The proportion of first pregnancies increased as the maximum gravidity dropped, although only substantially once the maximum gravidity reached was four or lower (Figure 5.8). In addition, the proportion of pregnancies to women aged 35 or over decreased as the maximum gravidity reached decreased.

The age specific pregnancy rates reduced steadily from assuming a maximum of gravidity six onwards (Figure 5.9). The pregnancy rates of older women dropped the greatest since they were more likely to have higher gravidity pregnancies. Pregnancies to women aged 45-49 years were virtually eliminated if no women reached beyond gravidity five. As the maximum gravidity reached decreased, the pregnancy rates of younger women started to fall as well (Figure 5.9).

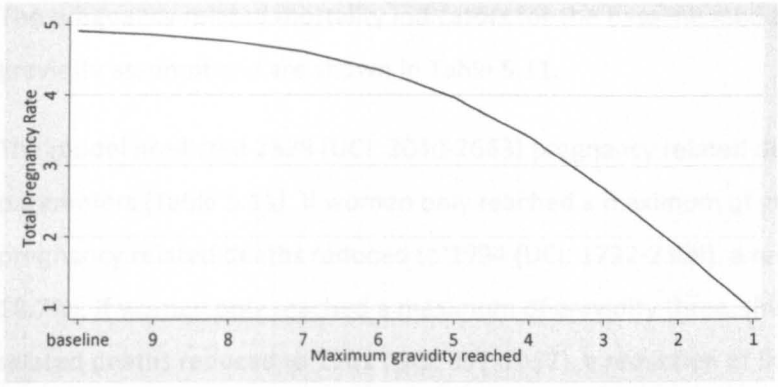

Figure 5.7: Changes in the total pregnancy rate as result of assuming women have a decreasing number of pregnancies.

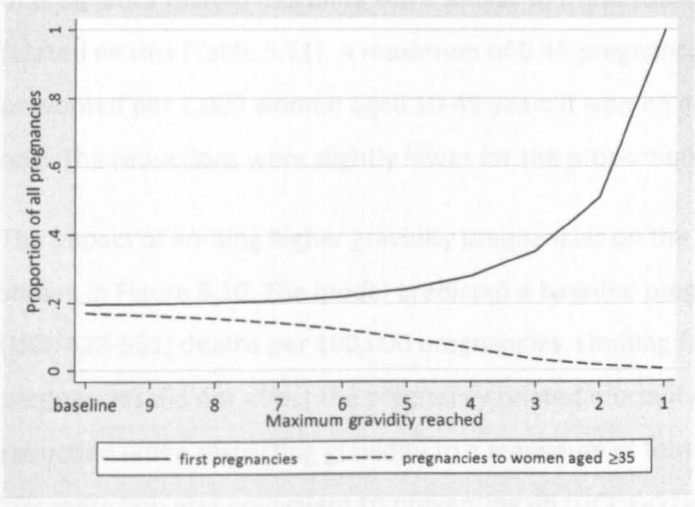

Figure 5.8: Proportion of first pregnancies and pregnancies to women aged 35 or older assuming different maximum gravidity reached by women.

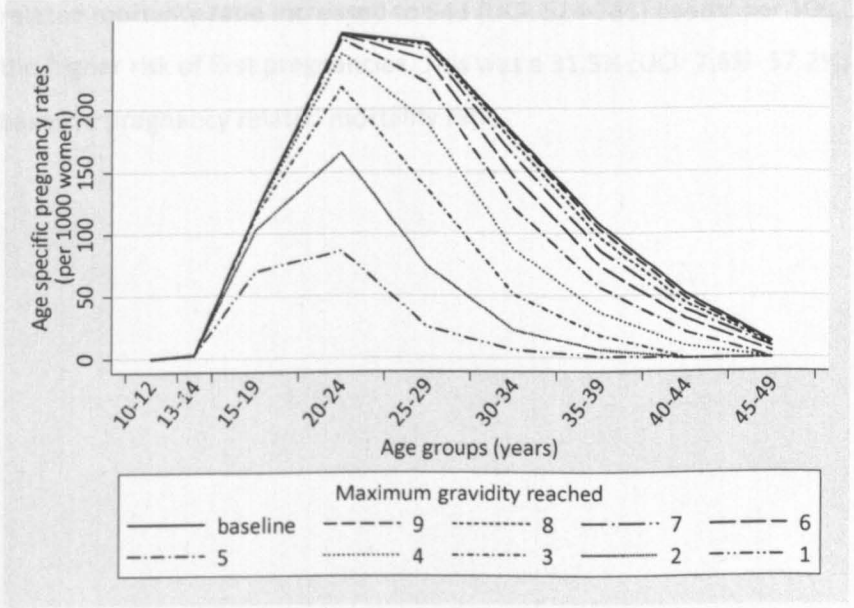

Figure 5.9: Age specific pregnancy rates as result of assuming different maximum gravidity reached by women.

The pregnancy related mortality indicators for the baseline model and models with different gravidity assumptions are shown in Table 5.11.

The model predicted 2328 (UCI: 2040-2663) pregnancy related deaths using baseline parameters (Table 5.11). If women only reached a maximum of gravidity six, the number of pregnancy related deaths reduced to 1994 (UCI: 1732-2304), a reduction of 14.4% (UCI: 11.1%-18.7%). If women only reached a maximum of gravidity three, the number of pregnancy related deaths reduced to 1161 (UCI: 992-1357), a reduction of 50.1% (UCI: 44.0%-56.3%).

The percentage reductions for both the pregnancy related mortality rate and the lifetime risk of pregnancy related mortality were similar to those found for the number of pregnancy related deaths (Table 5.11). A maximum of 0.45 pregnancy related deaths could potentially be prevented per 1,000 women aged 10-49 years if women only reached a maximum of gravidity one. The reductions were slightly lower for the proportionate mortality ratio (Table 5.11).

The impact of limiting higher gravidity pregnancies on the pregnancy related mortality ratio is shown in Figure 5.10. The model predicted a baseline pregnancy related mortality ratio of 489 (UCI: 428-561) deaths per 100,000 pregnancies. Limiting family size to a maximum of five pregnancies did not affect the pregnancy related mortality ratio, but there was a small reduction when restricting gravidity to a maximum of four (9.4% reduction, UCI: 1.3%-18.0%). The reduction was equivalent to preventing 46 (UCI: 6-92) deaths per 100,000 pregnancies. When families were restricted to a maximum of one pregnancy per woman, the pregnancy related mortality ratio increased to 643 (UCI: 524-781) deaths per 100,000 pregnancies, due to the higher risk of first pregnancies. This was a 31.5% (UCI: 7.6%- 57.2%) increase from the baseline pregnancy related mortality ratio.

Table 5.11: Pregnancy related mortality indicators for the baseline model and models assuming women reached different maximum gravidities.

Maximum gravidity reached	Pregnancy related mortality indicators (95% UCI)				
	Number of pregnancy related deaths	PRMRatio - per 100,000 pregnancies	PRMRate per 1000 women	Lifetime risk of pregnancy related death	Proportionate mortality ratio
baseline	2328 (2040- 2663)	489 (428- 561)	0.61 (0.53- 0.69)	0.02 (0.02- 0.03)	23.7 (21.4- 26.3)
9	2295 (2006- 2626)	488 (426- 558)	0.60 (0.52- 0.68)	0.02 (0.02- 0.03)	23.4 (21.1- 26)
% difference	*-1.4 (-2.1- -0.9)*	*-0.4 (-1.1- 0.2)*	*-1.4 (-2.2- -0.9)*	*-1.5 (-2.2- -0.9)*	*-1.1 (-1.7- -0.7)*
8	2249 (1959- 2583)	487 (424- 560)	0.58 (0.51- 0.67)	0.02 (0.02- 0.03)	23.1 (20.7- 25.7)
% difference	*-3.4 (-5.0- -2.2)*	*-0.5 (-2.2- 0.7)*	*-3.4 (-5.1- -2.2)*	*-3.5 (-5.2- -2.3)*	*-2.6 (-4.0- -1.7)*
7	2154 (1879- 2486)	482 (420- 556)	0.56 (0.49- 0.65)	0.02 (0.02- 0.03)	22.3 (20- 24.9)
% difference	*-7.5 (-10.5- -5.3)*	*-1.6 (-4.8- 0.7)*	*-7.5 (-10.6- -5.3)*	*-7.7 (-10.8- -5.4)*	*-5.9 (-8.3- -4.1)*
6	1994 (1732- 2304)	471 (409- 545)	0.52 (0.45- 0.6)	0.02 (0.02- 0.02)	21.0 (18.7- 23.5)
% difference	*-14.4 (-18.7- -11.1)*	*-3.8 (-8.6- -0.1)*	*-14.4 (-18.8- -11.1)*	*-14.7 (-19.1- -11.3)*	*-11.5 (-15.0- -8.7)*
5	1784 (1539- 2069)	463 (399- 537)	0.46 (0.4- 0.54)	0.02 (0.02- 0.02)	19.2 (17.0- 21.6)
% difference	*-23.4 (-28.8- -18.8)*	*-5.5 (-12.2- 0.2)*	*-23.5 (-29.0- -18.9)*	*-23.9 (-29.5- -19.3)*	*-19.1 (-23.7- -15.1)*
4	1476 (1268- 1708)	443 (380- 513)	0.38 (0.33- 0.44)	0.02 (0.01- 0.02)	16.4 (14.4- 18.5)
% difference	*-36.6 (-42.6- -30.9)*	*-9.4 (-18.0- -1.3)*	*-36.8 (-42.8- -31.1)*	*-37.3 (-43.5- -31.5)*	*-30.8 (-36.4- -25.7)*
3	1161 (992- 1357)	442 (377- 517)	0.30 (0.26- 0.35)	0.01 (0.01- 0.01)	13.3 (11.6- 15.3)
% difference	*-50.1 (-56.3- -44)*	*-9.7 (-21.0- 1.3)*	*-50.3 (-56.6- -44.2)*	*-50.8 (-57.1- -44.7)*	*-43.7 (-49.8- -37.8)*
2	920 (772- 1080)	505 (424- 594)	0.24 (0.2- 0.28)	0.01 (0.01- 0.01)	10.9 (9.3- 12.5)
% difference	*-60.4 (-65.9- -54.9)*	*3.4 (-10.7- 17.8)*	*-60.7 (-66.0- -55.1)*	*-61.1 (-66.6- -55.7)*	*-54.2 (-59.7- -48.3)*
1	597 (486- 725)	643 (524- 781)	0.15 (0.13- 0.19)	0.01 (0.00- 0.01)	7.3 (6.0- 8.7)
% difference	*-74.3 (-79.0- -69.3)*	*31.5 (7.6- 57.2)*	*-74.5 (-79.2- -69.5)*	*-74.9 (-79.4- -69.9)*	*-69.2 (-74.2- -63.6)*

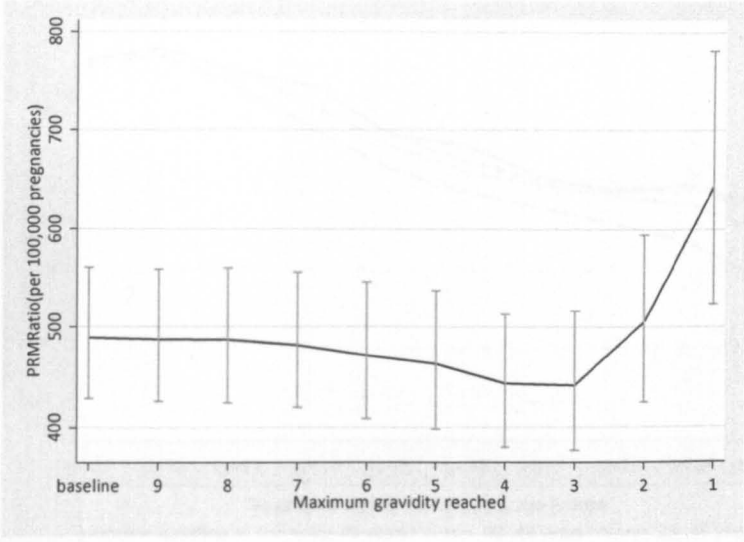

Figure 5.10: Model predicted changes in the pregnancy related mortality ratio under different assumptions of maximum gravidity reached by women.

Scenario two: eliminate conceptions to older women.

The total pregnancy rate reduced from 4.91 pregnancies per woman to 4.06 if conceptions to women aged 35 or older were eliminated. Due to the small number of conceptions to women aged 45 or older, the impact on the total pregnancy rate was relatively small (Figure 5.11).

If no conceptions occurred to older women, the higher gravidity progression ratios reduced by the greatest percentages since older women were more likely to have higher gravidity pregnancies (Figure 5.12).

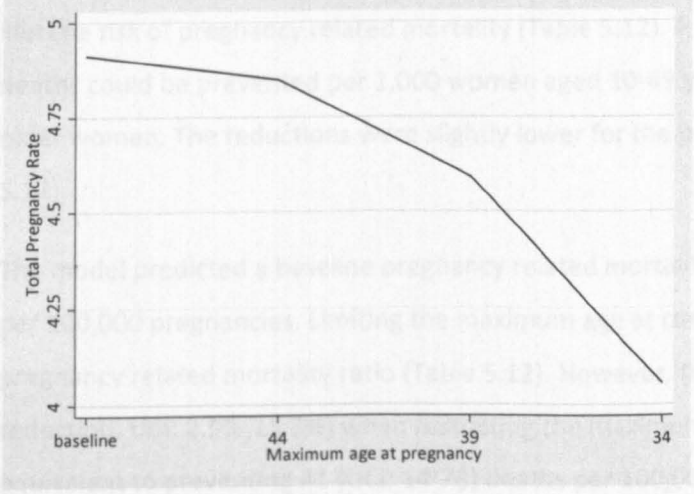

Figure 5.11: Changes in the total pregnancy rate assuming no conceptions to older maternal ages.

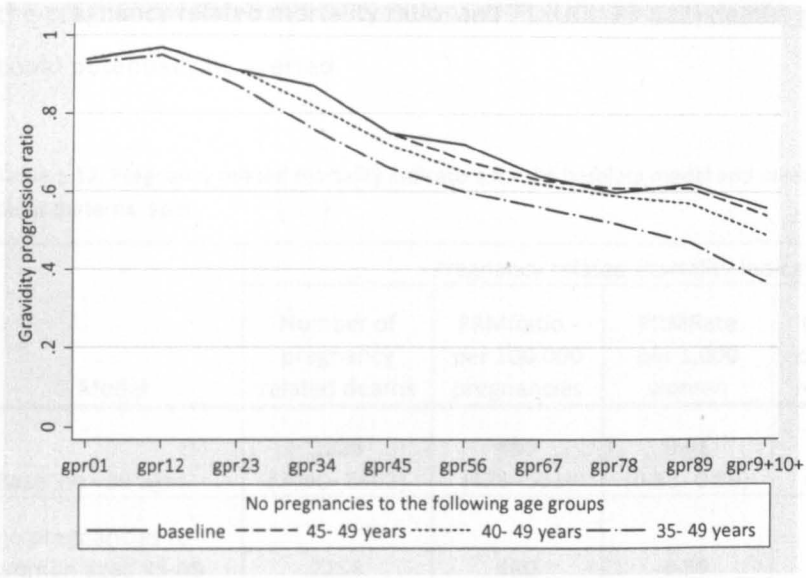

Figure 5.12: Gravidity progression ratios among women alive at the end of age 49 years in the baseline model and the comparison models assuming no conceptions to older maternal ages.

The pregnancy related mortality indicators for the baseline model and models assuming no conceptions to older women are shown in Table 5.12.

The model predicted 2328 (UCI: 2040-2663) pregnancy related deaths using baseline parameters (Table 5.12). If there were no conceptions to women aged 45-49, the number of pregnancy related deaths reduced to 2254 (UCI: 1975-2579), a small reduction of 3.1 % (UCI: 0.9%-7.3%). If no women older than 34 were to fall pregnant, the number of pregnancy related deaths reduced to 1654 (UCI: 1454-1965) deaths, a reduction of 28.8% (UCI: 22.8%-36.0%).

Similar percentage reductions were found for the pregnancy related mortality rate and the lifetime risk of pregnancy related mortality (Table 5.12). A maximum of 0.18 pregnancy related deaths could be prevented per 1,000 women aged 10-49 year old assuming no conceptions to older women. The reductions were slightly lower for the proportionate mortality ratios (Table 5.12).

The model predicted a baseline pregnancy related mortality ratio of 489 (UCI: 428- 561) deaths per 100,000 pregnancies. Limiting the maximum age at conception to age 44 did not affect the pregnancy related mortality ratio (Table 5.12). However, there was a small reduction (8.3% reduction, UCI: 2.9%-15.3%) when restricting the maximum age at conception at 39 years old, equivalent to preventing 41 (UCI: 14-78) deaths per 100,000 pregnancies. Further, if no women older than 34 were to fall pregnant, there was a 14.3% (UCI: 7.0%-22.9%) reduction in

the pregnancy related mortality ratio, and 71 (UCI: 33-121) deaths per 100,000 pregnancies could potentially be averted.

Table 5.12: Pregnancy related mortality indicators for the baseline model and models assuming no conceptions to older maternal ages.

Model	Pregnancy related mortality indicators (95% UCI)				
	Number of pregnancy related deaths	PRMRatio - per 100,000 pregnancies	PRMRate per 1,000 women	Lifetime risk of pregnancy related death	Proportionate mortality ratio
Baseline - all ages	2328 (2040- 2663)	489 (428- 561)	0.61 (0.53- 0.69)	0.02 (0.02- 0.03)	23.7 (21.4- 26.3)
no pregnancies to women aged 45-49 years	2254 (1975- 2579)	480 (420- 550)	0.59 (0.51- 0.67)	0.02 (0.02- 0.03)	23.1 (20.8- 25.7)
% difference	*-3.1 (-7.3- -0.9)*	*-1.9 (-6.2- 0.3)*	*-3.1 (-7.4- -0.9)*	*-3.3 (-7.7- -1.0)*	*-2.4 (-5.7- -0.7)*
no pregnancies to women aged 40-49 years	2000 (1768- 2286)	449 (396- 514)	0.52 (0.46- 0.6)	0.02 (0.02- 0.02)	21.0 (19.1- 23.4)
% difference	*-14.0 (-20.6- -9.0)*	*-8.3 (-15.3- -2.9)*	*-14.1 (-20.7- -9.0)*	*-14.6 (-21.4- -9.3)*	*-11.1 (-16.6- -7.1)*
no pregnancies to women aged 35-49 years	1654 (1454- 1865)	419 (368- 473)	0.43 (0.38- 0.49)	0.02 (0.01- 0.02)	18.0 (16.2- 19.9)
% difference	*-28.8 (-36- -22.8)*	*-14.3 (-22.9- -7.0)*	*-28.9 (-36.1- -22.9)*	*-29.6 (-37.0- -23.4)*	*-23.8 (-29.9- -18.6)*

Scenario three: eliminate conceptions to young adolescents (<15 years old)

There was a negligible impact on the parameters of interest if conception was restricted to women aged 15 or over since there were only 531 (0.1%) pregnancies to girls under 15 years old in the model (Table 5.13).

Table 5.13: Pregnancy related mortality indicators for the baseline model, and comparison scenario of no conceptions to girls aged 10-14.

Model	Pregnancy related mortality indicators (95% UCI)				
	Number of pregnancy related deaths	PRMRatio - per 100,000 pregnancies	PRMRate per 1000 women	lifetime risk of pregnancy related death	proportionate mortality ratio
Baseline- all ages	2328 (2040- 2663)	489 (428- 561)	0.61 (0.53- 0.69)	0.02 (0.02- 0.03)	23.7 (21.4- 26.3)
no pregnancies to girls aged 10-14 years	2309 (2023- 2643)	487 (426- 558)	0.60 (0.53- 0.69)	0.02 (0.02- 0.03)	23.5 (21.2- 26.1)
% difference	-0.8 (-2.3- -0.2)	-0.6 (-2.1- 0.1)	-0.8 (-2.3- -0.2)	-0.8 (-2.3- -0.2)	-0.6 (-1.8- -0.1)

Scenario four: eliminate conceptions to all adolescents (<20 years old)

Using $f_a^{new}[i]$ which did not adjust for differential fecundity by age, the total pregnancy rate increased slightly from 4.91 to 4.96 pregnancies per woman. Gravidity progression ratios reduced for higher gravidity levels as delayed childbearing effectively reduced the reproductive span of women in the cohort (Figure 5.13). Using $f_a^{new\_adj}[i]$, which adjusted for differential fecundity by age, the total pregnancy rate rose to 5.24 pregnancies per woman. The gravidity progression ratio reductions were slightly lower than those observed without adjustment (Figure 5.13).

Restricting conceptions to women aged 20 or older resulted in a substantial increase in the pregnancy rates for 20-24 year olds due to delayed childbearing. The pregnancy rate adjusting for fecundity, which takes account of sub-fecundity in the adolescent period, was higher for women aged 20-24 compared to rates without adjustment (Figure 5.14). Similarly, the fecundity adjusted pregnancy rates, which took account of sub-fecundity in older maternal ages were slightly lower for women aged 30 or older compared to the rates without adjustment (Figure 5.14).

Eliminating conceptions to adolescents had little effect on any of the pregnancy related mortality indicators, whether adjusting for fecundity or not (Table 5.14).

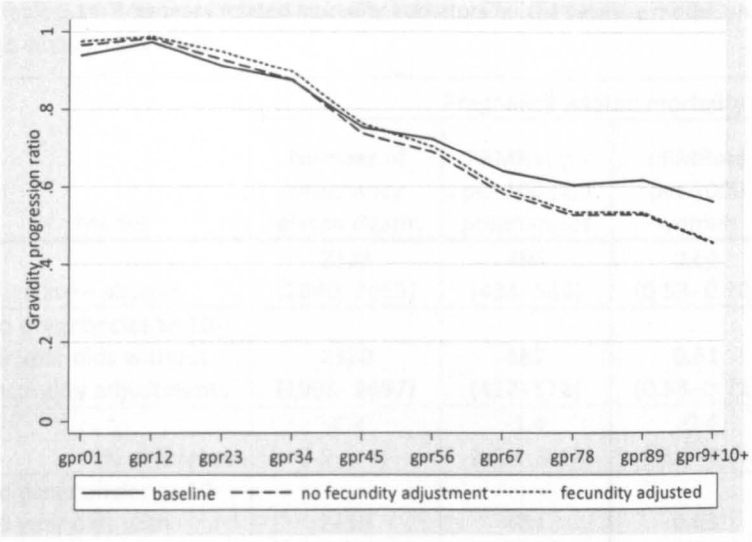

Figure 5.13: Gravidity progression ratio in the baseline model and model assuming no conceptions to adolescents (<20 years old).

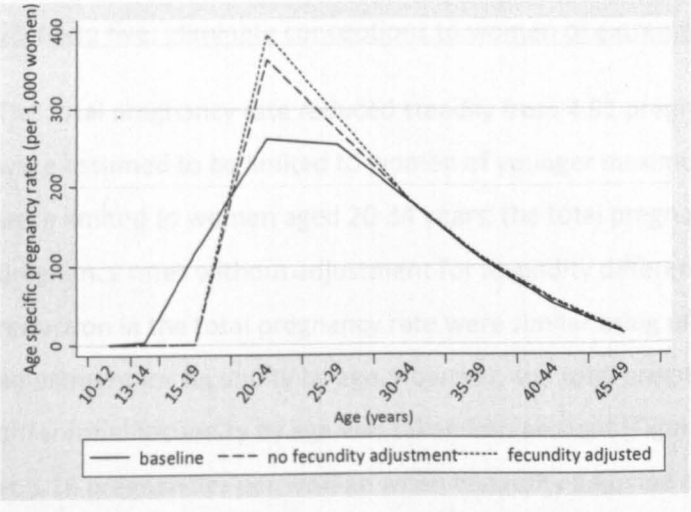

Figure 5.14: Age specific pregnancy rate in the baseline model and models assuming no conceptions to adolescents (<20 years old)

Table 5.14: Pregnancy related mortality indicators for the baseline model, and comparison model of no conceptions to women aged 10-19.

Model	Pregnancy related mortality indicators (95% UCI)				
	Number of pregnancy related deaths	PRMRatio - per 100,000 pregnancies	PRMRate per 1000 women	Lifetime risk of pregnancy related death	Proportionate mortality ratio
Baseline – all ages	2328 (2040- 2663)	495 (433- 569)	0.61 (0.53- 0.70)	0.02 (0.02- 0.03)	23.8 (21.5- 26.5)
no pregnancies to 10-19 year olds without fecundity adjustments	2320 (1995- 2697)	487 (422- 571)	0.61 (0.53- 0.71)	0.02 (0.02- 0.03)	23.7 (21.3- 26.8)
% difference	*-0.4 (-5.3- 4)*	*-1.4 (-6.4- 3.1)*	*-0.4 (-5.5- 4.0)*	*-0.2 (-5.2- 4.1)*	*-0.3 (-4.3- 3.1)*
no pregnancies to 10-19 year olds with fecundity adjustments	2419 (2086- 2797)	484 (422- 565)	0.63 (0.55- 0.74)	0.03 (0.02- 0.03)	24.5 (22.0- 27.5)
% difference	*3.9 (-1.2- 8.3)*	*-2.5 (-7.3- 1.8)*	*3.9 (-1.3- 8.4)*	*4.1 (-0.9- 8.5)*	*3.0 (-0.9- 6.4)*

Scenario five: eliminate conceptions to women of extreme ages.

The total pregnancy rate reduced steadily from 4.91 pregnancies per woman as conceptions were assumed to be limited to women of younger maximum ages (Figure 5.15). If conceptions were limited to women aged 20-34 years, the total pregnancy rate would be 4.07 using pregnancy rates without adjustment for fecundity differentials by age. The patterns of reduction in the total pregnancy rate were similar using pregnancy rates with or without adjustment for fecundity by age. However, the total pregnancy rate was consistently higher if differential fecundity by age was taken into account (Figure 5.15). The total pregnancy peaked at 5.16 pregnancies per woman when fecundity adjusted pregnancy rates were used.

Compared to the baseline estimates, there were between 3% to 22% reductions in the gravidity progression from six to seven when fecundity differentials by age were not taken into account. The percentage reductions generally increased with increasing gravidity (Figure 5.16). The percentage reductions to the gravidity progression ratios were slightly lower when using fertility schedules adjusting for fecundity differentials by age, but the patterns were similar (Figure 5.16). There were larger reductions to the higher gravidity progression ratios since older women were more likely to have higher gravidity conceptions.

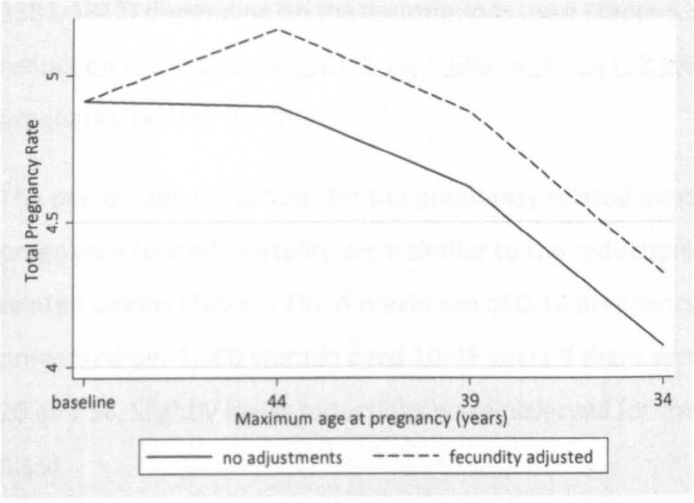

Figure 5.15: Changes in the total pregnancy rate as result of assuming no conceptions to adolescents (<20 years old), and truncating the end of the reproductive span at different ages.

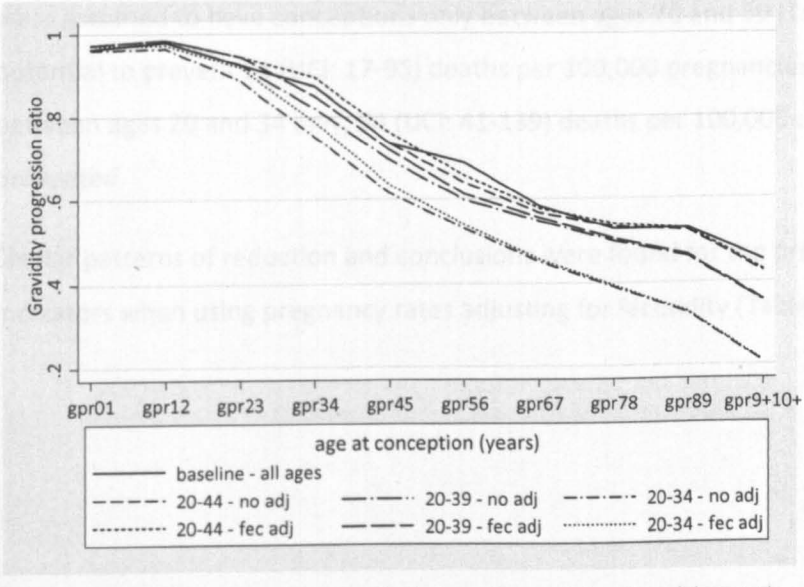

Figure 5.16: Gravidity progression ratio in the baseline model and model assuming no conceptions to adolescents (<20 years old), and truncating the end of the reproductive span at different ages.

The pregnancy related mortality indicator estimates for the baseline model and models assuming no conceptions to adolescents and older maternal ages using pregnancy rates without adjustment for fecundity differentials are shown in Table 5.15. The corresponding results using pregnancy rates with adjustment for fecundity differentials are shown in Table 5.16. The model predicted 2328 (UCI: 2040-2663) pregnancy related deaths using baseline parameters Table 5.15. Using pregnancy rates without adjustment for differential fecundity by age, the number of pregnancy related deaths ranged from 2239 (UCI: 1914-2595) to 1609 (UCI:

1381-1842) depending on the assumptions used (Table 5.15). This was equivalent to a reduction range of 3.8% (UCI: 1.1%-9.6%) to 30.8% (23.8%-38.5%) from the baseline number of pregnancy related deaths.

The percentage reductions for the pregnancy related mortality rate and the lifetime risk of pregnancy related mortality were similar to the reductions found for the number of pregnancy related deaths (Table 5.15). A maximum of 0.19 pregnancy related deaths could potentially be prevented per 1,000 women aged 10-49 years if there were only conceptions to women aged 20 and 34. Slightly lower reductions were observed for the proportionate mortality ratio (Table 5.15).

The model predicted a baseline pregnancy related mortality ratio of 489 (UCI: 428-561) deaths per 100,000 pregnancies. Using pregnancy rates without adjustment for differential fecundity by age, significant reduction of the pregnancy related mortality ratio was observed if women were assumed to have conceptions only between ages 20 and 39 (Table 5.15). There was a potential to prevent 51 (UCI: 17-95) deaths per 100,000 pregnancies. If women conceived between ages 20 and 34 only, 84 (UCI: 41-139) deaths per 100,000 deaths may potentially be prevented.

Similar patterns of reduction and conclusions were found for the pregnancy related mortality indicators when using pregnancy rates adjusting for fecundity (Table 5.16).

Table 5.15: Pregnancy related mortality indicators for the baseline model and comparison models, using pregnancy rates without adjustment for fecundity differentials, assuming no conceptions to women younger than 20, and truncating the end of the reproductive span at different ages.

Model	Pregnancy related mortality indicators (95% UCI)				
	Number of pregnancy related deaths	PRMRatio - per 100,000 pregnancies	PRMRate per 1000 women	Lifetime risk of pregnancy related death	Proportionate mortality ratio
Baseline - all ages	2328 (2040- 2663)	489 (428- 561)	0.61 (0.53- 0.69)	0.02 (0.02- 0.03)	23.7 (21.4- 26.3)
Pregnancies only women aged 20-44	2239 (1914- 2595)	473 (403- 549)	0.58 (0.5- 0.68)	0.02 (0.02- 0.03)	23.0 (20.3- 25.8)
% difference	*-3.8 (-9.6- 1.1)*	*-3.5 (-9.3- 1.5)*	*-3.9 (-9.7- 1.1)*	*-3.9 (-9.7- 1.1)*	*-3.0 (-7.6- 0.8)*
Pregnancies only to women aged 20-39	1964 (1688- 2264)	438 (376- 505)	0.51 (0.44- 0.59)	0.02 (0.02- 0.02)	20.7 (18.3- 23.2)
% difference	*-15.6 (-22.9- -9.2)*	*-10.4 (-18.2- -3.5)*	*-15.7 (-23- -9.2)*	*-16.0 (-23.5- -9.5)*	*-12.5 (-18.6- -7.3)*
Pregnancies only women aged 20-34	1609 (1381- 1842)	406 (348- 465)	0.42 (0.36- 0.48)	0.02 (0.01- 0.02)	17.6 (15.5- 19.7)
% difference	*-30.8 (-38.5- -23.8)*	*-17.0 (-26.2- -8.6)*	*-31.0 (-38.7- -23.9)*	*-31.5 (-39.3- -24.4)*	*-25.6 (-32.5- -19.4)*

Table 5.16: Pregnancy related mortality indicators for the baseline model and comparison models, using pregnancy rates with adjustment for fecundity differentials, assuming no conceptions to women younger than 20, and truncating the end of the reproductive span at different ages.

Model	Pregnancy related mortality indicators (95% UCI)				
	Number of pregnancy related deaths	PRMRatio - per 100,000 pregnancies	PRMRate per 1000 women	Lifetime risk of pregnancy related death	Proportionate mortality ratio
Baseline - all ages	2328 (2040- 2663)	489 (428- 561)	0.61 (0.53- 0.69)	0.02 (0.02- 0.03)	23.7 (21.4- 26.3)
Pregnancies only to women aged 20-44 only	2332 (2004- 2698)	467 (401- 541)	0.61 (0.52- 0.7)	0.02 (0.02- 0.03)	23.7 (21.1- 26.5)
% difference	*0.2 (-5.9- 5.1)*	*-4.7 (-10.5- 0.1)*	*0.2 (-5.9- 5.2)*	*0.1 (-5.9- 5.1)*	*0.1 (-4.6- 3.9)*
Pregnancies only to women aged 20-39	2049 (1773- 2346)	433 (374- 496)	0.53 (0.46- 0.61)	0.02 (0.02- 0.02)	21.5 (19.1- 23.9)
% difference	*-11.9 (-19.5- -5.1)*	*-11.5 (-19.1- -4.6)*	*-12.0 (-19.6- -5.1)*	*-12.3 ((-20.1- -5.4)*	*-9.4 (-15.7- -4.0)*
Pregnancies only to women aged 20-34	1689 (1459- 1925)	401 (346- 458)	0.44 (0.38- 0.5)	0.02 (0.01- 0.02)	18.3 (16.2- 20.4)
% difference	*-27.3 (-35.3- -19.9)*	*-17.9 (-26.9- -9.5)*	*-27.5 (-35.5- -20.0)*	*-28.1 (-36.2- -20.5)*	*-22.5 (-29.5- -16.1)*

Scenario six: eliminate conceptions to women of extreme ages and higher gravidities

Using pregnancy rate without adjustment for fecundity, the total pregnancy rate reduced from 4.91 to 4.32 pregnancies per woman if only woman aged 20-39 had pregnancies and reached a maximum of gravidity six (Figure 5.17). This decreased further to 2.79 pregnancies per woman if women only reached a maximum of gravidity three. The patterns of reduction were similar using pregnancy rates with adjustment for fecundity differential by age. However, the total pregnancy rate level was consistently higher if differential fecundity by age was taken into account (Figure 5.17).

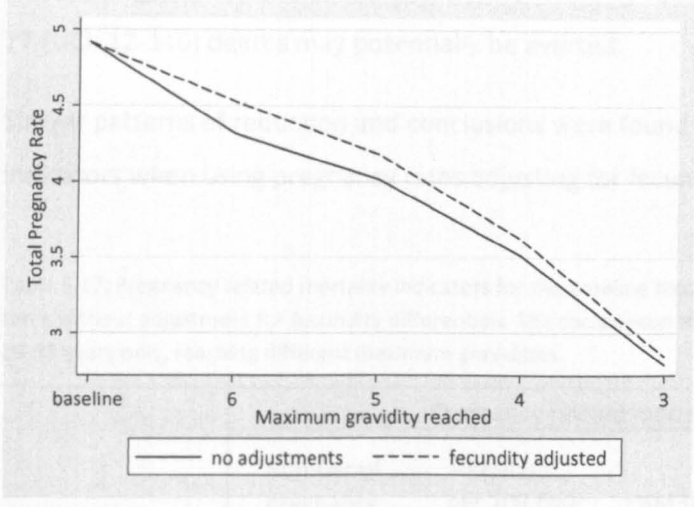

Figure 5.17: Changes in the total pregnancy rate assuming conceptions to women aged 20-39, reaching different maximum gravidities.

The impact of restricting conceptions to women aged 20-39 and reaching different maximum gravidities on the pregnancy related mortality indicators, using pregnancy rates without adjustment for fecundity differentials, are shown in Table 5.17. The corresponding results using pregnancy rates with adjustment for fecundity differentials are shown in (Table 5.18).

The model predicted 2328 (UCI: 2040-2663) pregnancy related deaths using baseline parameters. Using pregnancy rates without adjustment for differential fecundity by age, the number of pregnancy related deaths ranged from 1812 (UCI: 1538-2093) to 1128 (UCI: 929-1337) depending on the assumptions used (Table 5.17). This was equivalent to a reduction range between 22.1% (UCI: 15.3%-29.1%) and 51.5% (UCI: 44.1%-58.4%).

The percentage reductions for the pregnancy related mortality rate and the lifetime risk of pregnancy related mortality were similar to the reductions found for the number of pregnancy

related deaths (Table 5.17). A maximum of 0.31 pregnancy related deaths could potentially be prevented per 1,000 women aged 10-49 years if there were only conceptions to women aged 20 and 39, reaching a maximum of gravidity three. Slightly lower reductions were observed for the proportionate mortality ratio (Table 5.17).

The model predicted a baseline pregnancy related mortality ratio of 489 (UCI: 428-561) deaths per 100,000 pregnancies. Using pregnancy rates not adjusting for differential fecundity by age, there was a potential to prevent 58 (UCI: 20-101) pregnancy related deaths per 100,000 pregnancies if women only had pregnancies between ages 20 and 39 years and reached a maximum gravidity of six (Table 5.17). If women only reached a maximum gravidity of three, 77 (UCI: 12-140) deaths may potentially be averted.

Similar patterns of reduction and conclusions were found for the pregnancy related mortality indicators when using pregnancy rates adjusting for fecundity (Table 5.18).

Table 5.17: Pregnancy related mortality indicators for the baseline model and comparison models, using pregnancy rates without adjustment for fecundity differentials. The comparison models assumed conceptions to women aged 20-39 years only, reaching different maximum gravidities.

Model	Pregnancy related mortality indicators (95% UCI)				
	Number of pregnancy related deaths	PRMRatio - per 100,000 pregnancies	PRMRate per 1000 women	Lifetime risk of pregnancy related death	Proportionate mortality ratio
baseline	2328 (2040- 2663)	489 (428- 561)	0.61 (0.53- 0.69)	0.02 (0.02- 0.03)	23.7 (21.4- 26.3)
Conception to women aged 20-39 years, and maximum gravidity of					
Six:	1812 (1538- 2093)	432 (366- 499)	0.47 (0.4- 0.54)	0.02 (0.02- 0.02)	19.4 (17.0- 21.8)
% difference	*-22.1 (-29.1- -15.3)*	*-11.8 (-19.7- -4.0)*	*-22.3 (-29.2- -15.4)*	*-22.7 (-29.9- -15.9)*	*-18.0 (-23.9- -12.3)*
Five:	1681 (1421- 1949)	430 (363- 499)	0.44 (0.37- 0.51)	0.02 (0.01- 0.02)	18.3 (15.9- 20.6)
% difference	*-27.8 (-35.0- -21.0)*	*-12.2 (-21.0- -3.9)*	*-27.9 (-35.2- -21.1)*	*-28.4 (-35.8- -21.6)*	*-22.9 (-29.3- -16.9)*
Four:	1423 (1198- 1668)	415 (349- 487)	0.37 (0.31- 0.43)	0.01 (0.01- 0.02)	15.9 (13.7- 18.2)
% difference	*-38.8 (-46.3- -31.5)*	*-15.2 (-25.6- -4.9)*	*-39.1 (-46.5- -31.6)*	*-39.5 (-47- -32.1)*	*-33.0 (-39.6- -26.1)*
Three:	1128 (929- 1337)	413 (340- 490)	0.29 (0.24- 0.35)	0.01 (0.01- 0.01)	13.0 (11.0- 15.1)
% difference	*-51.5 (-58.4- -44.1)*	*-15.6 (-27.7- -2.7)*	*-51.7 (-58.7- -44.4)*	*-52.2 (-59.1- -44.8)*	*-45.1 (-51.9- -38.1)*

Table 5.18: Pregnancy related mortality indicators for the baseline model and comparison models, using pregnancy rates with adjustment for fecundity differentials. The comparison models assumed conceptions to women aged 20-39 years only, reaching different maximum gravidities.

Model	Pregnancy related mortality indicators (95% UCI)				
	Number of pregnancy related deaths	PRMRatio - per 100,000 pregnancies	PRMRate per 1000 women	Lifetime risk of pregnancy related death	Proportionate mortality ratio
baseline	2328 (2040- 2663)	489 (428- 561)	0.61 (0.53- 0.69)	0.02 (0.02- 0.03)	23.7 (21.4- 26.3)
Conception to women aged 20-39 years, and maximum gravidity of					
Six:	1873 (1601- 2152)	425 (363- 489)	0.49 (0.42- 0.56)	0.02 (0.02- 0.02)	20.0 (17.6- 22.3)
% difference	*-19.5 (-26.9- -12.7)*	*-13.0 (-21.1- -5.5)*	*-19.6 (-2.70- -12.7)*	*-20.1 (-27.4- -13.2)*	*-15.8 (-21.8- -10.0)*
Five:	1725 (1464- 1985)	423 (359- 488)	0.45 (0.38- 0.52)	0.02 (0.02- 0.02)	18.7 (16.3- 20.9)
% difference	*-25.9 (-33.2- -18.9)*	*-13.5 (-22.1- -5.2)*	*-26.0 (-33.4- -19)*	*-26.5 (-34.0- -19.5)*	*-21.2 (-27.6- -15.2)*
Four:	1441 (1215- 1691)	407 (343- 478)	0.37 (0.31- 0.44)	0.01 (0.01- 0.02)	16.1 (13.9- 18.4)
% difference	*-38.1 (-45.4- -30.5)*	*-16.7 (-26.7- -6.5)*	*-38.3 (-45.6- -30.7)*	*-38.8 (-46.3- -31.2)*	*-32.2 (-39.1- -25.5)*
Three:	1129 (938- 1336)	405 (336- 480)	0.29 (0.24- 0.35)	0.01 (0.01- 0.01)	13.0 (11.1- 15.1)
% difference	*-51.4 (-58.4- -43.8)*	*-17.2 (-29.1- -4.0)*	*-51.7 (-58.6- -44.0)*	*-52.2 (-59.1- -44.5)*	*-45.1 (-51.9- -37.7)*

Scenario seven: eliminate and reduce conceptions to women for a combination of high risk groups.

Women were assumed to have conceptions between ages 20 and 44 years only, reaching a maximum of gravidity six. In step one of the fertility reductions, I assumed 50% reductions to the baseline pregnancy rates of women aged 40-44 years and women who were gravidity three to five. Using pregnancy rates without adjustment for fecundity differentials by age, the total pregnancy rate reduced from a baseline of 4.91 to 3.82 pregnancies per woman (Figure 5.18).

If further fertility reduction in step two were imposed, step one and a 20% reduction to the baseline pregnancy rates of women aged 35-39 and gravidity two women, the total fertility rate reduced to 3.71 pregnancies per woman. The patterns of reduction were similar when using pregnancy rates adjusting for fecundity, but the magnitude of the total pregnancy rates were consistently higher (Figure 5.18).

The proportion of first pregnancies increased notably after fertility reduction step one (Figure 5.19). Concurrently there was considerable reduction in the proportion of pregnancies to women aged 35 or over (Figure 5.19). A further 20% reduction in the baseline pregnancy rates to women aged 35-39 and gravidity two women did not affect the proportions much further.

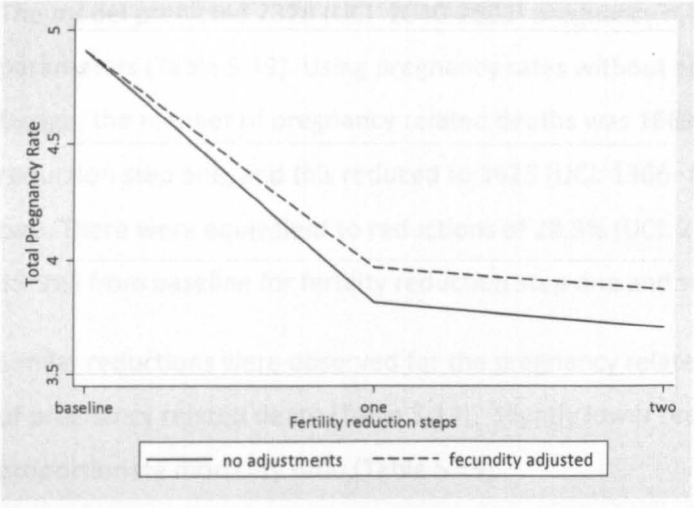

Figure 5.18: Changes in the total pregnancy rate assuming pregnancies to women aged 20-44 only, reaching a maximum of gravidity six. Fertility reduction step one assumed 50% reductions to the baseline pregnancy rates of women aged 40-44 and gravidity three to five women. Fertility reduction step two assumed fertility reduction step one, in addition to a 20% reduction to the baseline pregnancy rates of women aged 35-39, and gravidity two women who were unaffected by fertility step one.

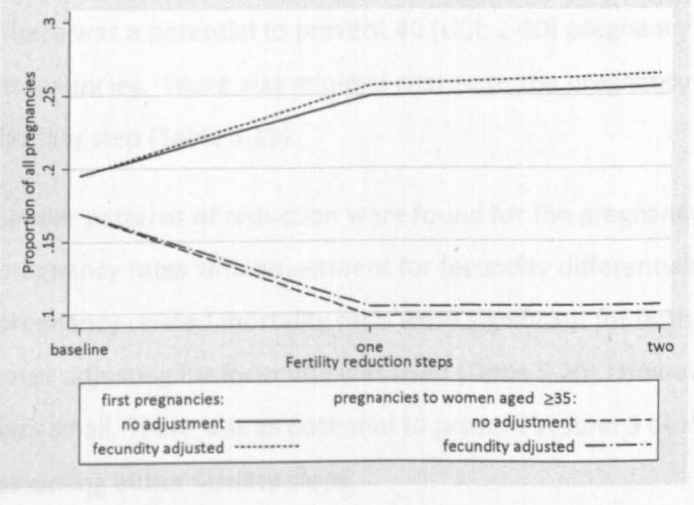

Figure 5.19: Proportion of conceptions which are first pregnancies, or conceptions to women aged 35 or older in different models including the baseline. Fertility reduction step one assumed 50% reductions to the baseline pregnancy rates of women aged 40-44 and gravidity three to five women. Fertility reduction step two assumed fertility reduction step one, in addition to a 20% reduction to the baseline pregnancy rates of women aged 35-39, and gravidity two women who were unaffected by fertility step one.

The pregnancy related mortality indicator estimates for the baseline model and models assuming different fertility reductions, using pregnancy rates without adjustment for fecundity differentials, are shown in Table 5.19. The corresponding results using pregnancy rates with adjustment for fecundity differential are shown in Table 5.20.

The model predicted 2328 (UCI: 2040-2663) pregnancy related deaths using baseline parameters (Table 5.19). Using pregnancy rates without adjustment for differential fecundity by age, the number of pregnancy related deaths was 1669 (UCI: 1403- 1957) after fertility reduction step one, and this reduced to 1628 (UCI: 1366- 1909) after fertility reduction step two. There were equivalent to reductions of 28.3% (UCI: 22.2%- 34.1%) and 30.1% (UCI: 24.0%- 35.9%) from baseline for fertility reduction step one and step two respectively

Similar reductions were observed for the pregnancy related mortality rate and the lifetime risk of pregnancy related death (Table 5.19). Slightly lower reductions were observed for the proportionate mortality ratio (Table 5.19).

The model predicted a baseline pregnancy related mortality ratio of 489 (UCI: 428-561) deaths per 100,000 pregnancies. Using pregnancy rates without adjustment for differential fecundity by age, significant reduction for the pregnancy related mortality ratio was only observed for fertility reduction step one (conceptions to women aged 20-44 only, maximum gravidity six, 50% reductions to the baseline pregnancy rates of 40-44 year olds and gravidity 3-5 women). There was a potential to prevent 40 (UCI: 2-80) pregnancy related deaths per 100,000 pregnancies. There was minimal change to the pregnancy related mortality ratio in the second fertility step (Table 5.19).

Similar patterns of reduction were found for the pregnancy related mortality indicators using pregnancy rates with adjustment for fecundity differentials by age. The reductions in the pregnancy related mortality ratio were significant for both fertility steps when the pregnancy rates adjusting for fecundity was used (Table 5.20). However, the magnitude of reductions was small. There was as potential to prevent around 9 deaths per 100,000 pregnancies assuming either fertility steps.

Table 5.19: Pregnancy related mortality indicators for the baseline model, and comparison models, using pregnancy rates without adjustment for fecundity differentials. The comparison models assumed conceptions to women aged 20-44 only, reaching a maximum of gravidity six, in addition to further fertility reductions for women aged 35-44 and gravidity two to five women.

Model	Pregnancy related mortality indicators (95% UCI)				
	Number of pregnancy related deaths	PRMRatio - per 100,000 pregnancies	PRMRate per 1000 women	Lifetime risk of pregnancy related death	Proportionate mortality ratio
Baseline – all ages	2328 (2040- 2663)	489 (428- 561)	0.61 (0.53- 0.69)	0.02 (0.02- 0.03)	23.7 (21.4- 26.3)
Conceptions to 20-44 year olds only, maximum gravidity six and:					
Fertility reduction step one[1]	1669 (1403- 1957)	450 (377- 527)	0.43 (0.36- 0.51)	0.02 (0.01- 0.02)	18.1 (15.7- 20.7)
% difference	*-28.3 (-34.1- -22.2)*	*-8.2 (-15.7- -0.3)*	*-28.5 (-34.4- -22.4)*	*-28.8 (-34.8- -22.7)*	*-23.4 (-29.0- -17.9)*
Fertility reduction step two[2]	1628 (1366- 1909)	451 (378- 530)	0.42 (0.35- 0.50)	0.02 (0.01- 0.02)	17.8 (15.4- 20.3)
% difference	*-30.1 (-35.9- -24.0)*	*-7.8 (-15.5- 0.3)*	*-30.3 (-36.2- -24.2)*	*-30.6 (-36.5- -24.4)*	*-25.0 (-30.5- -19.4)*

1: 50% reductions to the baseline pregnancy rates of 40-44 year olds and gravidity 3-5 women.

2: fertility step one (above) and 20% reductions to the baseline pregnancy rates to 35-39 year olds and gravidity two women who were unaffected by fertility step one

Table 5.20: Pregnancy related mortality indicators for the baseline model, and comparison models, using pregnancy rates with adjustment for fecundity differentials. The comparison models assumed conceptions to women aged 20-44 only, reaching a maximum of gravidity six, in addition to further fertility reductions for women aged 35-44 and gravidity two to five women.

Model	Pregnancy related mortality indicators (95% UCI)				
	Number of pregnancy related deaths	PRMRatio - per 100,000 pregnancies	PRMRate per 1000 women	Lifetime risk of pregnancy related death	Proportionate mortality ratio
Baseline – all ages	2328 (2040- 2663)	489 (428- 561)	0.61 (0.53- 0.69)	0.02 (0.02- 0.03)	23.7 (21.4- 26.3)
Conceptions to 20-44 year olds only, maximum gravidity six and:					
Fertility reduction step one[1]	1712 (1444- 1996)	443 (373- 517)	0.44 (0.37- 0.52)	0.02 (0.01- 0.02)	18.5 (16.1- 21)
% difference	*-26.5 (-32.6- -20.5)*	*-9.5 (-17- -2.0)*	*-26.7 (-32.8- -20.6)*	*-26.9 (-33.2- -21)*	*-21.8 (-27.2- -16.6)*
Fertility reduction step two[2]	1677 (1413- 1956)	445 (375- 519)	0.44 (0.37- 0.51)	0.02 (0.01- 0.02)	18.2 (15.8- 20.7)
% difference	*-28.0 (-34.1- -22)*	*-9.1 (-16.8- -1.5)*	*-28.1 (-34.3- -22.2)*	*-28.4 (-34.6- -22.4)*	*-23.1 (-28.4- -17.8)*

1: 50% reductions to the baseline pregnancy rates of 40-44 year olds and gravidity 3-5 women.

2: fertility step one (above) and 20% reductions to the baseline pregnancy rates to 35-39 year olds and gravidity two women who were unaffected by fertility step one

5.2.3 Sensitivity analysis

Using pregnancy rates calculated with different restrictions on the minimum number of follow up years increased the overall total pregnancy rate of the models slightly. However, there was negligible impact on the findings when comparing the baseline pregnancy related mortality indicators to comparison model indicators with observed/theoretical fertility assumptions (data not shown).

5.3 Discussion

I modelled the impact of fertility changes on various pregnancy related mortality indicators by varying the age-gravidity specific pregnancy rates in a compartmental model. A summary of the results for different scenarios can be found in Table 5.21. The results showed that the dramatic decline in fertility that occurred in Matlab between 1983-1993 and 2000-2005 accounted for a 28% reduction in the pregnancy related mortality rate, but it did not contribute to the reduction in the pregnancy related mortality ratio observed over this period.

By modelling a number of theoretical fertility scenarios, I gained greater insights into the fertility characteristics that may drive the change in pregnancy related mortality. As expected, the fertility scenarios with the greatest impact on the total number of pregnancy related deaths (and therefore on the rate and life time risk) were those that restricted the total number of pregnancies women had. If women reached a maximum of gravidity three, there would be around a 50% reduction in the number of pregnancy related deaths and the pregnancy related mortality rate. This was different for the pregnancy related mortality ratio which was driven by shifts away from higher maternal age pregnancies. The maximum reduction in the ratio was around 16% or 17% which was obtained if there were only conceptions to women aged 20-34 years or there were only conceptions to women aged 20-39, reaching a maximum gravidity of three, where only around 2.5% of all pregnancies were to women aged 35-39.

The substantial reductions observed for the pregnancy related mortality rate and the lifetime risk of pregnancy related mortality were unsurprising because of their direct links to fertility levels. The pregnancy related mortality rate can be calculated as the product of the pregnancy related mortality ratio and the general pregnancy rate. So any scenario that directly reduced the pregnancy rates would affect the pregnancy related mortality rate, even if the pregnancy

related mortality ratio did not change. If each woman only had a maximum of one pregnancy each, the pregnancy related mortality rate would reduce by 74.5%.

The scale of the percentage reduction was smaller for the pregnancy related mortality ratio compared to the pregnancy related rate because as the number of pregnancies to older women decreased, the proportion of higher risk, first pregnancies increased. Thus reductions gained were counteracted by the higher risk of first pregnancies accounting for an increasing proportion of all pregnancies.

The reductions in fertility had only modest impact on the pregnancy related ratios. In the baseline period in Matlab, women of higher gravidities were not found to be at increased risk of pregnancy related death after adjustment for maternal age, and adolescents aged 15-19 were not found to be at increased risk of pregnancy related death after adjusting for gravidity. Thus there would be no expected decrease in the pregnancy related mortality ratio if fertility levels to these groups were decreased or eliminated.

Past studies have often quoted these high gravidity groups as high risk groups, and thus it may be that the number of pregnancies for the baseline period of 1983-1993 was insufficient to detect any differences. However, results found in the baseline period were similar to the conclusion in the systematic review in chapter 3, which did not find firm conclusions on the association between higher parities and increased maternal mortality. Only very young adolescents (10-14 years old) and women with no previous pregnancies and older women had an increased risk of maternal death. Using all pregnancies from 1983-2005 in Matlab in the retrospective cohort study (chapter 4), there was some evidence that gravidity six or higher posed an increased risk of pregnancy related death if only maternal age was adjusted. However, this higher gravidity effect disappeared once other confounders were adjusted (chapter 4). Therefore it is unlikely that the effect of reducing higher gravidity pregnancies on pregnancy related mortality indicators was underestimated in this model.

Eliminating fertility to the very young adolescents (10-14 years old) had limited impact on the pregnancy related mortality ratios because there were a limited number of pregnancies affected.

The total fertility rate in Matlab reduced from 5.2 in 1983 to 2.8 in 2005 [323]. During this period, the model found that the pregnancy related rate reduced by 28% as a result of the observed age and gravidity distribution changes between 1983-1993 and 2000-2005. A 50%

reduction in the pregnancy related mortality rate was not achieved, as seen in the theoretical scenario (scenario one) where all women were assumed to have a maximum of three pregnancies each, for several reasons.

First, in scenario one, women were assumed to have a maximum of three pregnancies, but they did not have to have three pregnancies each. The pregnancy rates up to gravidity three were estimated using data from Matlab, and these took into account the women who had primary or secondary infertility, in addition to women who chose to have less than three pregnancies. In fact, this assumption resulted in an estimated total pregnancy rate of 2.7.

Second, not all pregnancies end in a live birth, and therefore the total pregnancy rate would be an overestimate of the total fertility rate. An estimated 20% of pregnancies end in miscarriages or stillbirths. So this suggests that a total pregnancy rate of 2.7 would be roughly equivalent to a total fertility rate of 2.2.

Third, a total fertility rate measures the average childbearing behaviour of the population. Within a population, individuals will still have higher gravidity births at older maternal ages. In contrast, my theoretical model did not allow any higher gravidity pregnancies, and as a result also eliminated many higher risk pregnancies to older women.

For these reasons, the observed reduction in the pregnancy related mortality rate between 1983-93 and 2000-05 was not equivalent to the theoretical reduction seen assuming a maximum of three pregnancies to each woman. A more comparable scenario would be scenario seven, where women were assumed to have pregnancies between the ages of 20 and 44, reaching a maximum of gravidity six, in addition to 20-50% reductions to the baseline pregnancy rates for women aged 35-44 years and to women of gravidity two to five. This scenario found an expected total pregnancy rate of 3.7, which is roughly equivalent to a total fertility rate of around 3. A 30% (UCI: 24%-36%) reduction in the pregnancy related mortality rate was observed for scenario seven, which is comparable to the 28% (UCI: 22%-33%) reduction found for the observed fertility changes in Matlab between 1983-93 and 2000-05. While scenario seven was a more appropriate comparison due more relaxed childbearing assumptions to higher gravidities, it is not directly comparable to the observed scenario. It assumed no pregnancies to women aged younger than 20, which are very common in Matlab.

Table 5.21: Summary of the impact of age/gravidity distribution changes on pregnancy related mortality indicators for different scenarios explored in this thesis.

Description of fertility schedules	Range of % difference[1] in each scenario compared to the baseline model				
	Number of pregnancy related deaths	PRMRatio - per 100,000 pregnancies	PRMRate per 1000 women	Lifetime risk of preg related death	Proportionate mortality ratio
Baseline model - observed pregnancy rates in Matlab, 1983-1993	0	0	0	0	0
Observed changes					
1994-1999 pregnancy rates, other parameters at 1983-1993 levels.	-21.6	-2.0	-21.8	-22.0	-17.6
2000-2005 pregnancy rates, other parameters at 1983-1993 levels.	-28.0	-1.7	-28.2	-28.4	-23.1
Theoretical changes					
Scenario 1- eliminate high gravidity conceptions	-1.4 - -74.3	-0.4 - +31.5	-1.4 - -74.5	-1.5 - -74.9	-1.1 - 69.2
Scenario 2 - eliminate conceptions to older women	-3.1 - -28.8	-1.9 - -14.3	-3.1 - -28.9	-3.3 - -29.6	-2.4 - -23.8
Scenario 3- eliminate conceptions to young adolescents(<15 years old)	-0.8	-0.6	-0.8	-0.8	-0.6
Scenario 4- eliminate conceptions to all adolescents(<20 years old)	-0.4	-1.4	-0.4	-0.2	-0.3
Scenario 5- eliminate conceptions to women of extreme ages	-3.8 - -30.8	-3.5 - -17.0	-3.9 - -31.0	-3.9 - -31.5	-3.0 - -25.6
Scenario 6- eliminate conceptions to women of extreme ages, and higher gravidities.	-22.1 -51.5	-11.8 - -15.6	-22.3 - -51.7	-22.7 - -52.2	-18 - -45.1
Scenario 7- eliminate and reduce conceptions to women for a combination of high risk groups.	-28.3 - -30.1	-7.8- -8.2	-28.5 - -30.3	-28.8 - -30.6	-23.4 - -25.0

1- using pregnancy rates without adjustment for fecundity differentials by age where appropriate.

5.3.1 Findings in the context of other studies

The methods used in the four studies which investigated the impact of fertility changes on maternal mortality have been described in detail in the Introduction, section 2.5.3. They are described briefly in the following selection, and the results of these four studies are compared to parallel scenarios from my research.

Trussell and Pebley used indirect standardisation to assess the impact of age/parity distribution changes in live births on maternal mortality. The authors used the published age/parity specific maternal mortality ratios from Matlab in 1968-1970 as the set of standard

mortality ratios. They reported a 10.5% reduction in the maternal mortality ratio and an 11.1% reduction in the maternal mortality rate assuming there were only births to women aged 20-39 years and assumed a constant general fertility rate. In their model, they redistributed all live births occurring to women aged 10-19 and half of live births to women aged 20-29 to age 20-29, and redistributed the other half of the original 20-29 births and all births at 30-49 to age 30-39.

Scenario five was comparable to the above the model by Trussell and Pebley. In scenario five, I assumed women limited their conceptions to age 20-39 and I calculated new fertility schedules assuming all women with an estimated conception date between ages 10 and 19 years waited until their 20th birthday to conceive their first pregnancy. Any subsequent pregnancies to these women were assumed to follow with the observed inter-pregnancy outcome interval. For scenario five, using pregnancy rates without adjustment for fecundity differentials by age, there was a 10.4% (UCI: 3.5%- 18.2%) reduction in the pregnancy related mortality ratio, and a 15.7% (UCI: 9.2%-23.0%) reduction in the pregnancy related mortality rate. So the results were comparable.

Trussell and Pebley went on further to eliminate all births to women younger than 20 and older than 39, and eliminated all births to women above parity 5 without redistributing the births. The authors reported a 21.1% reduction in the maternal mortality ratio and a 22.2% reduction in the maternal mortality rate (assuming constant general fertility rate).

In scenario six, I assumed women limited their childbearing to 20 to 39 years old and assumed women reached a maximum of gravidity five. Again, I calculated new fertility schedules as mentioned above. Without taking account of fecundity differentials by age, I found a reduction of 12.2% (UCI: 3.9%-21.0%) in the pregnancy related mortality ratio, and 27.9% (UCI: 21.1%-35.2%) in the pregnancy related mortality rate. The difference in the maternal mortality ratio reductions found between mine and the Trussell and Pebley model may be due the elimination of a large proportion of high risk first births to adolescents in the Trussell and Pebley model without redistributing these births back into the model. In my model, I was able to assume these first births were delayed but not eliminated by tracking women through all their pregnancies. I found a higher reduction in the maternal mortality rate because I used the modelled fertility changes as a result of delayed childbearing and elimination of higher gravidity conceptions. Trussell and Pebley, on the other hand, assumed that the general

fertility rate remained constant, though it is unclear how this could be the case if births were eliminated without redistribution.

Fortney used the same data as Trussell and Pebley and went on further to "eliminate all births to women <20,>39 or parity> 5, and redistribute a reduced number of births to parities <6 and to ages 20-39". The reductions found were 19.3% to the maternal mortality ratio and 55.6% to the maternal mortality rate. However, it was unclear exactly how the births were redistributed to different parities. In my models similar reductions were observed if there were only conceptions to women aged 20-39, reaching a maximum of gravidity three (scenario six). A 15.6% (UCI: 2.7%- 27.7%) reduction was observed for the pregnancy related mortality ratio, and the reduction was 51.7% (UCI: 44.4%- 58.7%) for the pregnancy related mortality rate.

Stover and Ross used indirect standardisation to investigate the independent impacts of changes in the observed age and parity distribution of live births on the maternal mortality ratio in 46 countries [218]. The set of parity specific maternal mortality ratios from Honduras (1990-1997) was used as the standard. Using reported birth order changes in consecutive Demographic and Health Surveys for Bangladesh between 1993 and 2004, the authors reported a 4% reduction in the maternal mortality ratio as result of parity shifts in live births in Bangladesh.

The authors noted that the percentage change in the maternal mortality ratio as a result of maternal age shifts of live births were small, but no percentage reductions were reported in the article.

Using the current model described in this chapter, there were no changes in the pregnancy related mortality ratio as a result of the combined effect of maternal age and gravidity distribution changes in pregnancies between 1983-1993 and 2000-2005 in Matlab, Bangladesh (% change = -1.7%, UCI: -8.9% - 5.9%). The reduction of 4% found by Stover and Ross fell within the 95% uncertainty interval of my result. However, since there were no uncertainty or confidence intervals reported for the Stover and Ross model, I was unable to comment on the significance of their results.

Högberg and Wall used direct standardisation to examine the effect of observed changes in the age and parity distribution of births on maternal mortality in Sweden [219]. The authors reported that between 1800-99 and 1951-1980 in Sweden, a 16.7% reduction in the number of maternal deaths was attributed to observed changes in the age and parity distribution of

births. During 1800-99 and 1951-1980, the proportion of first births to women aged 15 to 29 increased from around 15% to over 30%. The proportion of first births to women aged 30-49 also increased. In addition, the proportion of parity four or higher births out of all births to women aged 30-49 decreased from around 40% to around 10%.

Between 1983-1993 and 2000-2005 in Matlab, Bangladesh, a 28.1% (UCI: 22.7%-33.2%) reduction in the number of pregnancy related deaths could be attributed to observed age and gravidity distribution changes in pregnancies. During this period in Matlab, the proportion of first births increased from 30% to 41% for women aged 10-29. Also, the proportion of first births to women aged 30-49 years increased from 0.83% to 2.58% during this period in Matlab. The differences in the proportion of averted maternal deaths between the Högberg and Wall model and this model may be due to the higher increases in the proportion of first births to 15-19 year olds in Sweden. In addition, there was a higher relative risk for first births compared to second or third births in Sweden. For the period 1951-1980 in Sweden, the risk of maternal death for first births was around four times higher than second or third births for women aged 15-29 years. In 1983-1993 in Matlab, the odds ratio of pregnancy related death was 1.84 comparing gravidity zero to gravidity one pregnancies after adjusting for maternal age. Thus the increase in the proportion of first births in Sweden resulted in a proportionately higher number of maternal deaths than in Matlab for the same proportional change in the number of first pregnancies. This would lead to the observed smaller percentage reduction in the number of maternal deaths in Sweden.

5.3.2 Strengths and limitations

The model constructed allowed detailed manipulation of the age-gravidity specific pregnancy rates and examination of their subsequent impact on the pregnancy related mortality indicators. However, there were a number of assumptions and their implications should be assessed. Issues regarding model specification and fertility assumptions, and the methods used to estimate the parameters are discussed below.

Model structure

The model did not incorporate different birth interval lengths, and thus was not able to investigate the effect of birth interval changes on maternal mortality. A systematic review on the effect of birth spacing on maternal mortality found five studies that adjusted for

confounding factors [99]. The studies included in the review reported inconsistent results and the authors concluded that the association was unclear. The authors suggested further research to elucidate this relationship [99].

Longer birth intervals may delay subsequent childbearing and increase pregnancy rates in older maternal ages that may lead to increased overall pregnancy related mortality. Alternatively longer intervals could reduce the total fertility rate since women forgo having their last pregnancy at higher maternal ages due to time constraints, and thus the pregnancy related mortality may decrease.

Various factors may affect birth intervals, e.g. ill health, sub-fecundity, contraceptive use, breastfeeding and the death of the index child. Very long birth intervals (e.g. >70 months) are more likely to be related to ill health or sub-fecundity that may be independent risk factors for maternal mortality.

Child mortality is likely to be a driver of fertility. For example the subsequent fertility of a woman after the death of a child may alter due to physiological reasons (shortening of the postpartum amenorrhea period) or due to choice (replacement effect). However, the specific cause of fertility decline such as child loss, and contraception use were not modelled since these were unlikely to affect the impact of fertility shifts on maternal mortality.

This model considered the fertility behaviour of women based on their gravidity rather than live births or number of currently living children. The use of gravidity may be considered more complete since regardless of whether women carry their pregnancies to term, once exposed to pregnancy they are at risk of a pregnancy related death. However, the desired family size and ultimately the fertility behaviour would be based the number of previous live birth deliveries, and the number of currently living children, which may be related to child mortality as previously discussed.

It was not possible to identify parity in the Matlab data (see further details in section 4.2.3 in chapter 4), and so it wasn't possible to parameterise a model based on parity rather than gravidity. The number of living children was not used as compartments in the model due to the technical complexity of such models, in addition to the lack of accurate data in the Matlab dataset.

This model only allowed one pregnancy outcome per year for each woman. However, pregnancy outcomes such as spontaneous and induced abortions may have very short

gestational durations, and it would be possible to have another pregnancy within the same year. This assumption could potentially lead to an underestimation of pregnancy rates. In the Matlab surveillance site, only 0.72% of the 159,210 pregnancy outcomes (1983-2005) occurred to the same women in the same year, and therefore this should have limited impact on the results.

This model did not incorporate migration in/out of the cohort, and this was only taken into account in the parameter estimation stage. Taking into account migration could lead to changes in the pregnancy related mortality estimates. For example, if the major reason for migration into Matlab was marriage then the proportion of first pregnancies may increase as a result, increasing the pregnancy related mortality indicators.

In Matlab, women had up to 21 previous pregnancies excluding the index pregnancy. However, women were only assumed to have up to nine previous pregnancies excluding the index one in the model. Thus this model did not explore the impact of changes to very high gravidities on pregnancy related mortality indicators. It is possible that the risk of pregnancy related mortality was substantially higher for very high gravidity women. However, in Matlab between 1983 and 2005, only 0.66% of pregnancy outcomes were to women with more than 10 previous pregnancies. Therefore changes in these very high gravidity pregnancies would have limited impact on the pregnancy related mortality indicators.

This model does not explicitly address any operational or behaviour changes that may follow fertility reductions. Fertility reduction will reduce the number of births and therefore reduce the burden on health services. Higher capacity may lead to better quality of care, reducing the case fatality of obstetric complications. In addition, when couples have fewer children, their capacity and willingness to invest in care during pregnancy and delivery may be greater, resulting in decreased risk of maternal death. Without taking account of these factors, the number of pregnancy related deaths may be overestimated, leading to an underestimation of the impact of reduced fertility on pregnancy related mortality indicators.

Fertility assumptions

When estimating the new fertility schedules, the inter-pregnancy outcome intervals were assumed to stay constant regardless of whether women delayed childbearing or not. However, women may shorten their inter-pregnancy outcome intervals as a catch up strategy to achieve

their desired family size more rapidly. Past studies have shown delayed childbearing was associated with decreased birth intervals in the US and the Philippines [94, 330]. Therefore in this model, the new pregnancy rates estimated may have underestimated pregnancy rates at the young ages, and overestimated pregnancy rates in the older women. In turn this may have led to an overestimation of the pregnancy related mortality indicators since pregnancies at older maternal ages carries a higher risk of pregnancy related death. The percentage reduction expected would be underestimated as a result.

Women who had conceptions in their adolescence were assumed to delay their childbearing until age 20 in scenarios three to seven. These women were artificially aged by changing their birth years when estimating the new pregnancy rates. This implicitly assumed that these women also experienced other key life events such as migration at a later age in their lives due to the changes in their birthdays. Obviously these assumptions were unlikely to be realistic since changes to the age at childbearing would undoubtedly affect other important decision in women's lives. However, given the impossibility of predicting behaviour changes in women if they delayed childbearing, it is difficult to comment on how these assumptions may affect the pregnancy related mortality indicators.

Some theoretical fertility changes assumed complete elimination of conceptions to certain groups of women. In reality, this is unlikely to be achieved and the percent reduction should be viewed as the best possible achievement if targeted interventions to particular groups of women took place. In my model if women were assumed to have a maximum of one pregnancy each the total pregnancy rate was estimated to be 0.94. Even in China, where a one child policy was introduced in 1979, the total fertility rate has decreased from an estimated 2.93 in 1985-1980 to 1.7 in 2000-2005 [331]. A total fertility rate of one child per woman has not been achieved in China partially because it is mainly enforced in urban areas and for government employees [332]. In addition, there has been a relaxation of the one child policy in some areas, for example, two "only child" parents can now have two children.

Parameter estimates

The pregnancy rates were assumed to be constant over the five year age interval. However, this may not be true, especially at the extreme ages, where pregnancy rates were likely to be overestimated. This would lead to an overestimation of the pregnancy related mortality indicators.

Pregnancy rates at infrequent age/gravidity combinations were more likely to be biased due to the small number of follow up years, leading to more erratic fertility estimates that were unusually high. However, these rates only affected a very small number of women, and thus should have limited impact on the results. In addition, sensitivity analysis using pregnancy rates calculated assuming different minimum length of follow up did not change the conclusions of any of the comparisons.

The gestational age used to estimate the conception dates was missing for 38.7% of all pregnancies. Therefore the women years may have been estimated inaccurately leading to biased pregnancy rate estimates. It is difficult to speculate whether women with missing gestational age would have longer or shorter gestational age than women with information on gestational age.

Generalisability

The age-gravidity fertilities are context and temporal specific and the generalisability of the findings needs to be considered. The reductions observed for the pregnancy related mortality ratio in the scenarios described in this chapter should be towards the upper reductions expected as a result of any fertility changes that may be observed now in less developed countries. This is especially true for south Asian countries compared to sub-Saharan African countries.

First, several of the scenarios assumed complete elimination of conceptions to certain high risk groups such as women aged 45 or older. These are unlikely to be achieved in reality as previously mentioned.

Second, this model only follows one cohort of women, and any female children born to these women were not fed back into the model as they survive to reproductive age. So this model can be considered as a snapshot of a population in which there are exactly 100,000 ten year old girls entering into their reproductive age every year. However, this is rarely the case in less developed countries, where the age pyramid is usually much more bottom heavy with a higher proportion of younger women. With a younger female population in less developed countries, the high risk group of older women would contribute a smaller proportion to all births, even if these women have higher fertility rates compared to my model. Therefore, eliminating these births would have a smaller impact compared to the scenarios described in this chapter.

Third, there is some evidence from the systematic review (chapter 3) that the magnitude of the crude odds ratios may be lower in high fertility settings such as in sub-Saharan African countries. Therefore the reductions seen in the scenarios would be overestimated. However, the magnitude of the odds ratios is unlikely to be a major contributor because the odd ratios used were based on pregnancy outcomes in Matlab between 1983 and 1993 a period when there was relatively high fertility in Matlab.

Apart from the above points, in most south Asian countries with a Demographic Health Survey since 2005, the total fertility rates and the fertility rates of older women were lower than the pregnancy rates used in my baseline model (based on pregnancies in Matlab, 1983-93). The total fertility rates ranged from 2.5 in the Maldives [107] to 4.1 in Pakistan [109]. Pakistan had the highest age specific fertility rates for older women– they were 44 and 18 per 1,000 women aged 40-44 and 45-49 year olds respectively [109]. Therefore there is less scope to reduce pregnancies to older women and thereby reduce maternal mortality. Therefore the reduction described here is likely to be the maximum possible for south– Asian countries.

The current total fertility rates in sub-Saharan African countries are similar to the total pregnancy rates used in the baseline group. In addition, the fertility rates to older and higher parity women are high in sub-Saharan African countries. Of the 21 sub-Saharan with a DHS since 2005, the total fertility rates ranged from 3.8 to 7.0 and the age specific fertility rate to women aged 40-44 ranged from 30 to 117 per 1,000 women. The fertility rates to very young mothers (≤15 years old) were also high – over 2% of girls were already mothers at age 15 in 13 out of 21 countries. In my baseline model, only 0.5% of girls have conceived by the end of age 14. Therefore, the current fertility situation in most sub-Saharan African countries is more akin to my baseline model than compared to most South Asian countries. There is even some scope to reduce the pregnancy rates to very young adolescents which appears to be higher than in my baseline model in some sub-Saharan African countries.

6 DISCUSSION AND CONCLUSIONS

Of all the human development indicators, maternal mortality shows one of the widest discrepancies between rich and poor countries. Less developed countries are burdened with 99% of all maternal deaths. As an increasing number of less developed countries experience lower fertility, the age and parity at which women have pregnancies may shift.

The childbearing composition pattern shifts as a result of fertility changes may affect maternal mortality levels, but their exact impact remains largely unknown. The aim of this thesis was to quantify the impact of fertility changes on maternal mortality.

6.1 Overview of the thesis and summary of findings

First, I undertook a literature review to identify the factors that are associated with maternal age, parity and maternal mortality. My review did not focus on changes in birth intervals partly because a high quality systematic review conducted in 2007 found inconsistent evidence for an association between short birth intervals and maternal mortality [99]. In addition, only women with an inter-pregnancy interval of less than 6 months were found to be at increased risk of maternal death but such short intervals are extremely rare.

The results of the 2007 systematic review on birth intervals and maternal health, including maternal death has been described previously in section 2.4. Briefly, only original studies that adjusted for at least maternal age were included in the review. Of the 635 citations found, five studies investigating the relationship between birth interval length and maternal mortality were included in the review. The studies reported inconsistent findings for the association between short intervals and maternal mortality, and the authors concluded *"Less clear is the association between short intervals and the risks of maternal death and..."* Only three studies investigated longer birth intervals and maternal death, and two studies did not find an association.

The literature review revealed numerous factors that may confound the relationship between maternal age, parity and maternal mortality. Factors most consistently associated with these variables included current health status, use of health care services and socio-economic factors such as education and household economic status. The direction and strength of the associations differed between studies, further suggesting the importance of confounding, but

also the importance of contextual factors. Therefore any investigation into the relationship between maternal age/parity and maternal mortality must adjust for confounders, and the context must be taken into account when interpreting the findings.

I also explored the literature for studies examining the impact of changes in the maternal age and parity distribution of births on maternal mortality. I only found four previous studies, each having a number of important methodological limitations. The main limitation of the studies using direct standardisation was that a standard age or parity distribution of births had to be used, and these models could therefore not explore the impact of theoretical fertility changes on maternal mortality. The main limitation of the studies using indirect standardisation was that they either did not take account of the association between maternal age and parity, or did not explicitly take it into account because the births were redistributed by age only.

Redistributing or eliminating births from certain age or parity groups on a population level does not translate into clear assumptions for individual fertility behaviour.

I addressed these concerns by the construction of a compartmental model that tracked a hypothetical cohort of women through their reproductive lives (10-49 years old), and recorded the age and gravidity of each pregnancy women experienced. This model allowed me to take account of the association between maternal age and gravidity by using age-gravidity specific pregnancy rates, ensuring all women had a first pregnancy. In addition, I investigated how uncertainty in the parameter estimates may affect the expected maternal mortality indicators, which none of the studies investigated.

Second, I conducted a systematic review to summarise the strength of the association between maternal age/number of previous pregnancies and maternal mortality at the population level. My review included 63 studies, most of which investigated crude relationships only. None of the studies focused on maternal age and parity as the primary exposures of interest, resulting in a lack of detailed investigations for these relationships. The findings of the review suggest that at the crude level the risk of maternal death increased with age and number of previous pregnancies. In addition adolescent childbearing and first pregnancies were at increased risk of maternal death compared to older or higher gravidity women. The review did not allow me to draw firm conclusions about the causality of these associations since very few studies adjusted for confounders (including for maternal age and parity simultaneously). However, the stratification by fertility levels and an analysis of the few

studies adjusting for confounders suggest that the effect of higher number of previous pregnancies may be completely confounded by maternal age and socio-economic factors.

Third, to further examine the role of confounding in the relationship between maternal age, gravidity and pregnancy related mortality, I reported on a cohort study using surveillance data from Matlab, Bangladesh. The findings of the crude analyses were consistent with those from the systematic review. However, after adjustment for age and gravidity simultaneously and for socio-economic factors, the excess risk of maternal mortality in higher gravidities and in older adolescents (15-19 years) was completely confounded, and the causality of these associations is therefore questionable.

Lastly, I modelled the effect of fertility changes on maternal mortality to examine the impact of maternal age and gravidity distribution changes on maternal mortality. I used a compartmental model that tracked a hypothetical cohort of women through their reproductive lives (10-49 years old). The findings of my model were consistent with the literature when the age or gravidity distribution changes occurred in the context of little overall total fertility rate change. My model found much more modest impact of fertility changes on the pregnancy related mortality ratio than previous studies. This is due to the fact that I was able to properly account for all higher risk, first pregnancies.

In summary, women giving birth at very young (<15 years) and older (>=35 years) maternal ages, and women having their first pregnancies are at increased risk of maternal death. Changes in the age and gravidity distribution of pregnancies will have limited impact on the pregnancy related mortality ratio, but could have a substantial impact on the absolute number of pregnancy related deaths, the pregnancy related mortality rate, the lifetime risk of pregnancy related death and the proportionate mortality ratio.

6.2 Strengths and limitations of the analyses

The strengths and limitations of the analyses included in the thesis have already been considered in the relevant chapters. A summary is given below.

To my knowledge, this is the most comprehensive review of the effect of maternal age or parity on maternal mortality at the population level. The review included data from both high and low income countries, and identified knowledge gaps in the literature which allowed subsequent methods to be developed accordingly. In particular, the review focused on

establishing the causality of the association between maternal age, parity and maternal mortality. I investigated this by stratifying the crude results of the systematic review by TFR level in an effort to partially control for unmeasured confounders. Second, I actively looked for studies that reported adjusted estimates which controlled for confounders.

There was high heterogeneity between studies in the meta-analyses. While the direction of associations was similar between studies, the magnitude of the odds ratios was different in some groups, especially when examining the effect of high maternal ages and higher number of previous pregnancies. It important to bear in mind that the interpretation of a random effects model assumes different underlying study estimates, with the summary odds ratio interpreted as the average of these different estimates.

I was unable to tease out the separate effects of maternal age and number of previous pregnancies since most studies do not adjust for confounders. Thus the crude summary odds ratios cannot be interpreted as representing the independent effects of maternal age or number of previous pregnancies.

The cohort study further explored causality using a large dataset from Bangladesh including over 150,000 pregnancies and 581 pregnancy related deaths. Studies from less developed countries rarely include such large sample sizes. Care was taken in clearly defining maternal age and gravidity and ascertaining all pregnancies and pregnancy related deaths. Most importantly, multiple confounders were taken into account and each potential confounder was assessed individually for whether and how it affected the association between maternal age/gravidity and pregnancy related mortality.

There may be residual confounding or unmeasured confounders that may affect the results of the cohort study. For example, current health status of women may confound the relationship between maternal/gravidity and pregnancy related death.

There were missing values for maternal and husband's formal years of education and birth to conception intervals which may have biased the results. The results restricting to pregnancies with no missing values on maternal or husband's education were similar for older maternal age and higher gravidity women. However, there was an insufficient number of pregnancies to gravidity zero and younger women using this restriction to make any firm conclusions on their risk of pregnancy related death.

The compartmental model allowed detailed manipulation of the age-gravidity pregnancy rates in such a way that realistic changes in the maternal age and gravidity distributions could be investigated.

The main limitations of my work relate to the generalisability of the findings. My model only took account of the direct effect of shifts in maternal age and gravidity distributions on pregnancy related mortality without considering the age structure of the population. In most sub-Saharan African countries, women aged between 40 to 49 years typically make up around 10-15% of women of reproductive age (10-49 years), whereas in my model they made up around 24% of women of reproductive age. With a younger female population, pregnancies to older women would contribute a smaller proportion to all pregnancies, even if these women have slightly higher pregnancy rates compared to my model. Therefore, eliminating these higher risk pregnancies may have a smaller impact on the pregnancy related mortality indicators. However, the percentage reduction found may be more applicable to sub-Saharan African countries than Asian countries due to the high pregnancy and maternal mortality rates assumed in the baseline model.

This model does not explicitly address any operational or behaviour changes that may follow fertility reductions. For example, a reduction in fertility in sub-Saharan Africa will lead to a reduced number of births and subsequently reduce burden on the health services. Reduced burden on an over-stretched health service may lead to better quality of care, and thus reduce the case fatality rate of obstetric complications. Without taking these factors into consideration, my models may have overestimated the number of pregnancy related deaths, leading to an underestimation of the impact of fertility reduction on pregnancy related mortality indicators.

6.3 Clinical and policy implications of the findings

The findings of this research have important implications for clinicians and policy makers.

From a clinical point of view, only adolescents younger than 15 years old, women over the age of 35 and women experiencing first pregnancies are at increased risk of pregnancy related death. Whilst teenage pregnancy or multigravidas may still be at higher risk of maternal death, the reasons for such effects are likely to be related to socio-economic rather than biological factors. In light of this, care providers should view pregnant adolescents as two heterogeneous groups, with different obstetric risk profiles: adolescents younger than 15 years old are at

higher risk of adverse maternal outcomes, while older adolescents are not once socio-economic factors are taken into account.

Preventing pregnancies to older adolescents may still be beneficial when considering social outcomes. In societies where childbearing is valued and women are expected to have children soon after marriage, preventing pregnancies to young girls may be through indirect methods such as delayed marriage through longer education for girls. More educated women may be more knowledgeable about the benefits of using skilled birth attendants and be better able to negotiate the public health systems to access health care, decreasing maternal mortality levels even further. Evidence from Matlab in Bangladesh suggests that even limited education (1-5 years) may reduce a woman's risk of pregnancy related mortality by around 40% compared to no formal education, even after other confounders such as maternal age and gravidity were adjusted for.

In settings where childbearing is acceptable outside of marriage, young girls need to grow up in environments in which they have aspirations beyond childbearing. With no demand for contraceptives, pregnancies to young girls cannot be prevented. Young girls may need to be given the opportunities to find out about different life choices available to them. This may be through several forms, such as, ensuring girls have the opportunity to go to school, educating parents where necessary and having the appropriate role models or mentors. If demand for contraceptives exists, then education to enable girls to find and access contraceptives would prevent some pregnancies.

Improved access to contraceptives may be resisted in some areas, especially in communities with strong religious objections to family planning or lower status for women. Education should be integrated to include the continuum of sexual and reproductive care, including family planning and use of skilled birth attendants. Any educational programmes should aim to engage the whole community including community elders, religious leaders, parents of young girls and boys, husbands, as well as young girls.

In more developed countries delayed childbearing has become more prevalent, and a higher proportion of pregnancies to older women are first pregnancies which have an even higher risk of adverse maternal outcomes. However, even when the relative risk of pregnancy related death to older women is higher, the absolute risk of death is still very low in more developed countries. With an emphasis on the low risk of maternal mortality for any age group, women should be made aware of the increased risk of pregnancy at older ages. So they can make

informed plans on childbearing. The focus should be on the control of preventable illness that may be aggravated during pregnancy such as diabetes and obesity.

From a policy point of view, my research findings have major implications for the promotion of family planning as a means of reducing maternal mortality in poor countries. The beneficial effects of fertility reductions on infant health are well established, and there is little doubt that effective family planning programmes will contribute to reductions in neonatal, infant and child mortality. Family planning will also prevent unwanted pregnancies, and the availability of a range of contraceptive methods will empower women by allowing them to choose their own fertilities. For maternal health, on the other hand, the picture is mixed. There is little doubt that a reduction in the total number of pregnancies will reduce the total number of maternal deaths. However, evidence that reduced childbearing to very young adolescents or to women of higher maternal ages will reduce the overall maternal mortality ratio is weak. The expected reductions are small- the maximum expected would be around 17%. Without improved access to high quality care for pregnant women, the high risk of death associated with pregnancy will not reduce dramatically, and will fall short of the 75% reduction required to achieve the Millennium Development Goal by 2015.

This study also has policy implications for Bangladesh. There is little evidence that the successful fertility reductions in Bangladesh have made a major contribution to the reduction in the maternal mortality ratio. This is contrary to the conclusions reached by Chowdhury and colleagues, who suggested reductions in adolescent (<20 years) childbearing may have contributed to the reductions in the maternal mortality ratio observed [329]. Another recent study found continued reductions in the maternal mortality ratio in Bangladesh [333].The authors also attributed the reductions, at least in part, to declines in fertility and shifts from high risk to low risk births (mainly from the reduction of high parity births).

The reasons for the decline in the maternal mortality ratio in Bangladesh are poorly understood [9, 329]. The reasons may be multifaceted, including a combination of improved access to health care including emergency obstetric care, improved access to family planning services (and a reduction in unwanted pregnancies), and societal changes such as increased female education, better household economic status or a decrease in traditional harmful practices. Most of these may be considered as contextual factors. In this research, there was some evidence that the adverse effect of first pregnancies disappeared in Matlab, Bangladesh from 1990 onwards, coinciding with improved access to better quality maternal health care.

6.4 Recommendation for future research

Maternal age and parity are important determinants of maternal mortality, and we should not neglect their roles. To consolidate the evidence further, the research on these relationships would benefit from additional studies that have a specific focus on maternal age and parity. In particular, research could be strengthened in the following aspects.

First, for improved comparability between studies from different settings, researchers should explicitly define the variable used to measure the number of past pregnancies. A clear standard definition should be adopted, excluding the index pregnancy and with multiple gestation pregnancies counting as one gravid event. This definition avoids ambiguity when women die undelivered or have multiple births.

Second, studies should adjust for appropriate socio-economic factors such as maternal education and household wealth. Crude and adjusted results should be presented so that the magnitude of confounding can be assessed. More accurate information on factors, such as household wealth, that take account of the changing socio-economic circumstances of women over their reproductive life, could reduce residual confounding in any further analyses.

Third, the analyses included in this thesis explored very few of the contextual factors which may be important for maternal mortality levels; for example, how the access to, and quality of care interact with the effect of maternal age /parity on maternal mortality. Access and use of health care are overlapping concepts. There may be a lack of access to health care due to insufficient community resources or other barriers. There may be access to health care but a lack of use by pregnant women or there can be access to and use of health care. In countries with lower fertility, access to good quality of care is almost universal and use of skilled birth attendants most commonly applies. In the systematic review, the lowest fertility settings generally had the strongest associations (except for the first pregnancy). Does this imply that universal access to good quality of care actually increases the strength of the effect of older maternal ages? Is this due to the very low risk of maternal death for gravidity one women aged 25-24 years, in the context of use of good quality health care, that any biological risks are magnified much more? Does this apply to less developed countries at different levels of care use?

Fourth, the compartmental model could be extended to include birth intervals and open populations to include in and out migration and annual entries of girls reaching their 10th

birthday. In countries with a high prevalence of HIV and AIDS, it may be interesting to model their contribution to fertility and subsequent maternal deaths. This extension could explore how the age structure (and possible changes in the age structure) of the population may have an effect on maternal mortality. However, given the lack of association between fertility changes on the maternal mortality ratio found in this study, this would be more for completeness and improved understanding of fertility changes rather than its impact on maternal mortality.

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Appendix A SYSTEMATIC REVIEW

A.1 Search Strategies

Pubmed

#1: maternal mortality

#2: (maternal mortal*) OR (maternal death*) OR (pregnancy-related (mortality OR mortalities)) OR (pregnancy-related (death or deaths)) OR (pregnancy-associated (mortality OR mortalities)) OR (pregnancy-associated (death OR deaths)) OR ("death of mother") OR (obstetric death*) OR (obstetric mortal*)

#3: #1 or #2

#4: parity OR Gravidity OR (birth order)

#5: (number of child*) OR (family size) OR parit* OR gravid* OR "parity-specific" OR "gravidity-specific"

#6: #4 OR #5

#7 #3 AND #6

#8: maternal age OR age factors

#9: ("age of mother") OR ("mother's age") OR "age-specific" OR age factor

#10 adolescent AND middle aged

#11 #8 or #9 or #10

#12: #3 AND #11

#13: #12 OR #7

#14: #3 and #11 Limits: Humans

#15: #3 and #11 Limits: Animals

#16: #15 not #14

#17: #12 not #16

#18: #12 not #16 Limits: Editorial, Letter, Case Reports

#19: #17 not #18

#20: #3 and #6 Limits: Humans

#21: #3 and #6 Limits: Animals

#22: #21 not #20

#23: #7 not #22

#24: #7not #22 Limits: Editorial, Letter, Case Reports

#25: #23 not #24

#26 #19 or #25

#27: Hlabisa or agincourt or ballabgarh or bandafassi or bandim or butajira or butajira or Chililab or chakaria or dikgale or dobowa or farafenni or filabavi or mirsarai or patiya or abhoynagar or Dhaka or iganga or mayuge or ifakara or karonga or kanchanaburi or kilifi or kintampo or kisumu or magu or manhica or mlomp or Nairobi or navrongo or niakhar or nouna or Ouagadougou or purworejo or rakai or rufiji or sapone or vadu or Manikganj or Joypurhat or wosera

#28: Leon and nicaragua

#29: Matlab and Bangladesh

#30: Search #27 or #28 or #29

#33: #30 and #3

#34: #33 and #30 Limits: Humans

#35: #33 and #30 Limits: Animals

#36: #35 not #34

#37: #33 not #36

#38: #33 and #3 Limits: Editorial, Letter, Case Reports

#39: #37 not #38

#26 or #39

EMBASE

#1: exp maternal mortality

#2: (maternal adj3 mortal$) or (maternal adj3 death$) or (pregnan$ adj2 mortal$) or (pregnan$ adj2 death$) or (death$ adj3 mother$) or (obstetric$ adj2 death$) or (obstetric$ adj2 mortal$)

#3: 1 or 2

#4: exp parity/

#5: exp birth order

#6: exp family size

#7 exp multipara/ or exp nullipara/ or exp primigravida/ or exp primipara/

#8: (number of child$) or parit$ or gravid$ or (famil$ adj3 size$) or (birth adj3 order) or "gravidity-specific" or "parity-specific"

#9: or/4-8

#10: exp maternal age

#11: (maternal adj4 age) or (maternal adj4 year$) or (age adj4 mother$) or "age-specific" or (age adj4 factor)

#12: 11 or 10

#13: 3 and 9

#14: animal experiment or animal model or animal tissue

#15: 13 not 14

#16: limit 15 to (editorial or letter)

#17: 15 not 16

#18: 3 and 12

#19: 18 not 14

#20: limit 19 to (editorial or letter)

#21: 19 not 20

#22: #21 or #17

#23: *Risk Factor/

#24: 23 and 3

#25: 24 not 14

#26: limit 25 to (editorial or letter)

#27: #25 not #26

#28: 27 or 22

#29. (leon and Nicaragua).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]

#30. (matlab and bangladesh).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]

#31. (Hlabisa or agincourt or ballabgarh or bandafassi or bandim or butajira or butajira or Chililab or chakaria or dikgale or dobowa or farafenni or filabavi or mirsarai or patiya or abhoynagar or Dhaka or iganga or mayuge or ifakara or karonga or kanchanaburi or kilifi or kintampo or kisumu or magu or manhica or mlomp or Nairobi or navrongo or niakhar or nouna or Ouagadougou or purworejo or rakai or rufiji or sapone or vadu or Manikganj or Joypurhat or wosera).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]

#32. 29 or 30 or 31

#33. 32 and 3

#34. 33 not 14

#35. limit 33 to (editorial or letter)

#36. 34 not 35

#37. 36 or 28

POPLINE

Age

#1: (="Maternal Mortality") & ="Maternal Age"

#2: (="Maternal Mortality") & ="age factors"

#3 (maternal mortal*/maternal death*)& (mother's age/age of mother/age of the mother/maternal age/age-specific)

#4 (pregnancy-related mortal*/pregnancy-related death*) & (mother's age/age of mother/age of the mother/maternal age/age-specific)

#5 (pregnancy-associated mortal*/pregnancy-associated death*) & (mother's age/age of mother/age of the mother/maternal age/age-specific)

#6 (death of the mother/death of mother) & (mother's age/age of mother/age of the mother/maternal age/age-specific)

#7 (obstetric death*/obstetric mortal*) & (mother's age/age of mother/age of the mother/maternal age/age-specific)

#8: ="Maternal Age" & (maternal mortal*/maternal death*/pregnancy-related mortal*/pregnancy-related death*/ pregnancy-associated mortal*/pregnancy-associated death*/ death of the mother/death of mother/ obstetric death*/obstetric mortal*)

#9: ="Age Factors" & (maternal mortal*/maternal death*/pregnancy-related mortal*/pregnancy-related death*/ pregnancy-associated mortal*/pregnancy-associated death*/ death of the mother/death of mother/ obstetric death*/obstetric mortal*)

#10: (="Maternal Mortality") & (mother's age/age of mother/age of the mother/maternal age/age-specific)

Number of previous pregnancies

#11: ="Maternal Mortality" & (="Parity" / ="Birth Order" / ="Pregnancy Rate" / ="Family Size" / ="Primiparity" / ="Nulliparity" / ="Multiparity")

#12: (maternal mortal*/maternal death*/pregnancy-related mortal*/pregnancy-related death*/pregnancy-associated mortal*/pregnancy associated death*/death of mother/death of the mother/obstetric death*/obstetric mortal*) & (gravid*/parit*/birth order/family size/parity-specific/gravidity-specific)

#13: ="Maternal Mortality" & (gravid*/parit*/birth order/family size/parity-specific/gravidity-specific)

#14: (="Parity" / ="Birth Order" / ="Pregnancy Rate" / ="Family Size" / ="Primiparity" / ="Nulliparity" / ="Multiparity") & (maternal mortal*/maternal death*/pregnancy-related

mortal*/pregnancy-related death*/pregnancy-associated mortal*/pregnancy associated death*/death of mother/death of the mother/obstetric death*/obstetric mortal*)

DSS:

#15 ="Maternal Mortality" & (Hlabisa /agincourt /ballabgarh /bandafassi /bandim /butajira /butajira /Chililab /chakaria /dikgale /dobowa /farafenni /filabavi /mirsarai /patiya /abhoynagar /Dhaka /iganga /mayuge /ifakara /karonga /kanchanaburi /kilifi /kintampo /kisumu /magu /manhica /mlomp /Nairobi /navrongo /niakhar /nouna /Ouagadougou /purworejo /rakai /rufiji /sapone /vadu /Manikganj /Joypurhat /wosera)

#16 ="Maternal Mortality" & (Leon & Nicaragua)

#17 ="Maternal Mortality" & (Matlab & Bangladesh)

#18 (maternal mortal*/maternal death*/pregnancy-related mortal*/pregnancy-related death*/pregnancy-associated mortal*/pregnancy associated death*/death of mother/death of the mother/obstetric death*/obstetric mortal*) & (Hlabisa /agincourt /ballabgarh /bandafassi /bandim /butajira /butajira /Chililab /chakaria /dikgale /dobowa /farafenni /filabavi /mirsarai /patiya /abhoynagar /Dhaka /iganga /mayuge /ifakara /karonga /kanchanaburi /kilifi /kintampo /kisumu /magu /manhica /mlomp /Nairobi /navrongo /niakhar /nouna /Ouagadougou /purworejo /rakai /rufiji /sapone /vadu /Manikganj /Joypurhat /wosera)

#19 (maternal mortal*/maternal death*/pregnancy-related mortal*/pregnancy-related death*/pregnancy-associated mortal*/pregnancy associated death*/death of mother/death of the mother/obstetric death*/obstetric mortal*) & (Matlab & Bangladesh)

Others:

#20: ="Maternal Mortality" & = "causes of death" & = "demographic factors"

A.2 Data Extraction Form

Systematic Review of Childbearing Composition and Maternal Mortality -Data Extraction Form

Report Identification Number

Date of Extraction / /

Reviewer

GENERAL INFORMATION

1 Title

2 First Author

3 Other Authors

4 Type of publication (e.g. journal, book chapter, government report)

5 Journal title/book title

6 Year of publication (or year of completion if unpublished)

7 Country of publication

8 Language of publication

CHARACTERISTICS OF THE STUDY

9 Country and Region/City of study

10 Study period

[/] to [/]

11 Study design [ ]

1 Cohort
2 Case control studies
a. traditional
b. nested
c. matched
3 Cross-sectional survey
4 Randomised control trial
5 CEMD
6 RAMOS
7 Others (please state) _____

12 Place of delivery [ ]

1 Home
2 Health facility
3 Mixed (please state) _____
4 Others (please state) _____
5 Unknown

13 Describe any specific exclusion criteria into study (e.g. unmarried women excluded)

14a Is there information regarding the proportion of women lost to follow-up (or non-responders or those not included in the analysis? (Y/N/NA) [ ]

14b If yes, percentage of women lost to followed/non-responding [ ]

15a Have the characteristics of the women lost to follow-up(non respondents or excluded from the analysis) been described (Y/N/NA) [ ]

15b If yes, are the characteristics different from the rest of the population? [ ]

16 Forms of reporting data [ ]

1 Crude only
2 Adjusted for confounding variables only
3 Crude and adjusted

17 Comments

STUDY METHODS - MATERNAL MORTALITY

18a Is a definition of maternal death included in the study (Y/N) ☐

18b If yes, were the following included in the study definition of maternal death (Y/N)

- 1 early deaths ☐
- 2 acc/incidental deaths ☐
- 3 unknown causes ☐
- 4 Other (please state) _____ ☐

18c The number of postpartum days included in the definition of study maternal deaths ☐

19 Number of maternal deaths ☐

20 Ascertainment of maternal deaths ☐

- 1 Vital statistics/census
- 2 Medical records
- 3 birth and death linkage
- 4 Active surveillance
- 5 Confidential enquiries
- 6 DSS
- 7 RAMOS
- 8 Survey
- 9 Clinical data collected for this study
- 10 Mixed (please state) _____
- 11 Other (please state) _____

21 Population at risk estimates (denominator used) ☐

- 1 live births
- 2 live births + stillbirths
- 3 pregnancies
- 4 Maternities/confinements/deliveries
- 5 Other (please state) _____

22 Number of women in the at risk group ☐

23 Ascertainment of population at risk ☐

- 1 Vital statistics/census
- 2 Medical records
- 3 Active surveillance
- 4 Survey - with VA
- 5 Survey - without VA
- 6 Unreported in study
- 7 Mixed (please state) _____
- 8 Other (please state) _____

24 Did the population at risk data cover the same period and population as the information on maternal deaths? (Y/N/NA) ☐

25 Comments

STUDY METHODS - Maternal Age

26 Was maternal age defined as the age of mother at the time of the pregnancy outcome? (Y/N/Unknown) ☐

27a Was the number of women with missing/unknown maternal age reported? (Y/N) ☐

27b If yes, how many women had missing maternal age ☐

28 Ascertainment of maternal age ☐

1 Vital statistics/census
2 Medical records
3 Active surveillance
4 Survey - self reported
5 Survey - reported by relatives
6 Unreported in the study
7 Mixed (please state) _____
8 Other (please state) _____

STUDY METHODS - Number of previous pregnancies

29 What was the study measurement used? ☐

1 Parity
2 Gravidity
3 Live birth order
4 Pregnancy order
5 Number of living children
6 Other (please state) _____

30a Does the study include a definition? (Y/N) ☐

30b If yes, please specify

31a Was the number of women with missing/unknown past pregnancy history reported? (Y/N) ☐

31b If yes, how many women had missing exposure information ☐

32 Ascertainment of number of previous pregnancies ☐

1 Vital statistics/census
2 Medical records
3 Active surveillance
4 Survey - self reported
5 Survey - reported by relatives
6 Unreported in the study
7 Mixed (please state) _____
8 Other (please state) _____

33 Comments

STUDY RESULTS - MATERNAL AGE

34a Was adjusted results reported? (Y/N)

34b If yes, what was the adjustment method?

1 Multivariable regression
2 Standardisation
3 Matching
4 Other (please state) _____

34c If yes, was a measure of number of previous pregnancy controlled for? (Y/N)

34d If yes, please list all variables adjusted for in the model

35 Reference group used for maternal age

36 Crude results by maternal age (fill in as much as possible, please include reference group)

maternal age group	no. of maternal death	no. of women at risk	OR/RR	lower CI	upper CI	p value

37 Adjusted results by maternal age (fill in as much as possible, please include reference group)

maternal age group	no. of maternal death	no. of women at risk	OR/RR	lower CI	upper CI	p value

38 Comments

STUDY RESULTS - NUMBER OF PREVIOUS PREGNANCIES

39a *Was adjusted results reported?* (Y/N) ☐

39b If yes, what was the adjustment method? ☐

1 Multivariable regression
2 Standardisation
3 Matching
4 Other (please state) _____

39c If yes, was maternal age controlled for? (Y/N) ☐

39d If yes, please list all variables adjusted for in the model

☐

40 Reference group used for number of previous pregnancy ☐

41 Crude results by number of previous pregnancy (fill in as much as possible, please include reference group)

maternal age group	*no. of maternal death*	*no. of women at risk*	OR/RR	lower CI	upper CI	p value

42 Adjusted results by maternal age (fill in as much as possible, please include reference group)

maternal age group	no. of maternal death	no. of women at risk	OR/RR	lower CI	upper CI	p value

43 Comments

☐

A.3 Newcastle-Ottawa quality assessment scale

The original Newcastle-Ottawa Scale [227] was modified to meet the needs of this study. Item 2 in the comparability section (in italics) was only included in the quality of assessment of studies reporting the relationship between number of previous pregnancies and maternal mortality.

Cohort studies and surveys

Selection

1 Representativeness of the exposed cohort
   - a *truly representative of the average ever pregnant woman in the community**
   - b somewhat representative of the average ever pregnant woman years in the community *
   - c selected group of users e.g. nurses, volunteers
   - d no description of the derivation of the cohort

2 Selection of the non exposed cohort
   - a drawn from the same community as the exposed cohort *
   - b *drawn from a different source*
   - c no description of the derivation of the non exposed cohort

3 Ascertainment of exposure
   - a *secure record* (e.g. surgical records) *
   - b structured interview *
   - c written self report
   - d no description

Comparability

1 Comparability of cohorts on the basis of the design or analysis
   - a study controls for age/parity
   - b study controls for any additional factor *

2 *Was a clear definition of a number of previous pregnancies included?*
   - *a yes **
   - *b no*

Outcome

1 Assessment of outcome
   - a independent blind assessment, using medical records/record linkage*
   - b detailed verbal autopsy with special effort to identify maternal deaths*
   - c reported by relative without further VA
   - d no description/unclear

2 Was follow-up long enough for outcomes to occur
   - a yes (at least up to the delivery of pregnancy)
   - b no

3 Adequacy of follow up/response of cohorts
   - a complete follow up - all subjects accounted for*

b subjects lost to follow up unlikely to introduce bias - small number lost/non responsive ≥ 80 % follow up/responded, or description provided of those lost/unresponsive*

c follow up/response rate < 80% and no description of those lost

d no statement

Case control studies

Selection

1 Is the case definition adequate?
   a yes, with independent validation *
   b yes, e.g. record linkage or based on self reports
   c no description
2 Representativeness of the cases
   a consecutive or obviously representative series of cases*
   b potential for selection biases or not stated
3 Selection of Controls
   a community controls *
   b hospital controls
   c no description

Comparability

1 Comparability of cases and controls on the basis of the design or analysis
   a study controls for age/previous pregnancy *
   b study controls for any additional factor ¯ (This criteria could be modified to indicate specific control for a second important factor)*
2 *Was a clear definition of a number of previous pregnancies included?*
   *a yes **
   b no

Exposure

1 Ascertainment of exposure
   a secure record (e.g. surgical records)*
   b structured interview where blind to case/control status*
   c interview not blinded to case/control status
   d written self report or medical record only
   e no description
2 Same method of ascertainment for cases and controls
   a yes *
   b no
3 Non-response rate
   a same rate for both groups*
   b non respondents described
   c rate different and no designation

A.4 Funnel plots to assess the publication bias of studies investigating the association between maternal age and maternal death

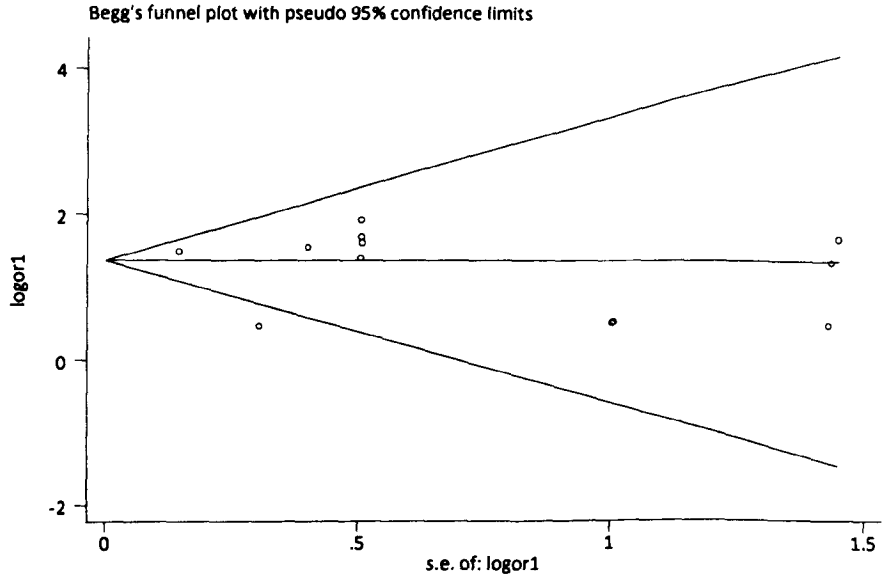

Figure A.1: Funnel plot to assess the publication bias of studies that investigated the crude odds of maternal death comparing girls aged<15/16 to women aged 20-24.

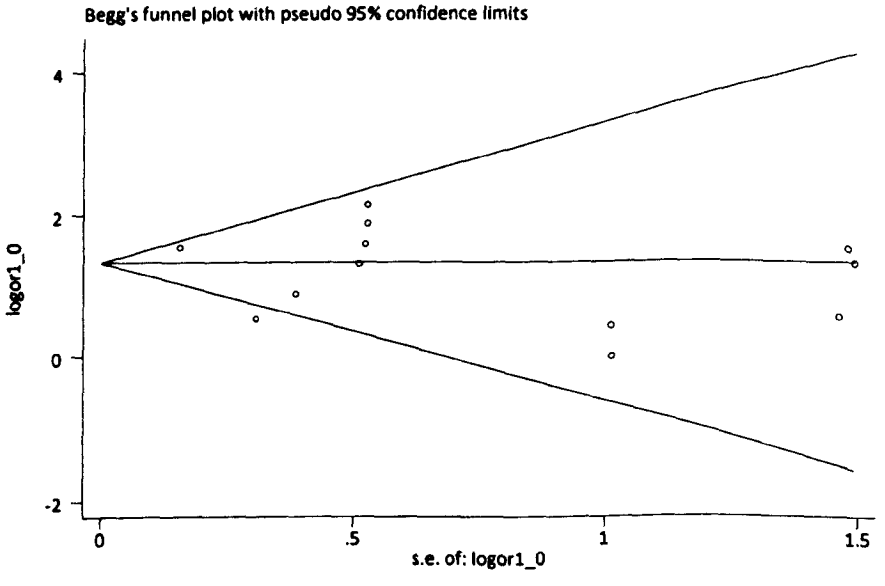

Figure A.2: Funnel plot to assess the publication bias of studies that investigated the crude odds of maternal death comparing girls aged<15/16 to adolescents aged 15/16-19.

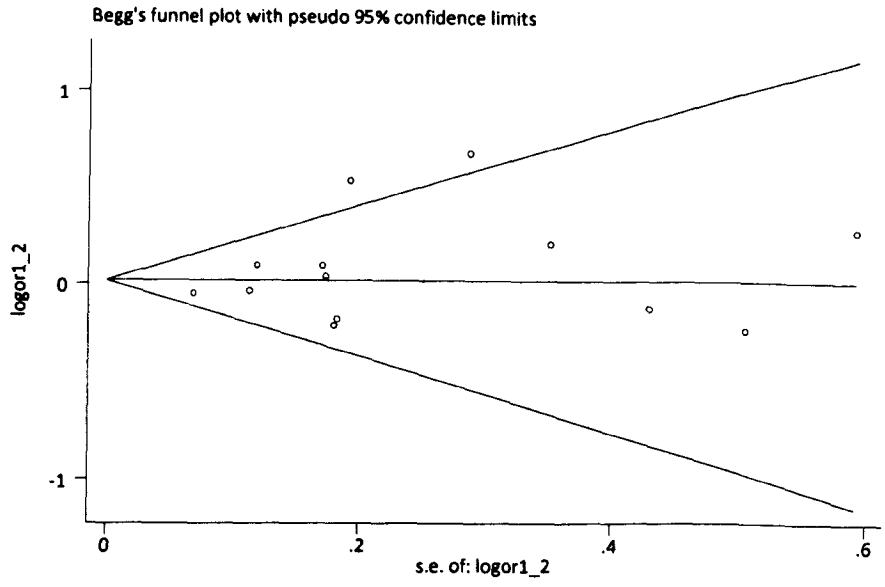

Figure A.3: Funnel plot to assess the publication bias of studies that investigated the crude odds of maternal death comparing adolescents aged 15/16-19 to women aged 20-24.

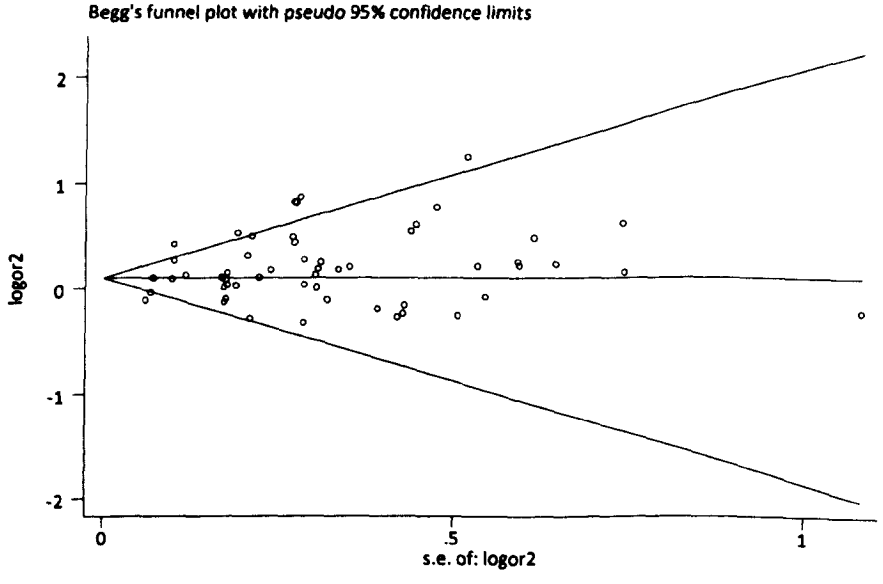

Figure A.4: Funnel plot to assess the publication bias of studies that investigated the crude odds of maternal death comparing women aged <20 to women aged 20-24.

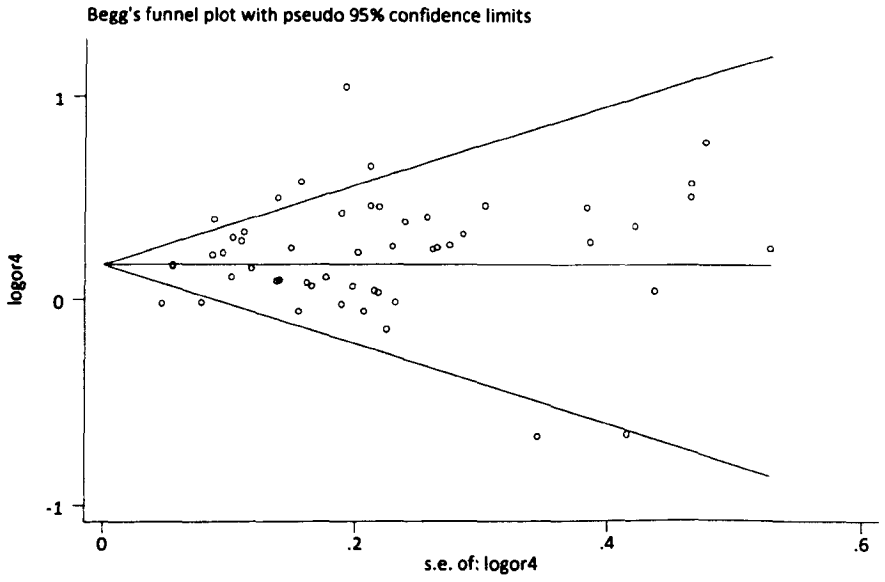

Figure A.5: Funnel plot to assess the publication bias of studies that investigated the crude odds of maternal death comparing women aged 25-29 to women aged 20-24.

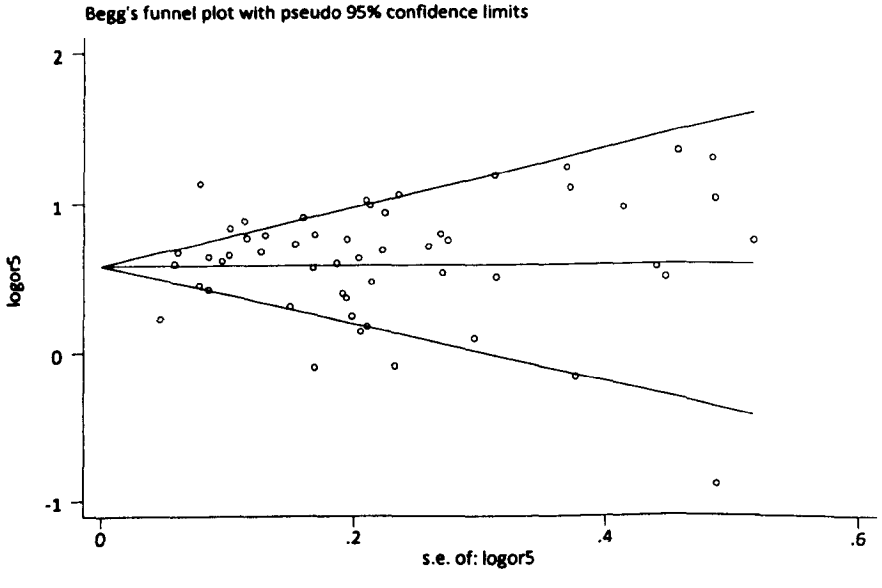

Figure A.6: Funnel plot to assess the publication bias of studies that investigated the crude odds of maternal death comparing women 30-34 to women aged 20-24.

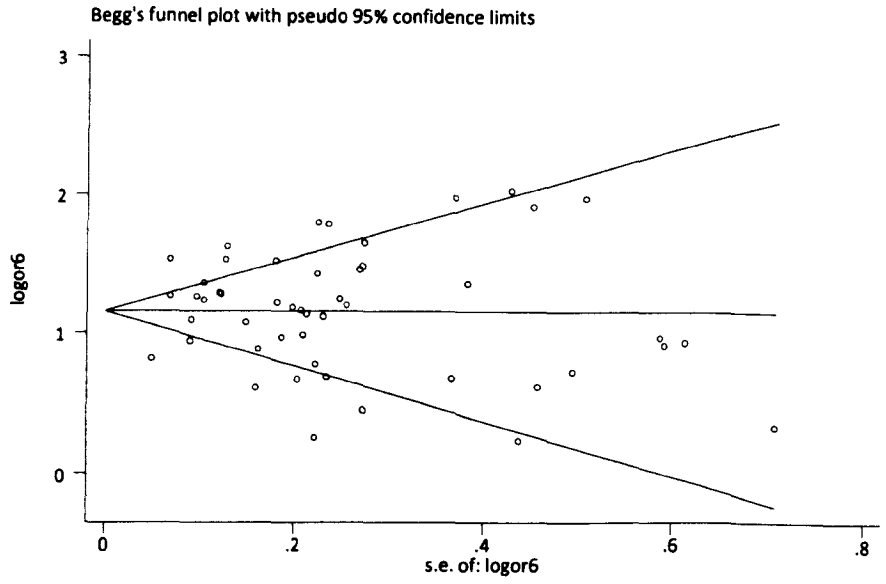

Figure A.7: Funnel plot to assess the publication bias of studies that investigated the crude odds of maternal death comparing women 35-39 to women aged 20-24.

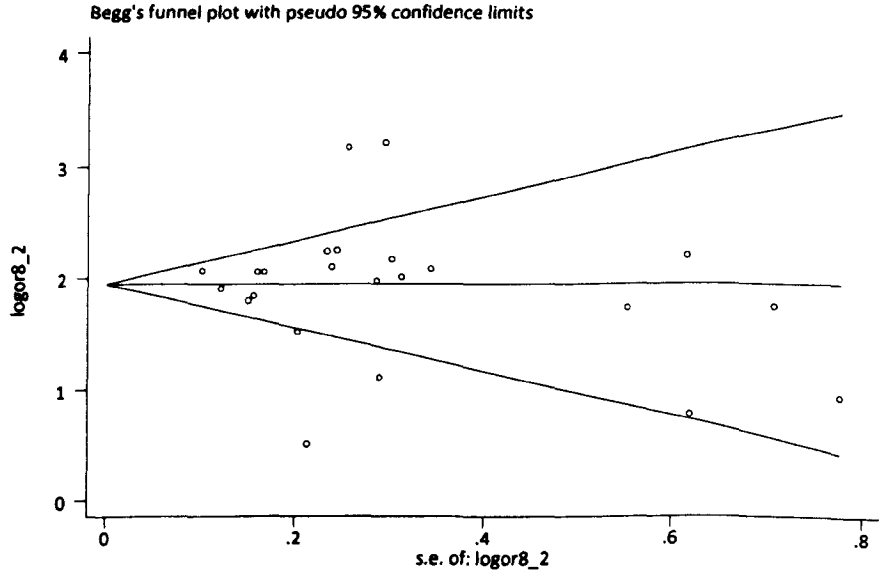

Figure A.8: Funnel plot to assess the publication bias of studies that investigated the crude odds of maternal death comparing women 40-44 to women aged 20-24.

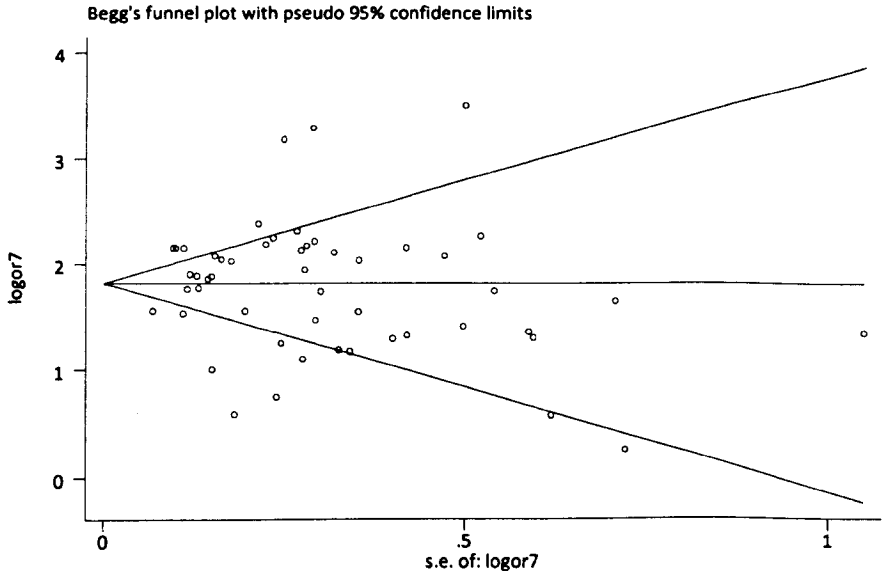

Figure A.9: Funnel plot to assess the publication bias of studies that investigated the crude odds of maternal death comparing women aged 40 or over to women aged 20-24.

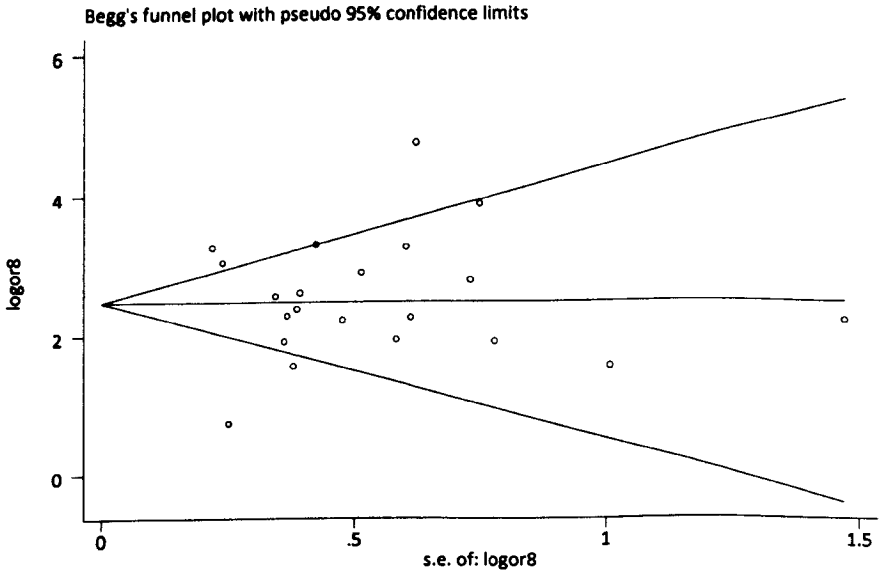

Figure A.10: Funnel plot to assess the publication bias of studies that investigated the crude odds of maternal death comparing women aged 45 or over to women aged 20-24.

A.5 Funnel plots to assess the publication bias of studies investigating the association between the number of previous pregnancies and maternal death

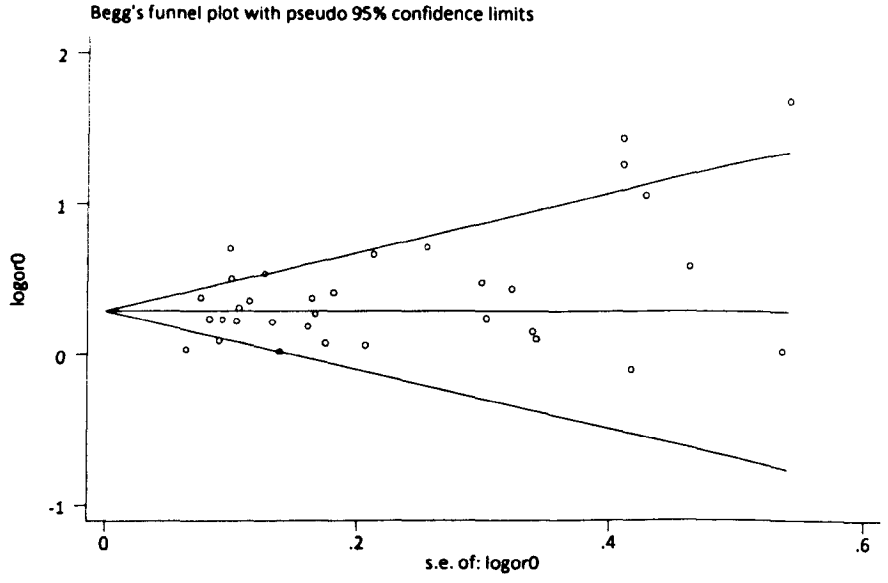

Figure A.11: Funnel plot to assess the publication bias of studies that investigated the crude odds of maternal death comparing women with no previous pregnancies to women with one previous pregnancy.

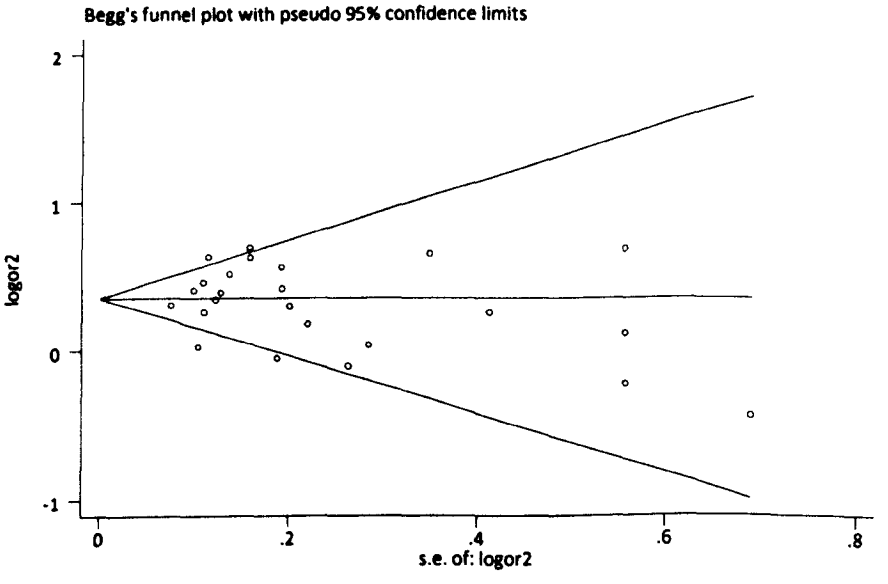

Figure A.12: Funnel plot to assess the publication bias of studies that investigated the crude odds of maternal death comparing women with two previous pregnancies to women with one previous pregnancy.

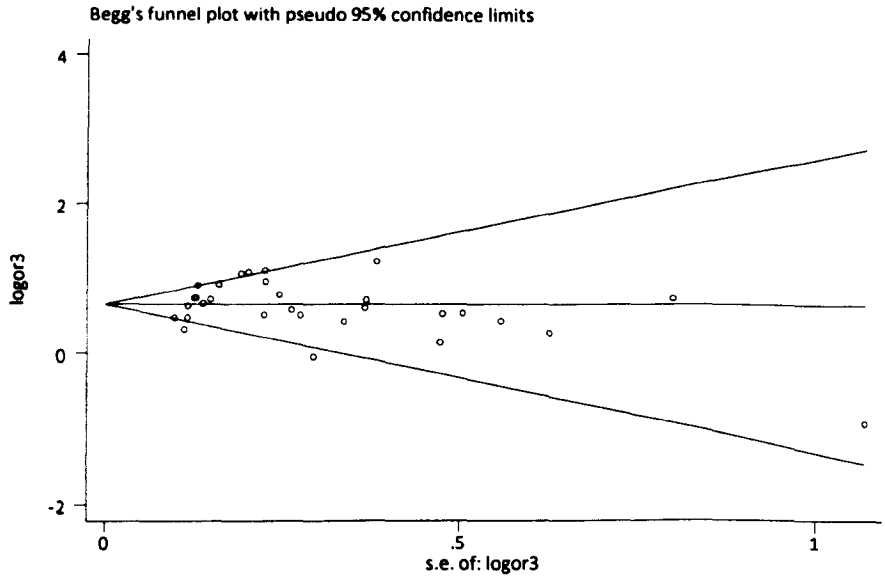

Figure A.13: Funnel plot to assess the publication bias of studies that investigated the crude odds of maternal death comparing women with three previous pregnancies to women with one previous pregnancy.

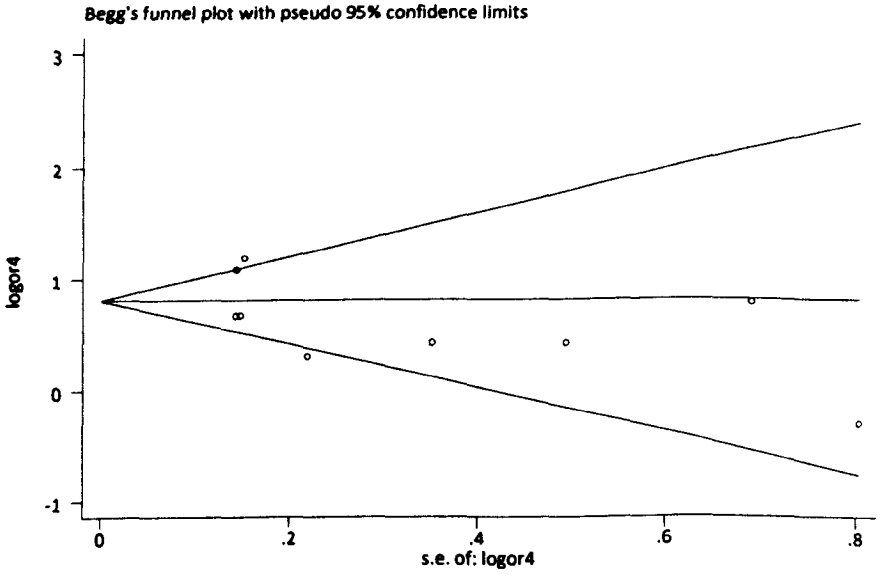

Figure A.14: Funnel plot to assess the publication bias of studies that investigated the crude odds of maternal death comparing women with four previous pregnancies to women with one previous pregnancy.

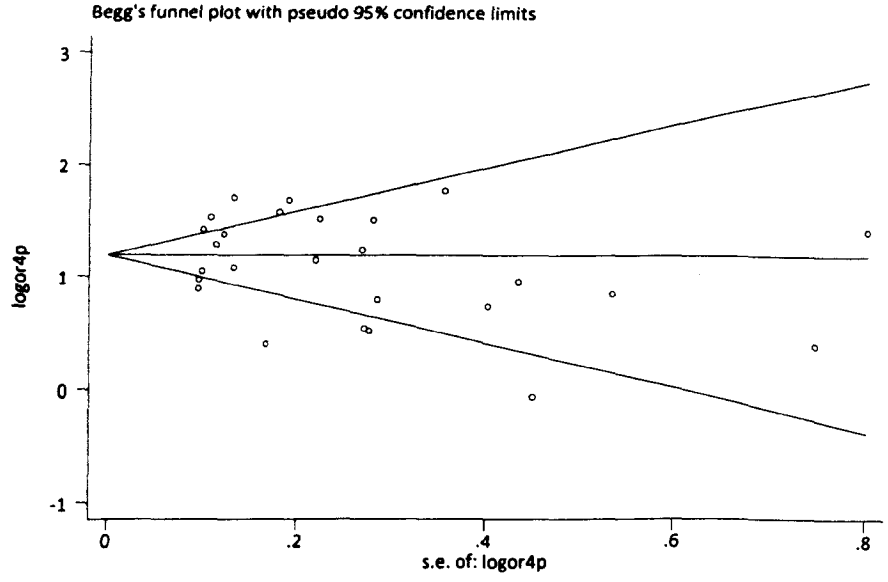

Figure A.15: Funnel plot to assess the publication bias of studies that investigated the crude odds of maternal death comparing women with four or more previous pregnancies to women with one previous pregnancy.

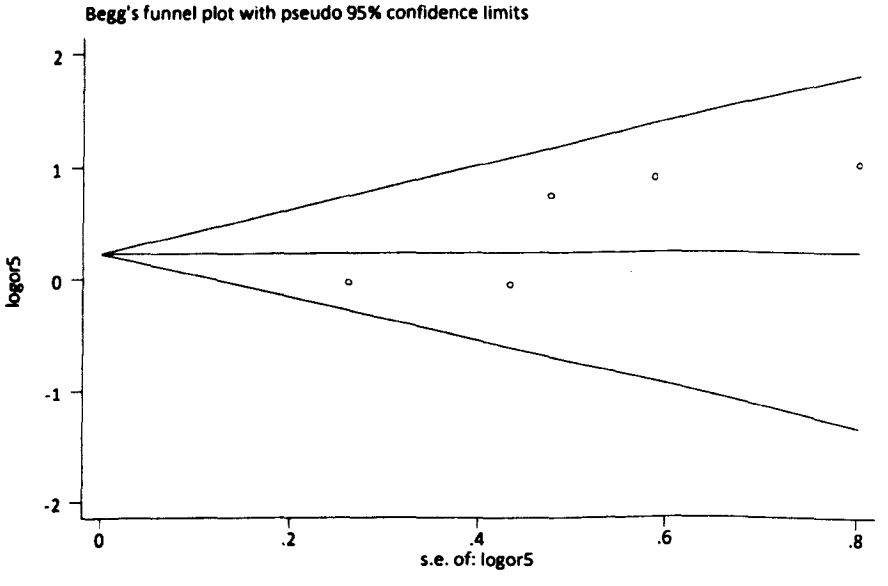

Figure A.16: Funnel plot to assess the publication bias of studies that investigated the crude odds of maternal death comparing women with five previous pregnancies to women with one previous pregnancy.

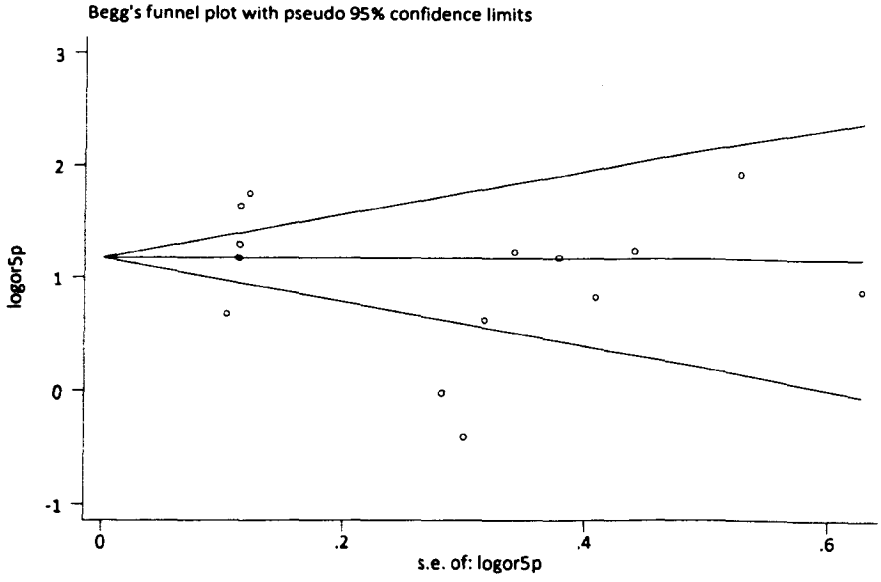

Figure A.17: Funnel plot to assess the publication bias of studies that investigated the crude odds of maternal death comparing women with five or more previous pregnancies to women with one previous pregnancy.

A.6 Forest plots of the association between maternal age and maternal death by study quality

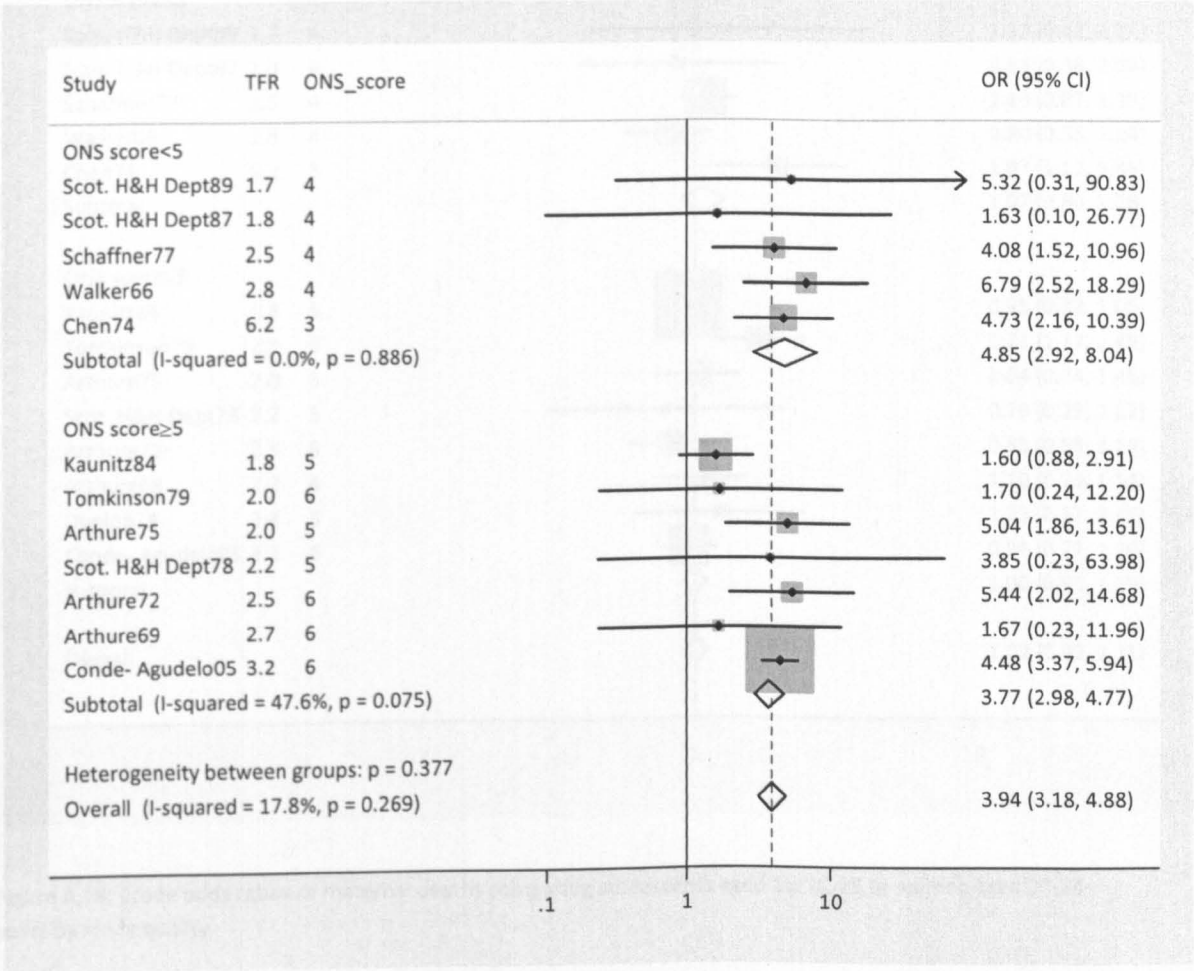

Figure A.18: Crude odds ratios of maternal deaths comparing girls aged <15/16 to women aged 20-24 years by study quality.

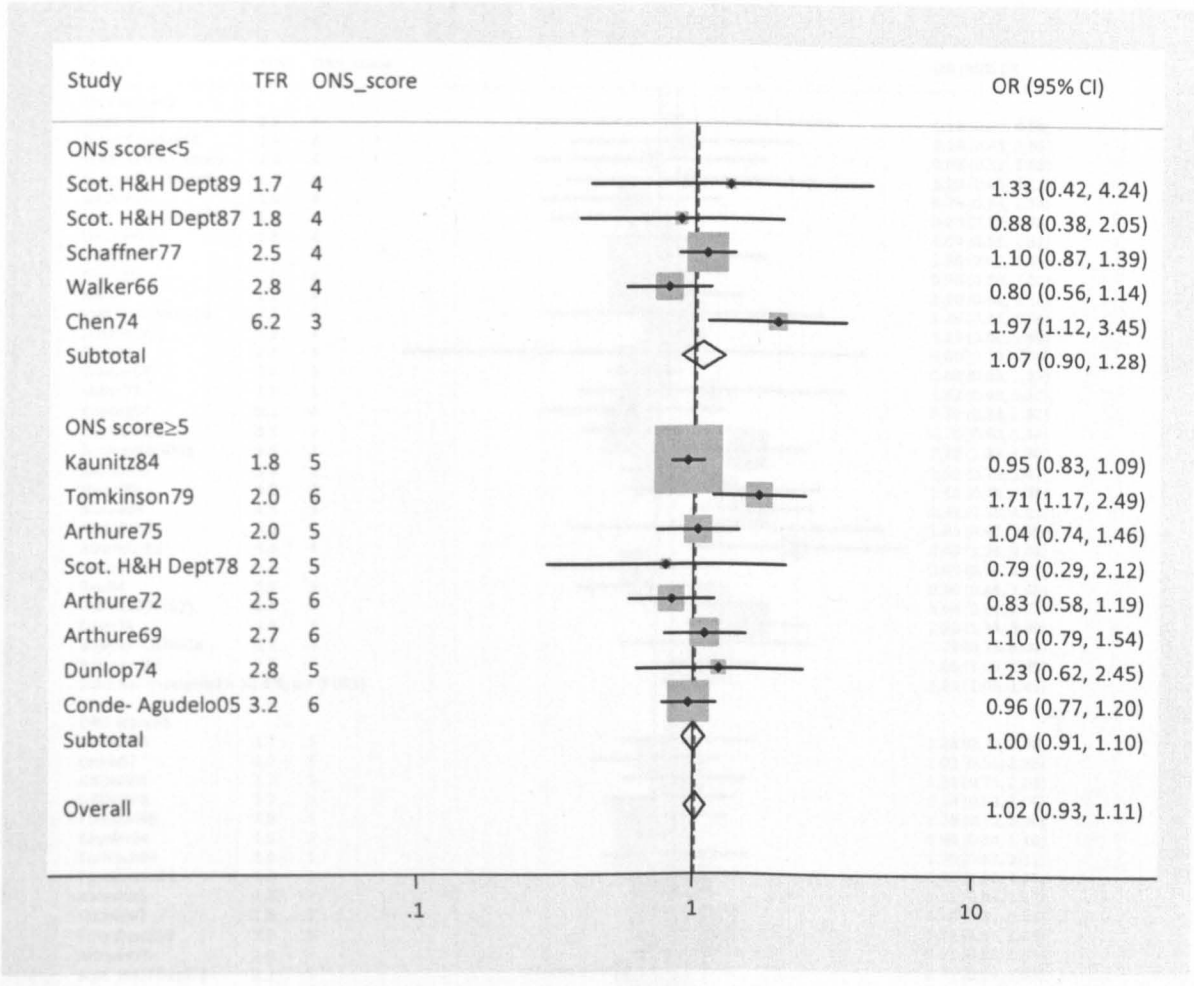

Figure A.19: Crude odds ratios of maternal deaths comparing adolescents aged 15/16-19 to women aged 20-24 years by study quality.

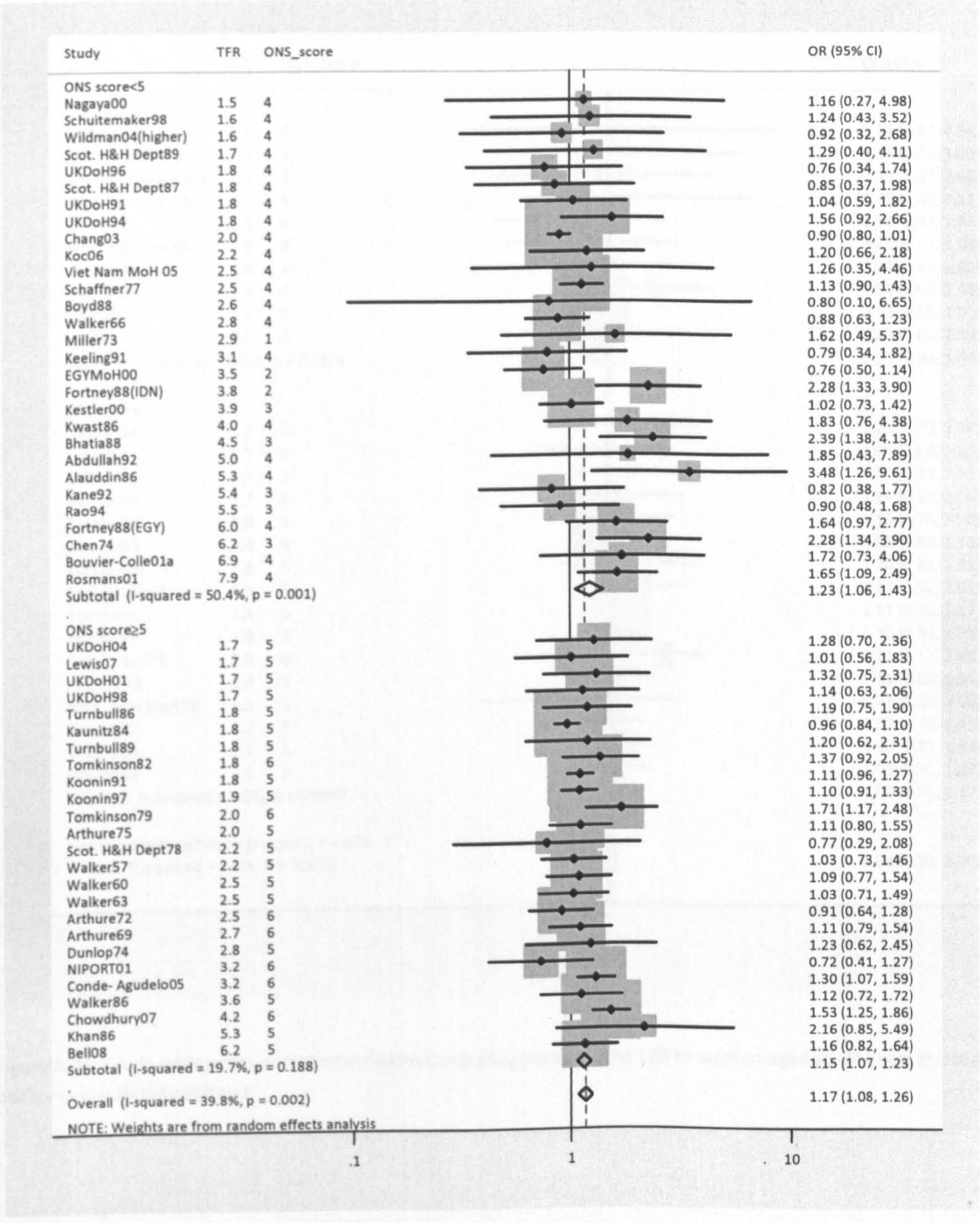

Figure A.20: Crude odds ratios of maternal deaths comparing women aged <20 to women aged 20-24 years by study quality.

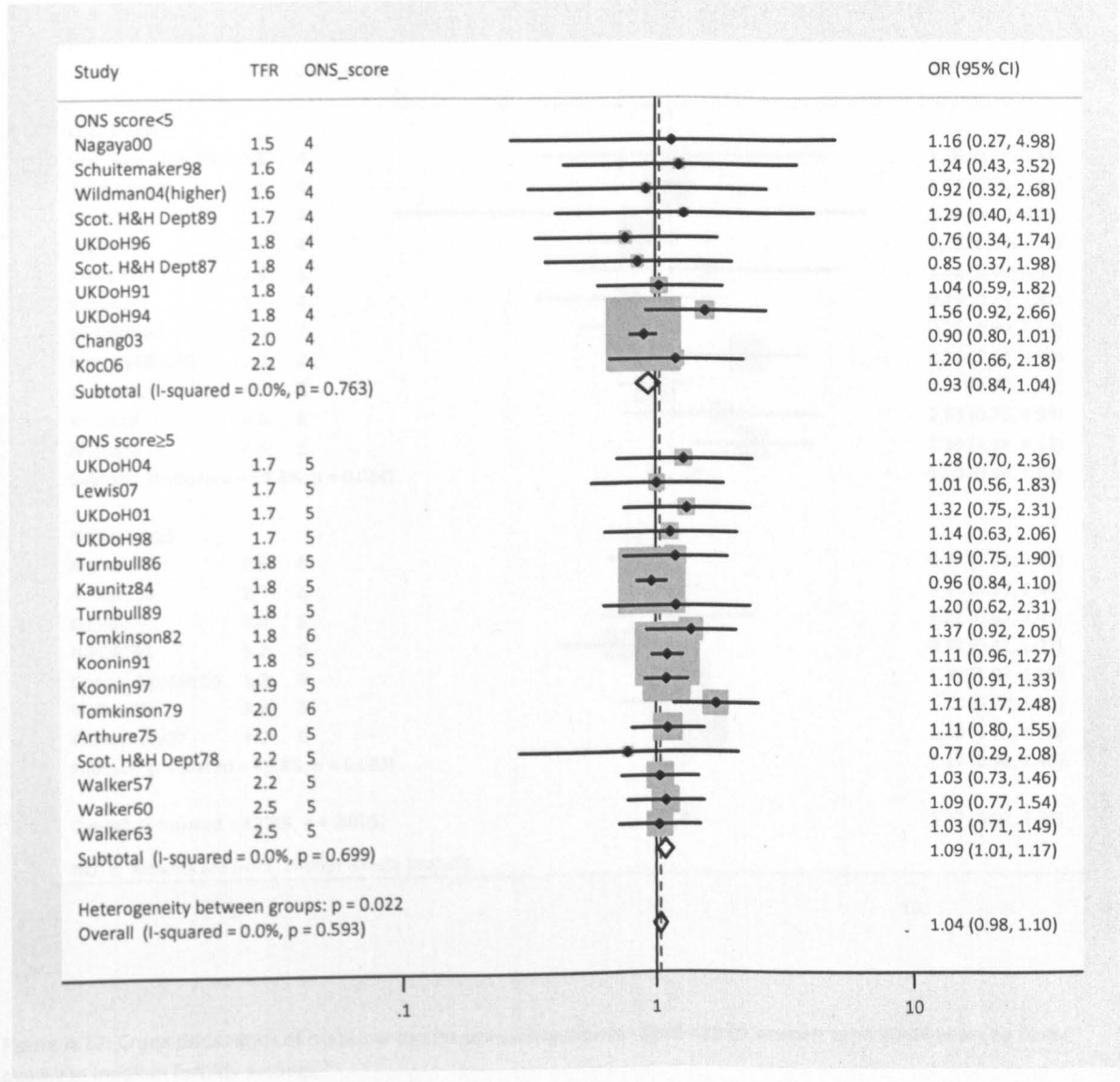

Figure A.21: Crude odds ratios of maternal deaths comparing women aged <20 to women aged 20-24 years by study quality in low fertility settings.

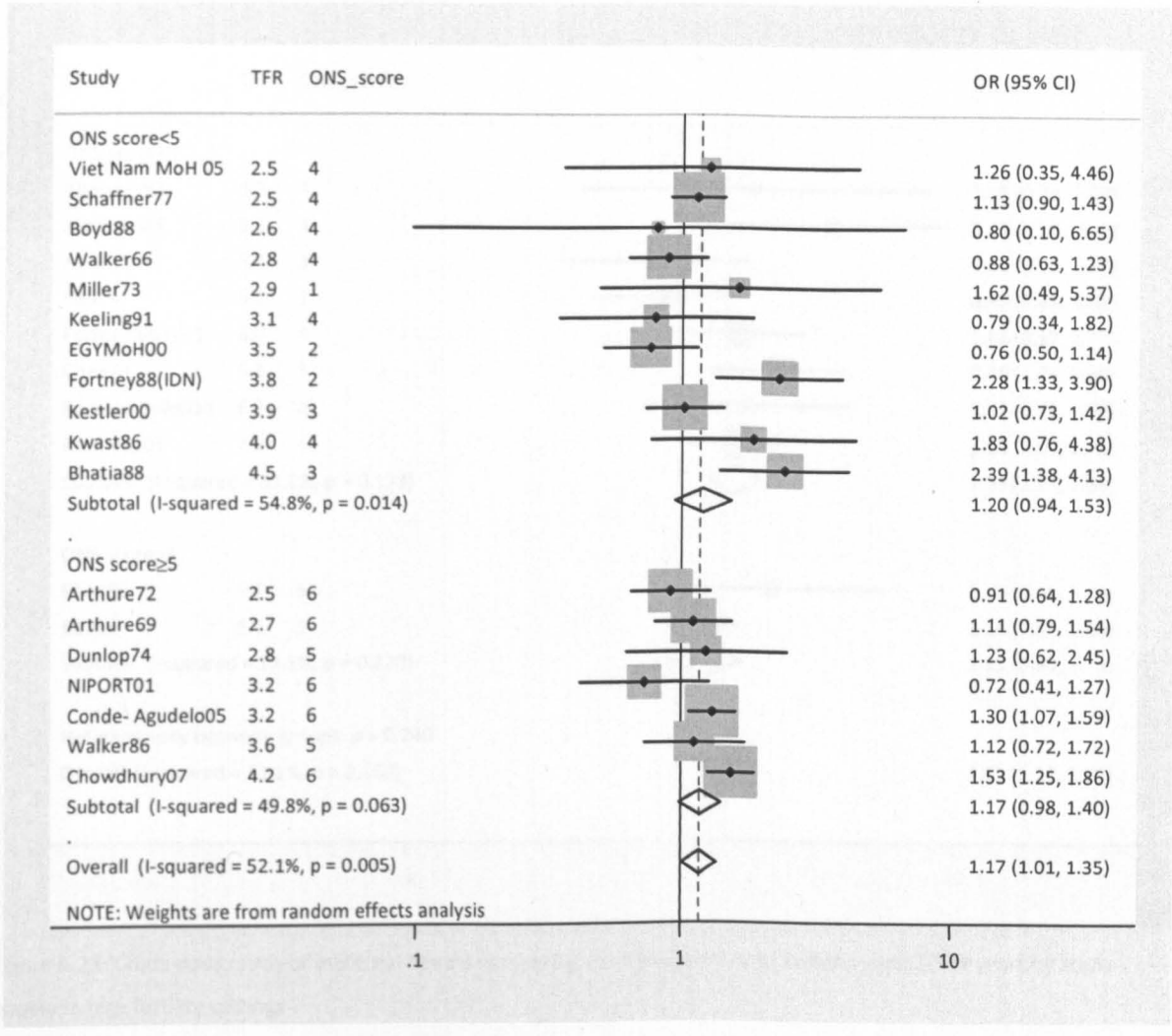

Figure A.22: Crude odds ratios of maternal deaths comparing women aged <20 to women aged 20-24 years by study quality in medium fertility settings

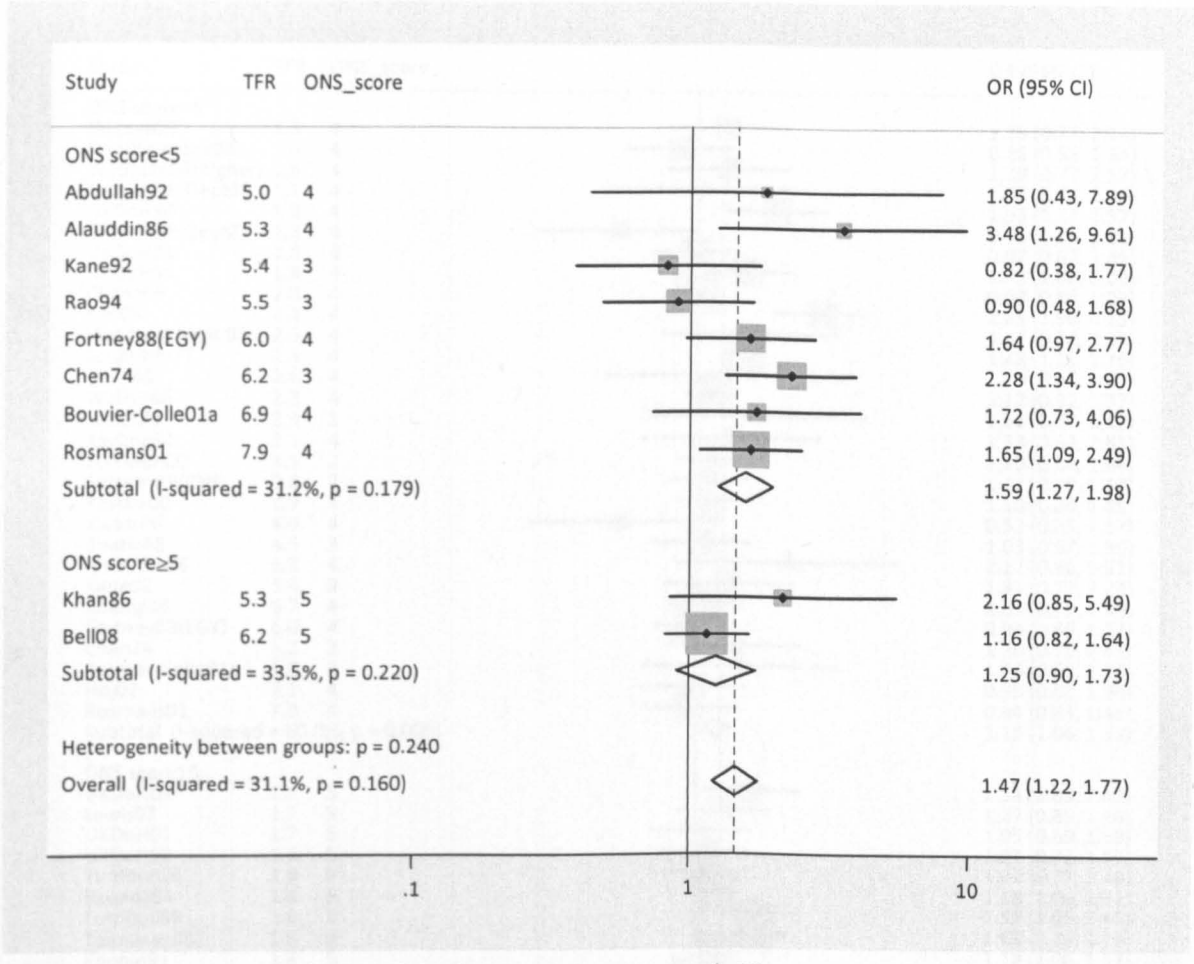

Figure A.23: Crude odds ratios of maternal deaths comparing women aged <20 to women aged 20-24 years by study quality in high fertility settings

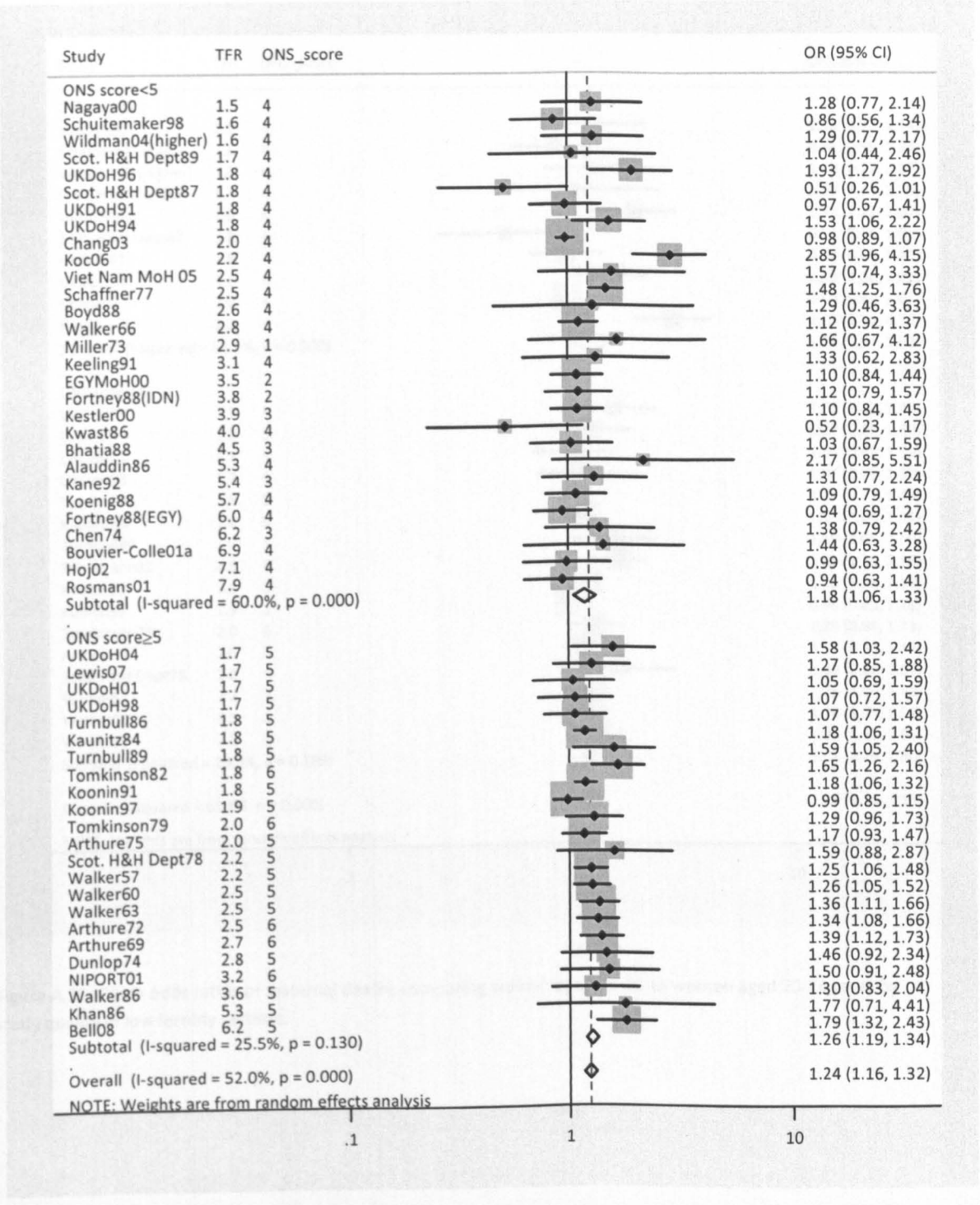

Figure A.24: Crude odds ratios of maternal deaths comparing women aged 25-29 to women aged 20-24 years by study quality.

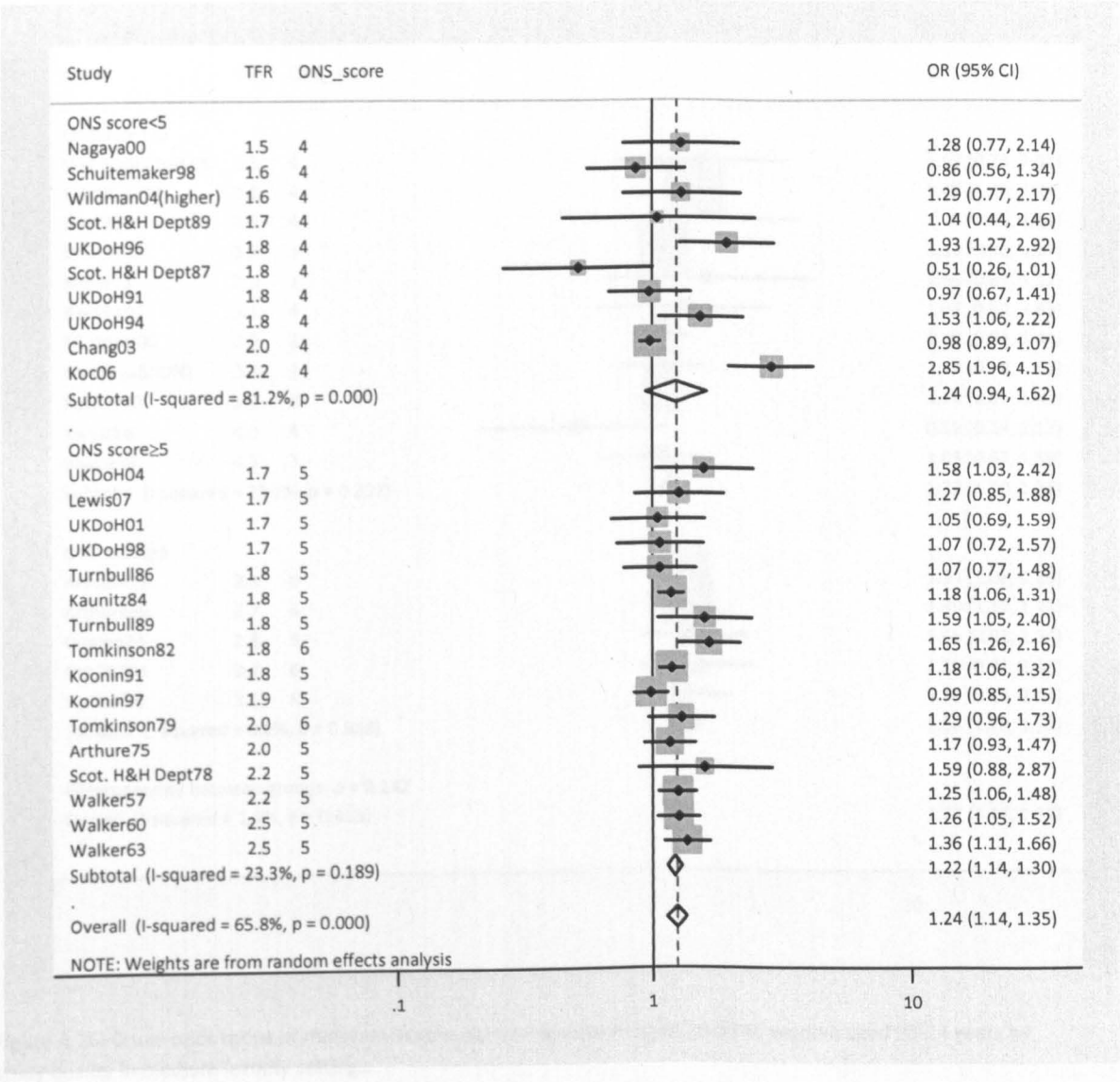

Figure A.25: Crude odds ratios of maternal deaths comparing women aged 25-29 to women aged 20-24 years by study quality in low fertility settings.

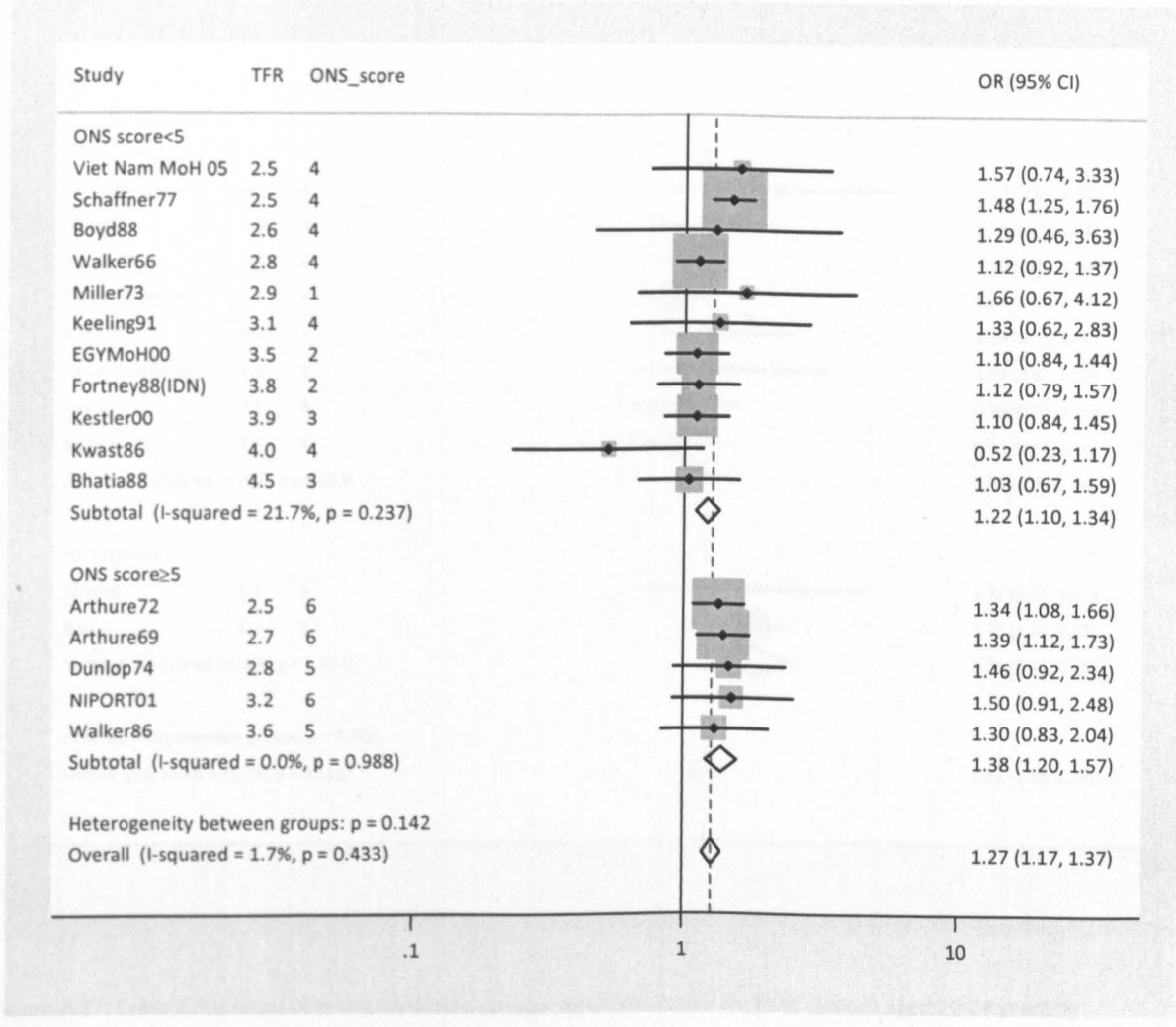

Figure A.26: Crude odds ratios of maternal deaths comparing women aged 25-29 to women aged 20-24 years by study quality in medium fertility settings.

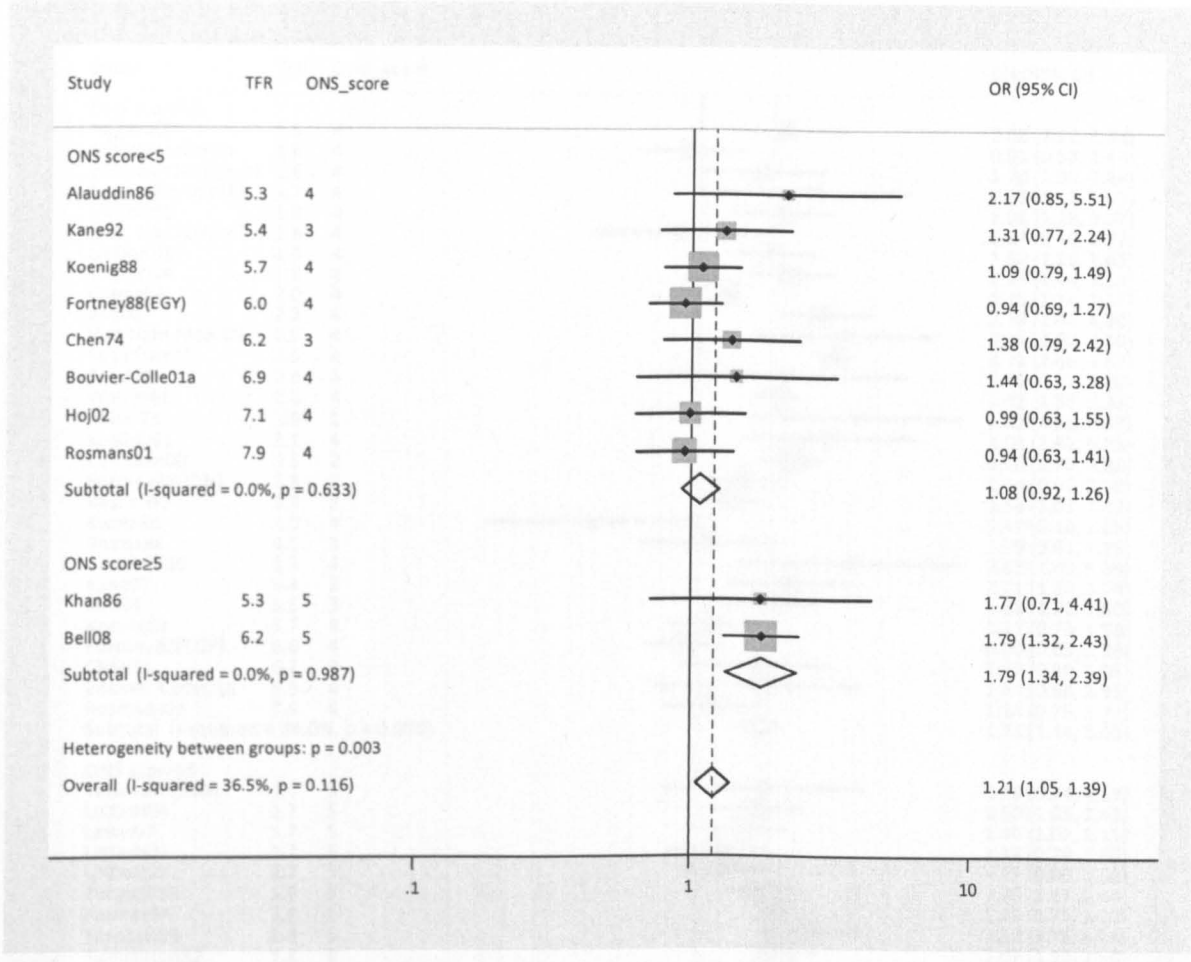

Figure A.27: Crude odds ratios of maternal deaths comparing women aged 25-29 to women aged 20-24 years by study quality in high fertility settings.

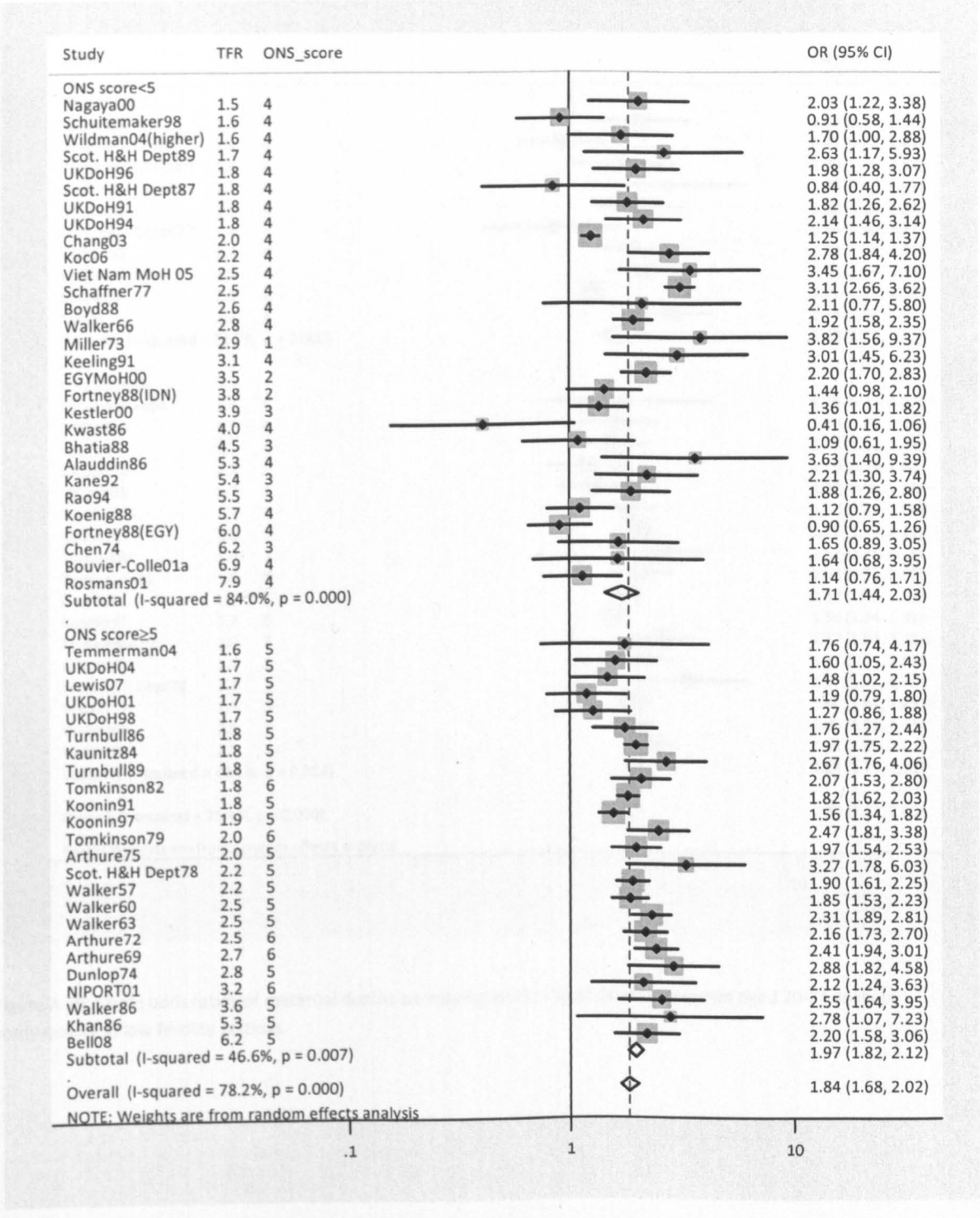

Figure A.28: Crude odds ratios of maternal deaths comparing women aged 30-34 to women aged 20-24 years by study quality.

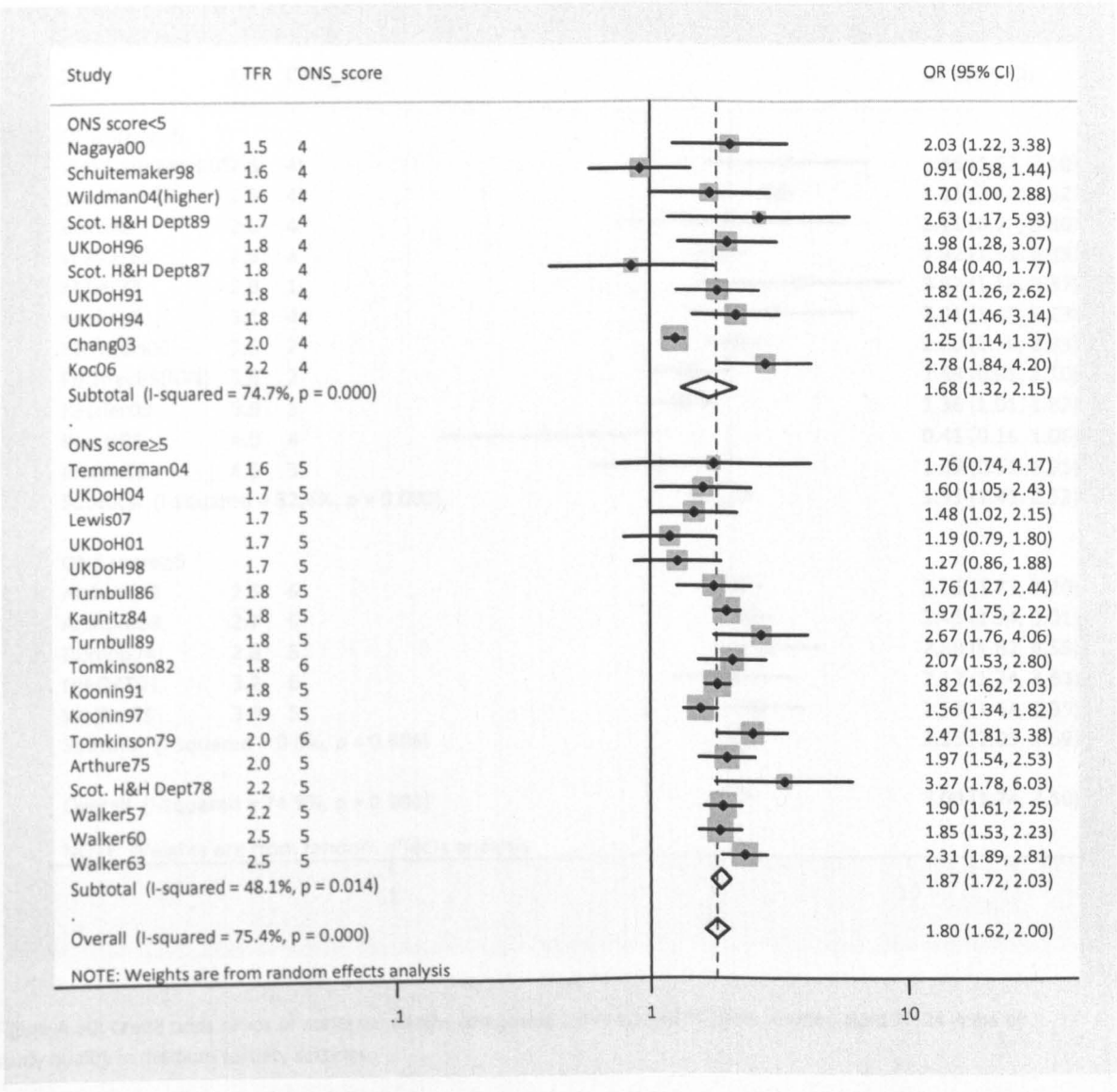

Figure A.29: Crude odds ratios of maternal deaths comparing women aged 30-34 to women aged 20-24 years by study quality in low fertility settings.

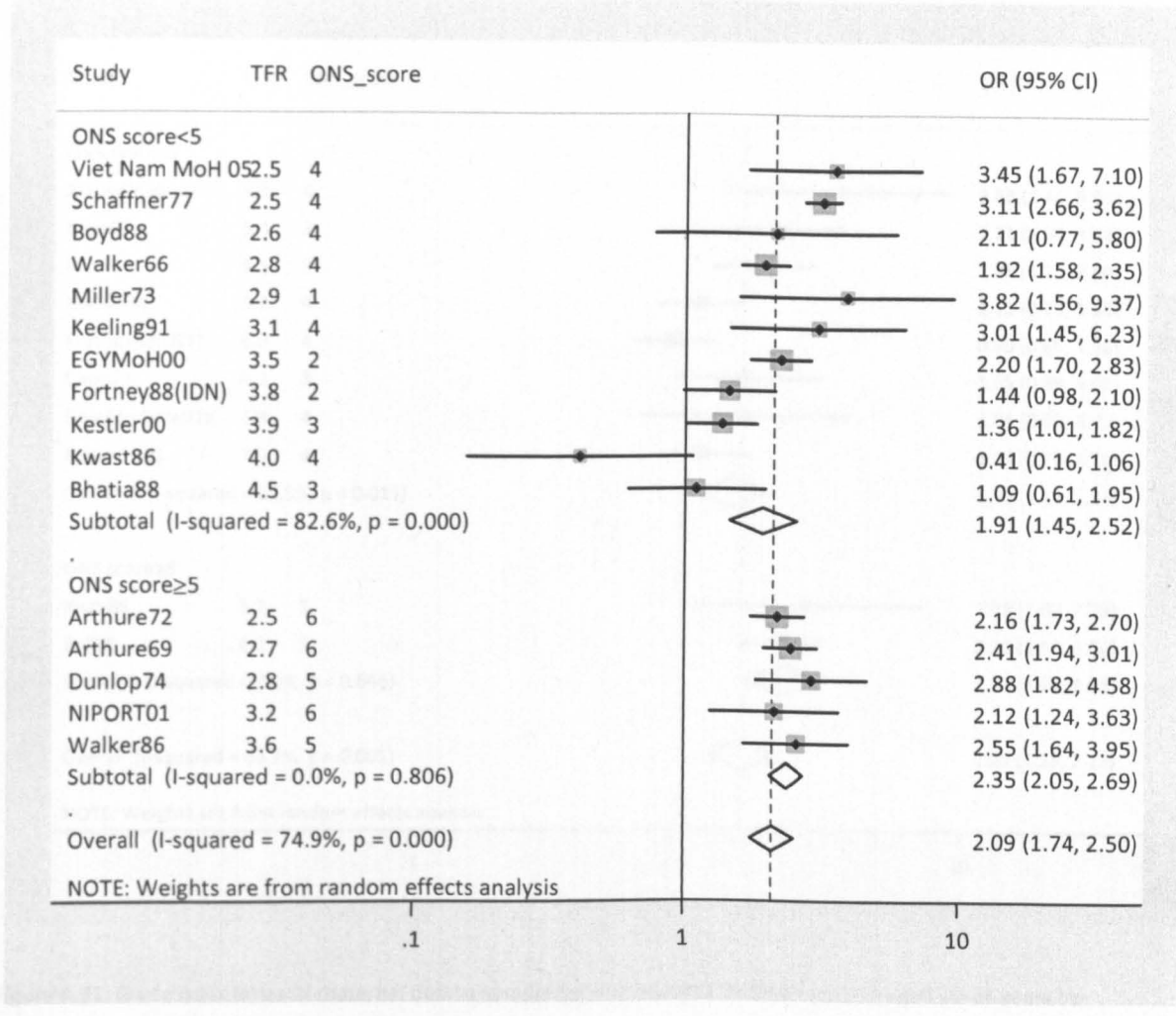

Figure A.30: Crude odds ratios of maternal deaths comparing women aged 30-34 to women aged 20-24 years by study quality in medium fertility settings.

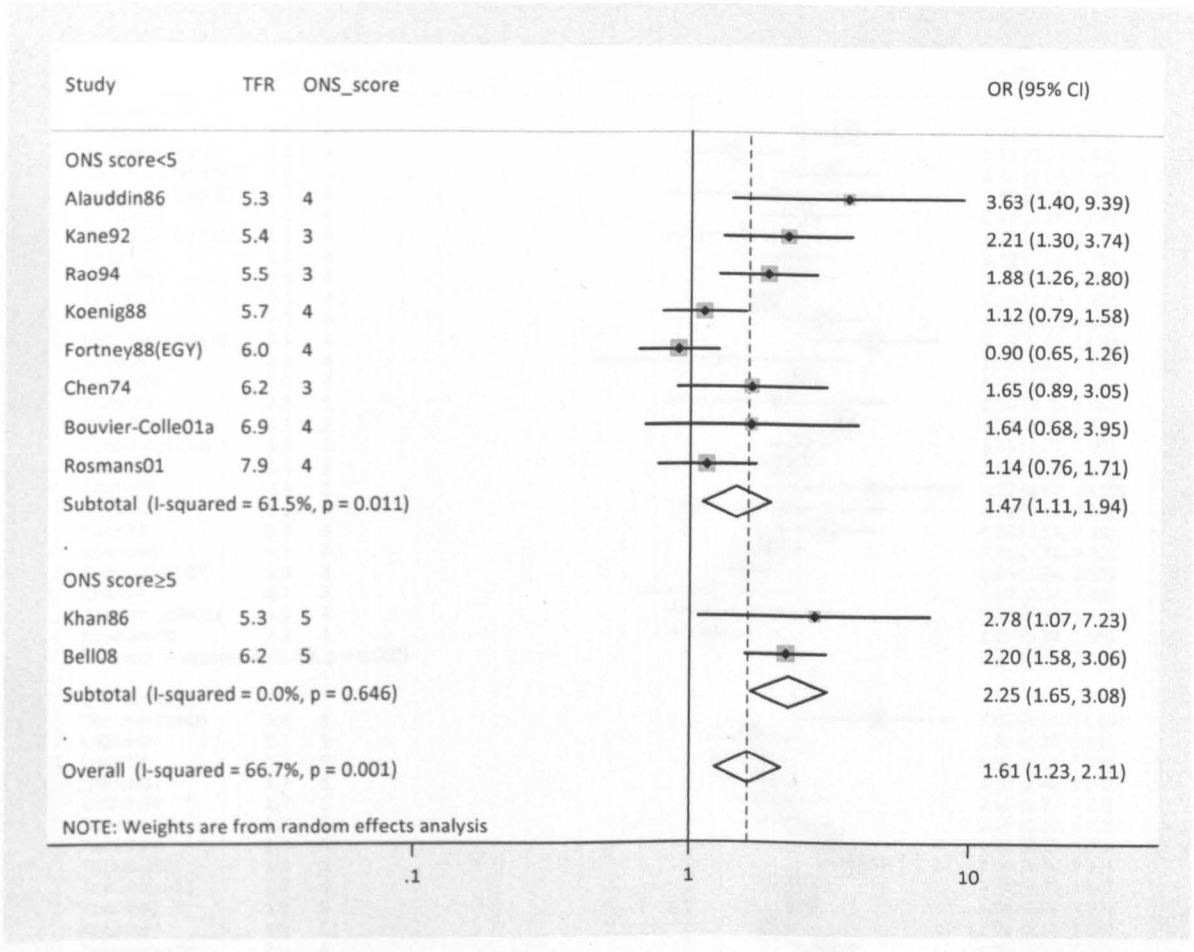

Figure A.31: Crude odds ratios of maternal deaths comparing women aged 30-34 to women aged 20-24 years by study quality in high fertility settings.

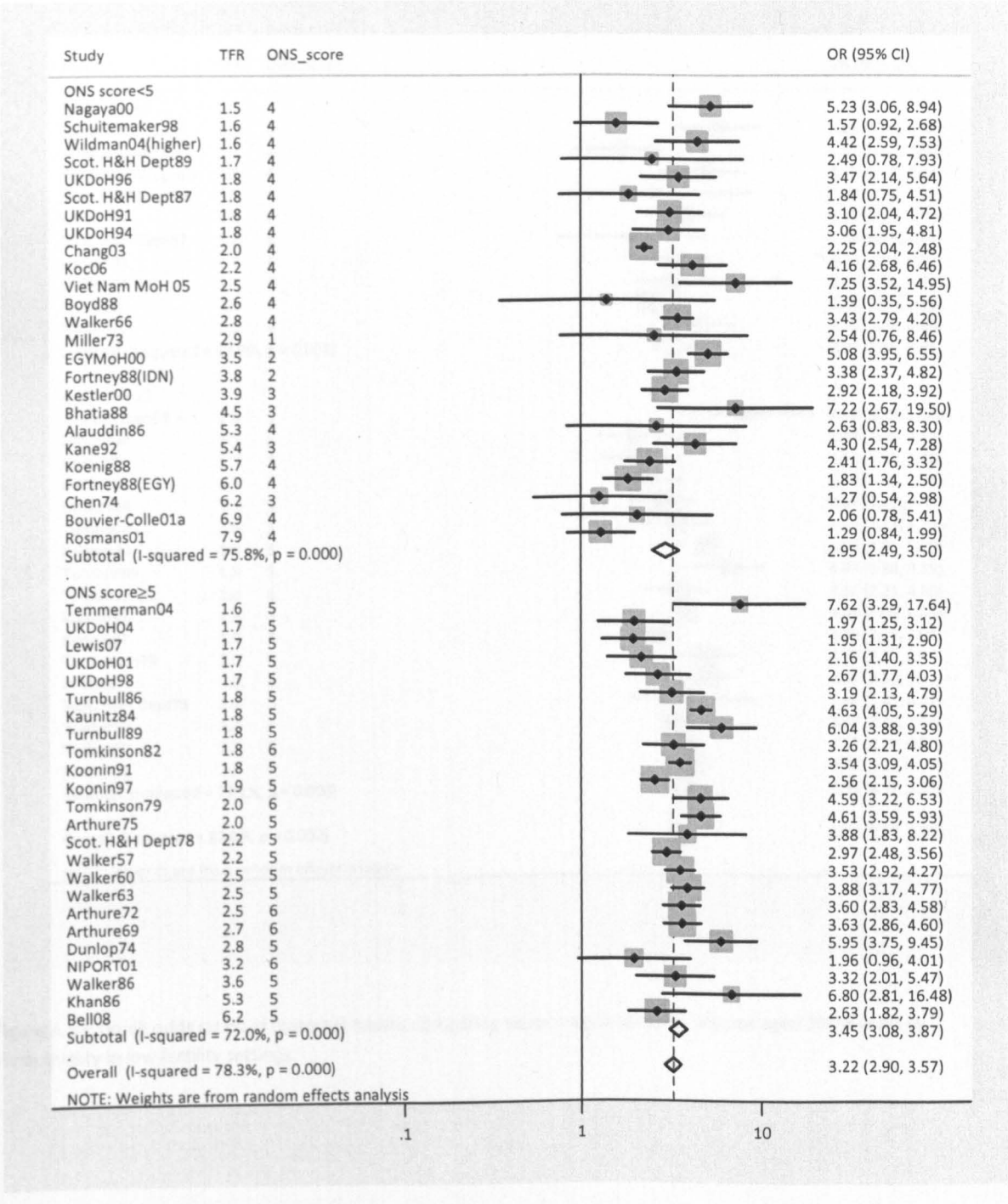

Figure A.32: Crude odds ratios of maternal deaths comparing women aged 35-39 to women aged 20-24 years by study quality.

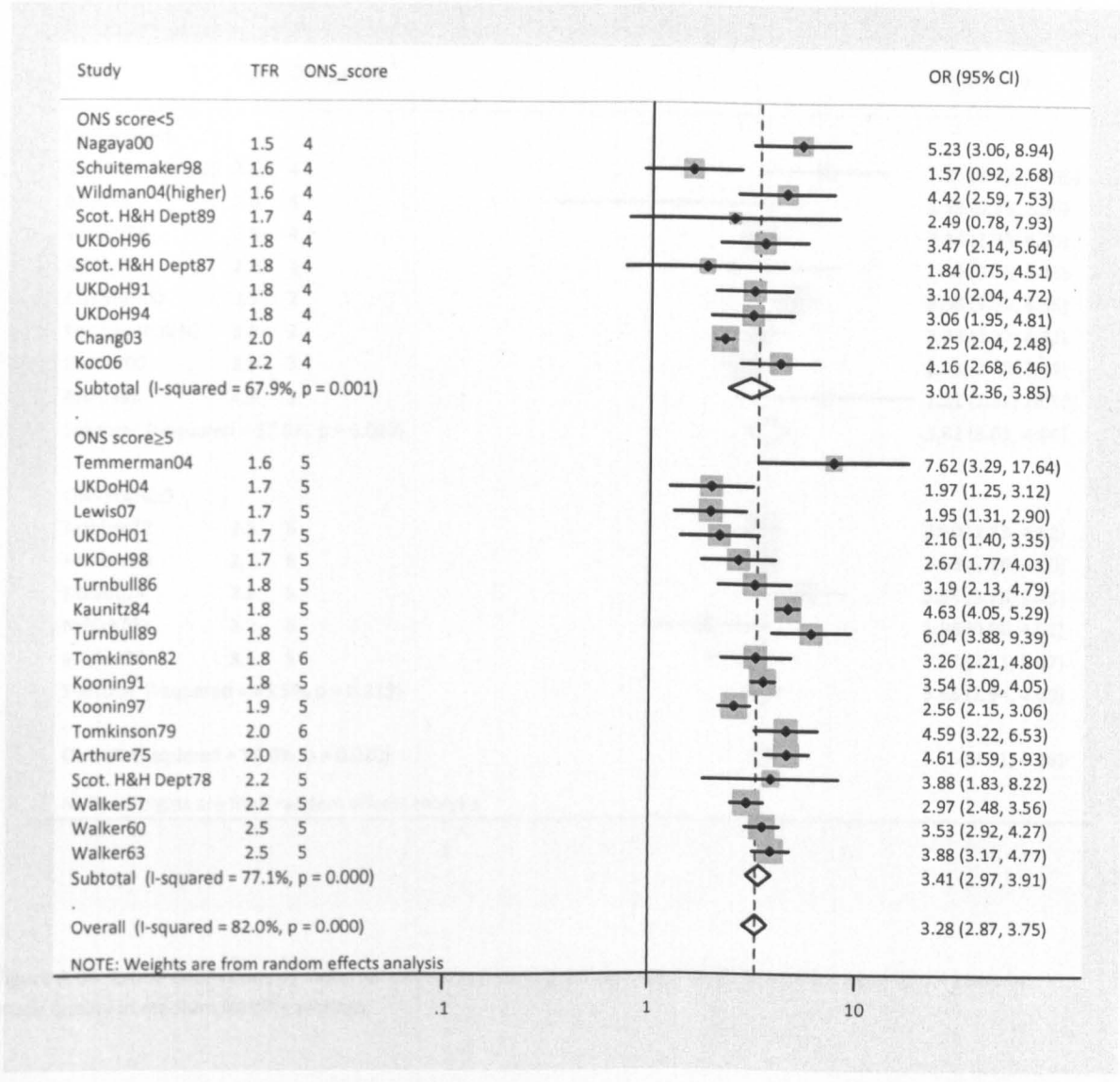

Figure A.33: Crude odds ratios of maternal deaths comparing women aged 35-39 to women aged 20-24 years by study quality in low fertility settings.

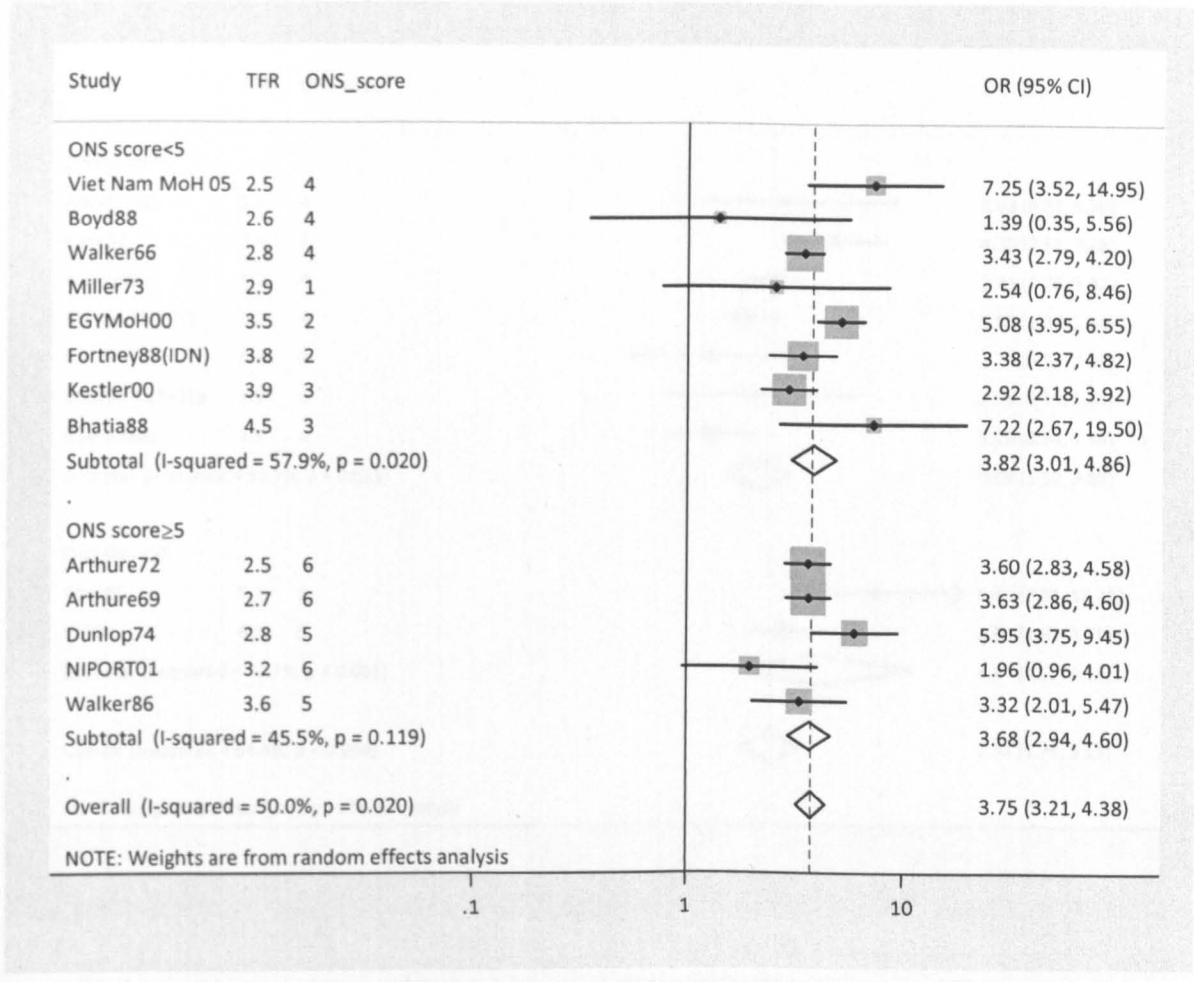

Figure A.34: Crude odds ratios of maternal deaths comparing women aged 35-39 to women aged 20-24 years by study quality in medium fertility settings.

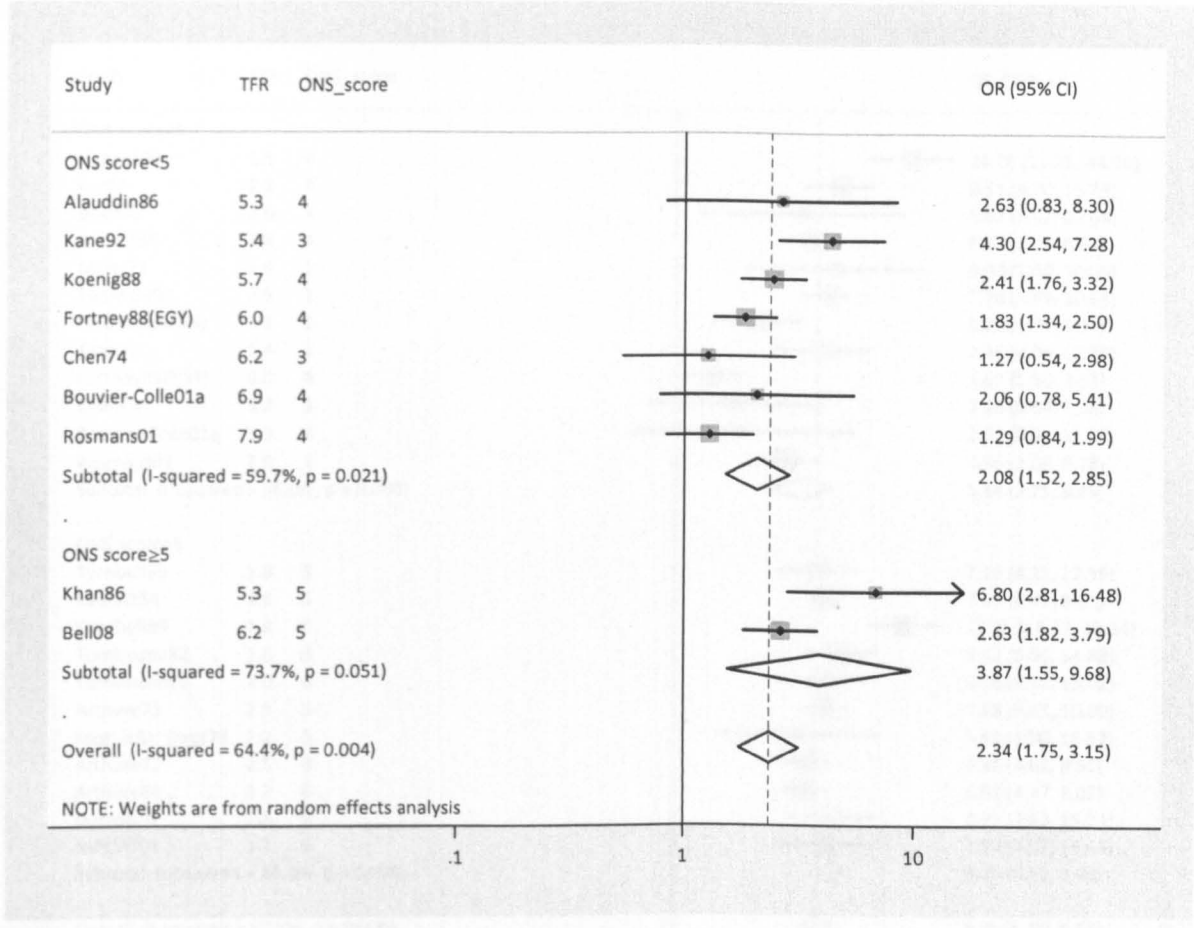

Figure A.35: Crude odds ratios of maternal deaths comparing women aged 35-39 to women aged 20-24 years by study quality in high fertility settings.

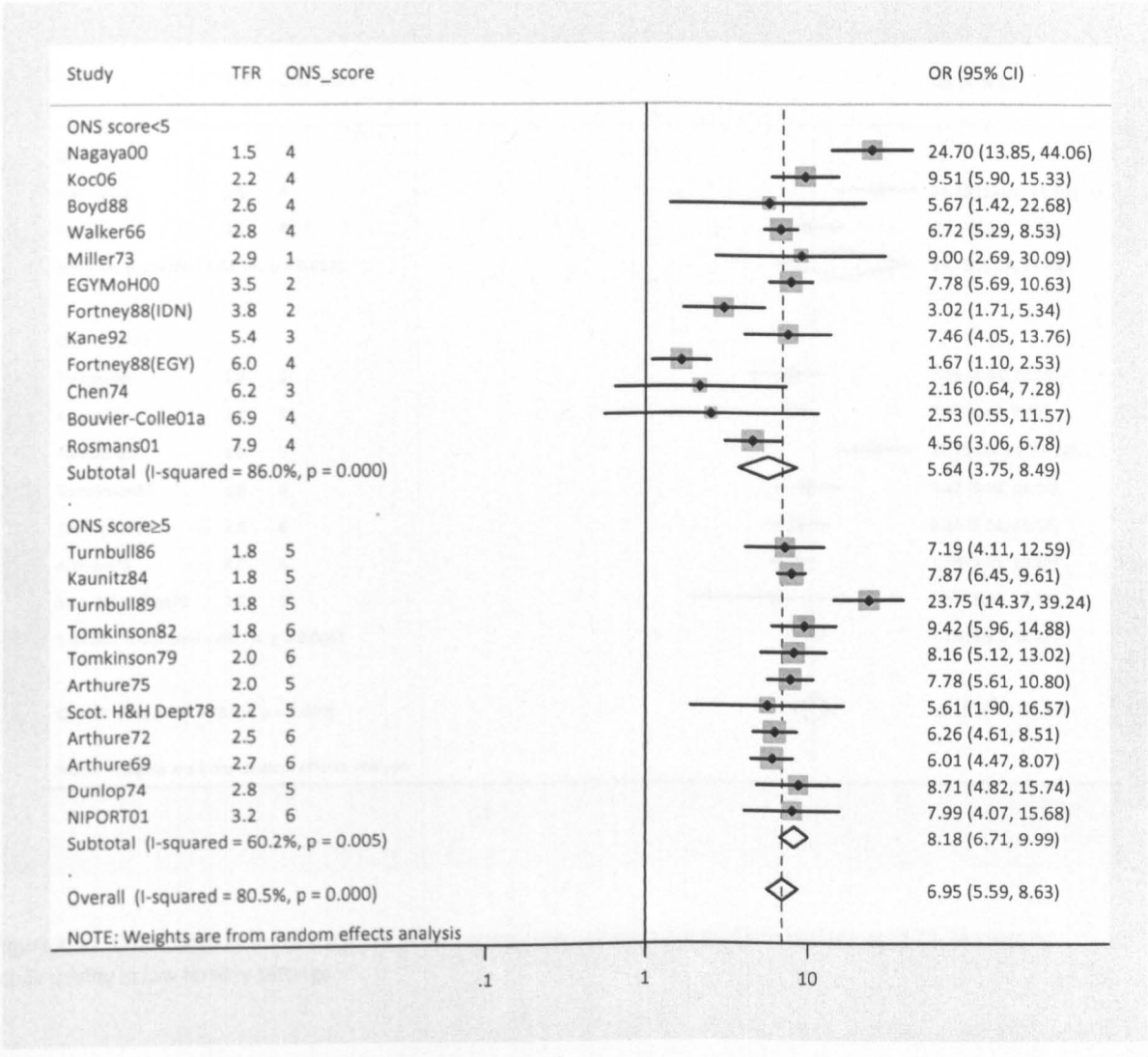

Figure A.36: Crude odds ratios of maternal deaths comparing women aged 40-44 to women aged 20-24 years by study quality.

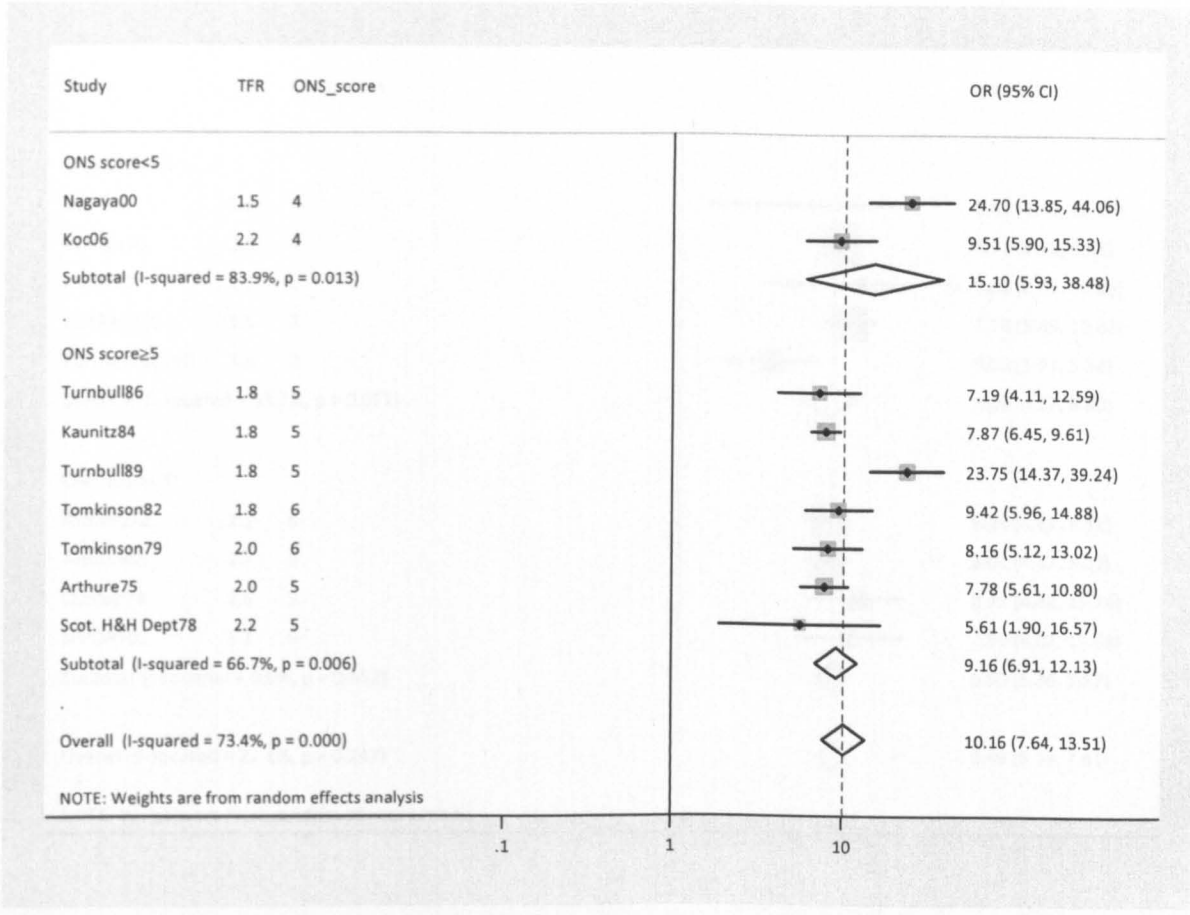

Figure A.37: Crude odds ratios of maternal deaths comparing women aged 40-44 to women aged 20-24 years by study quality in low fertility settings.

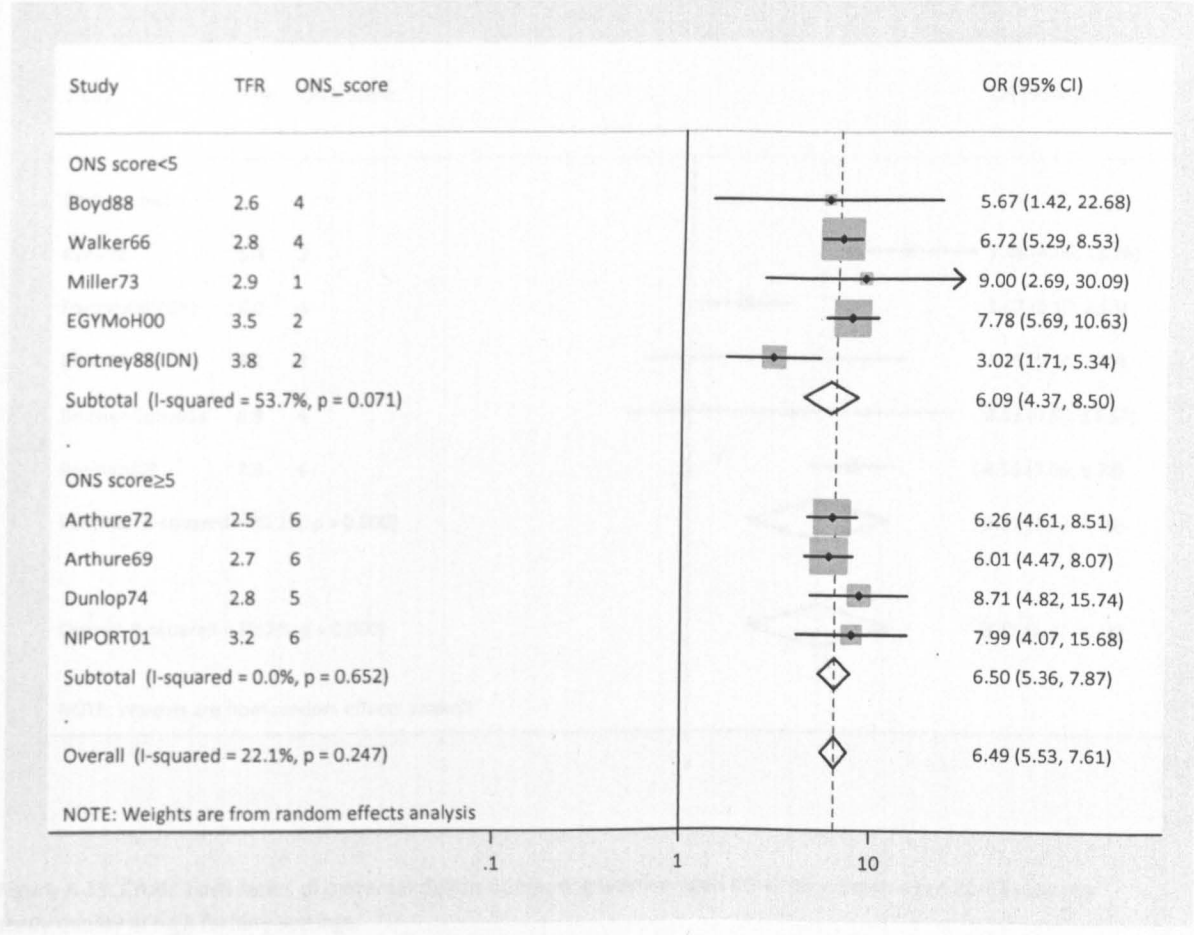

Figure A.38: Crude odds ratios of maternal deaths comparing women aged 40-44 to women aged 20-24 years by study quality in medium fertility settings.

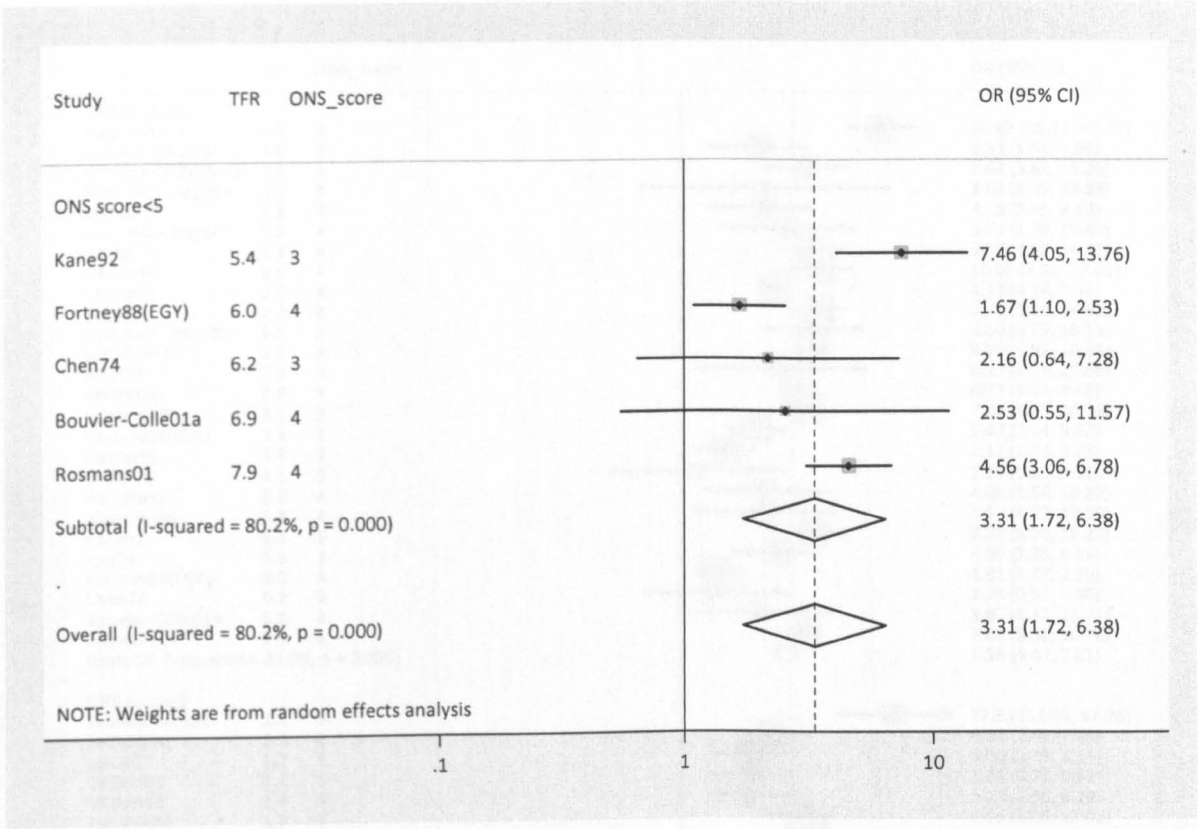

Figure A.39: Crude odds ratios of maternal deaths comparing women aged 40-44 to women aged 20-24 years by study quality in high fertility settings.

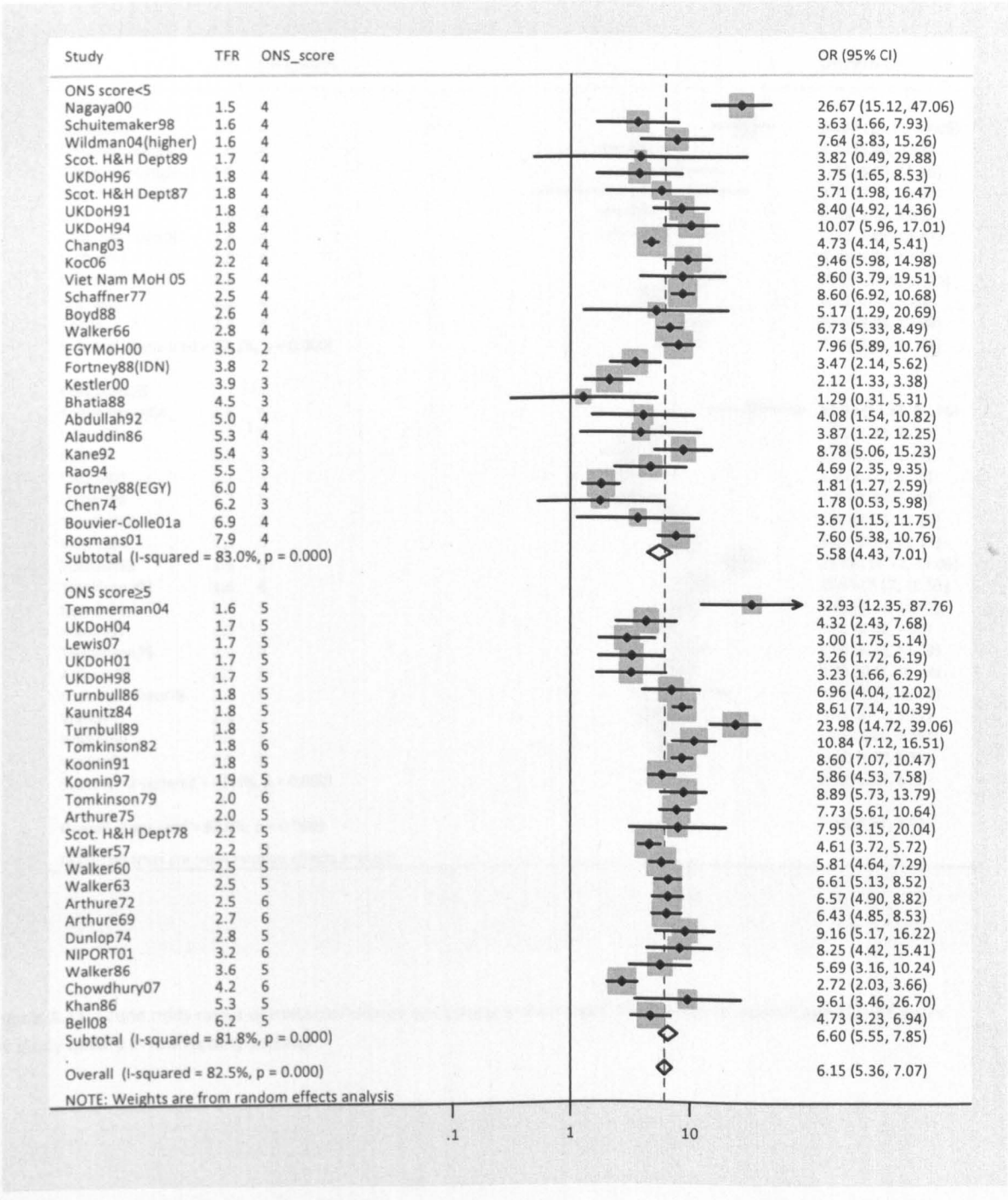

Figure A.40: Crude odds ratios of maternal deaths comparing women aged 40 or older to women aged 20-24 years by study quality.

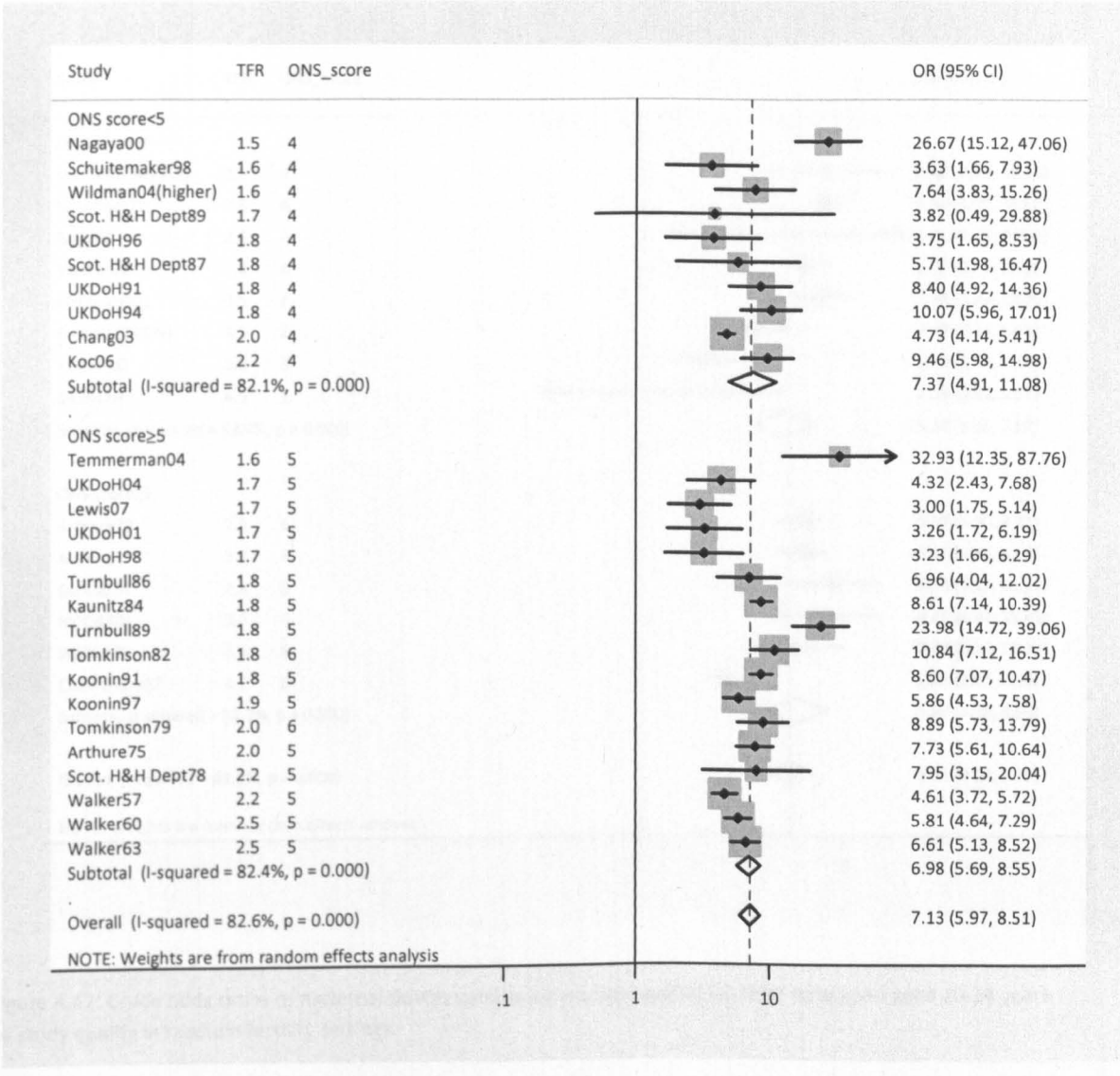

Figure A.41: Crude odds ratios of maternal deaths comparing women aged 40 or older to women aged 20-24 years by study quality in low fertility settings.

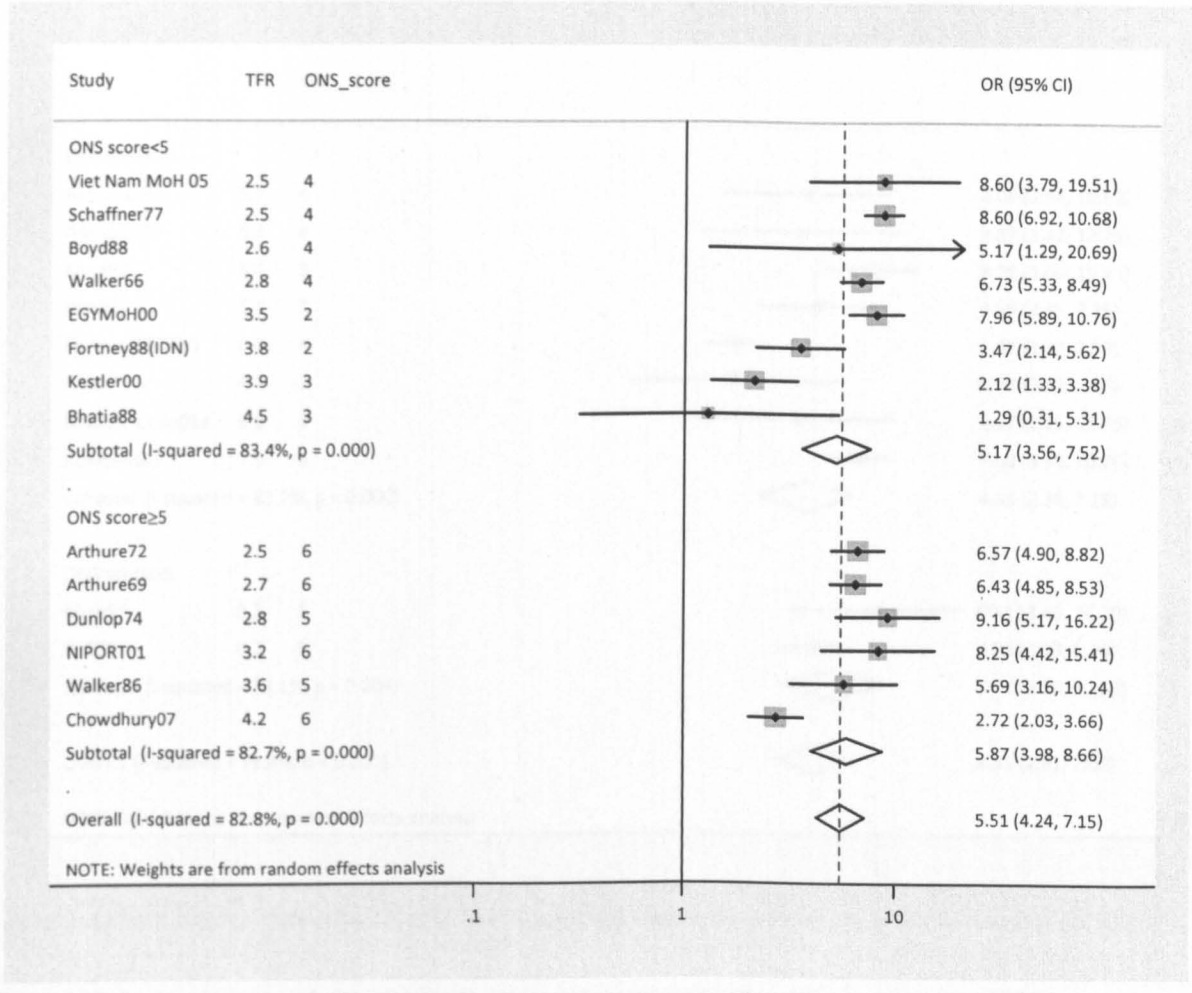

Figure A.42: Crude odds ratios of maternal deaths comparing women aged 40 or older to women aged 20-24 years by study quality in medium fertility settings.

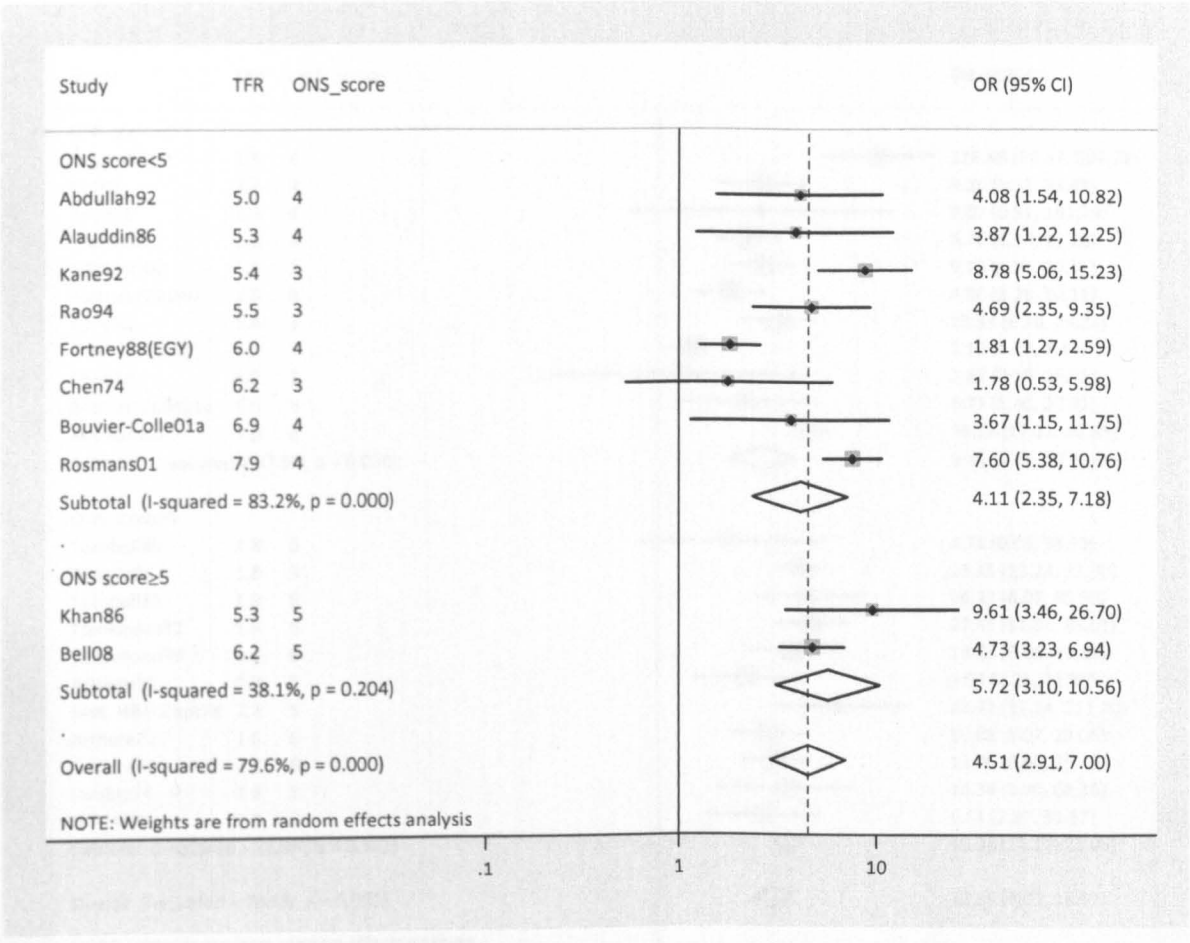

Figure A.43: Crude odds ratios of maternal deaths comparing women aged 40 or older to women aged 20-24 years by study quality in high fertility settings.

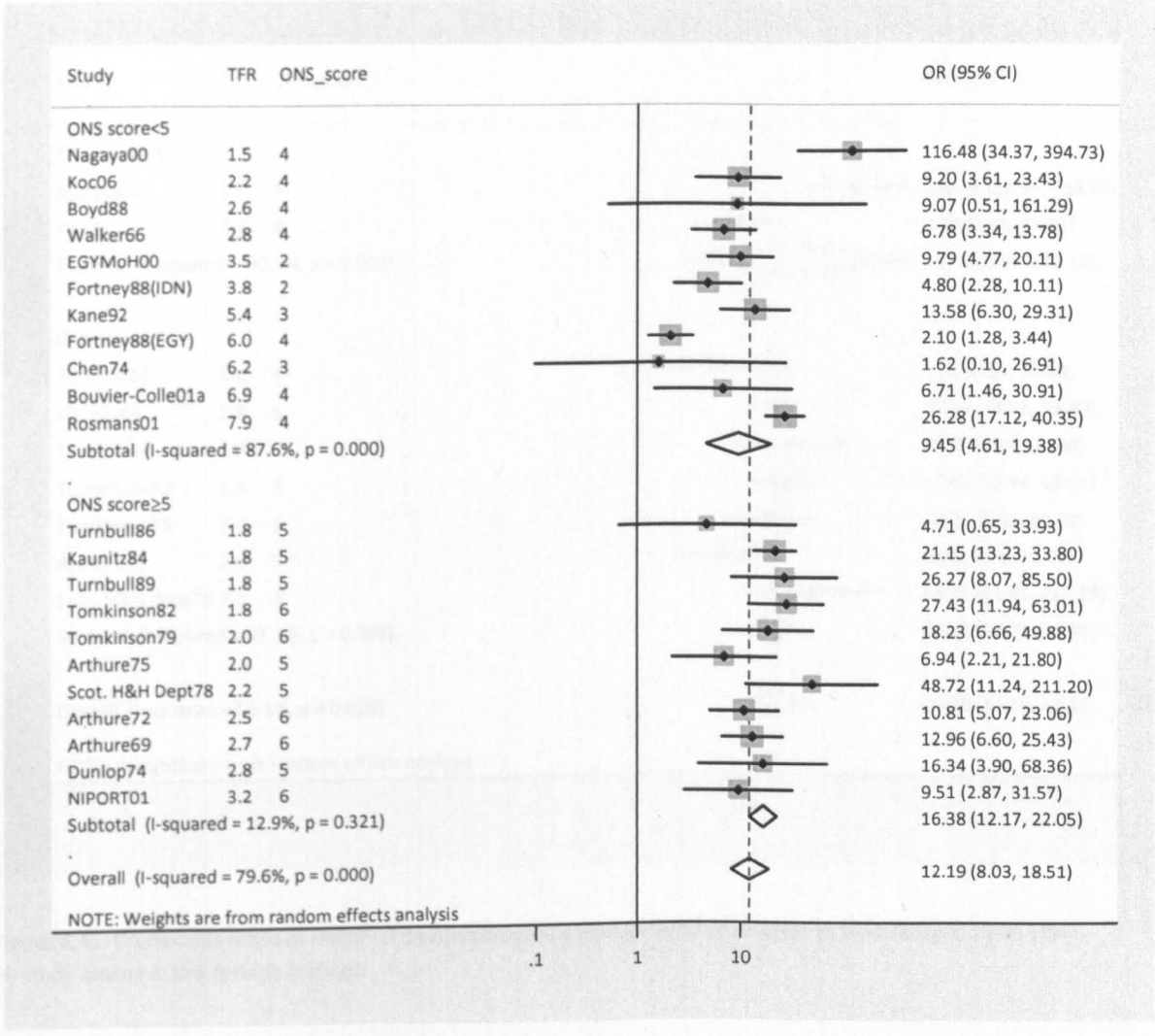

Figure A.44: Crude odds ratios of maternal deaths comparing women aged 45 or older to women aged 20-24 years by study quality.

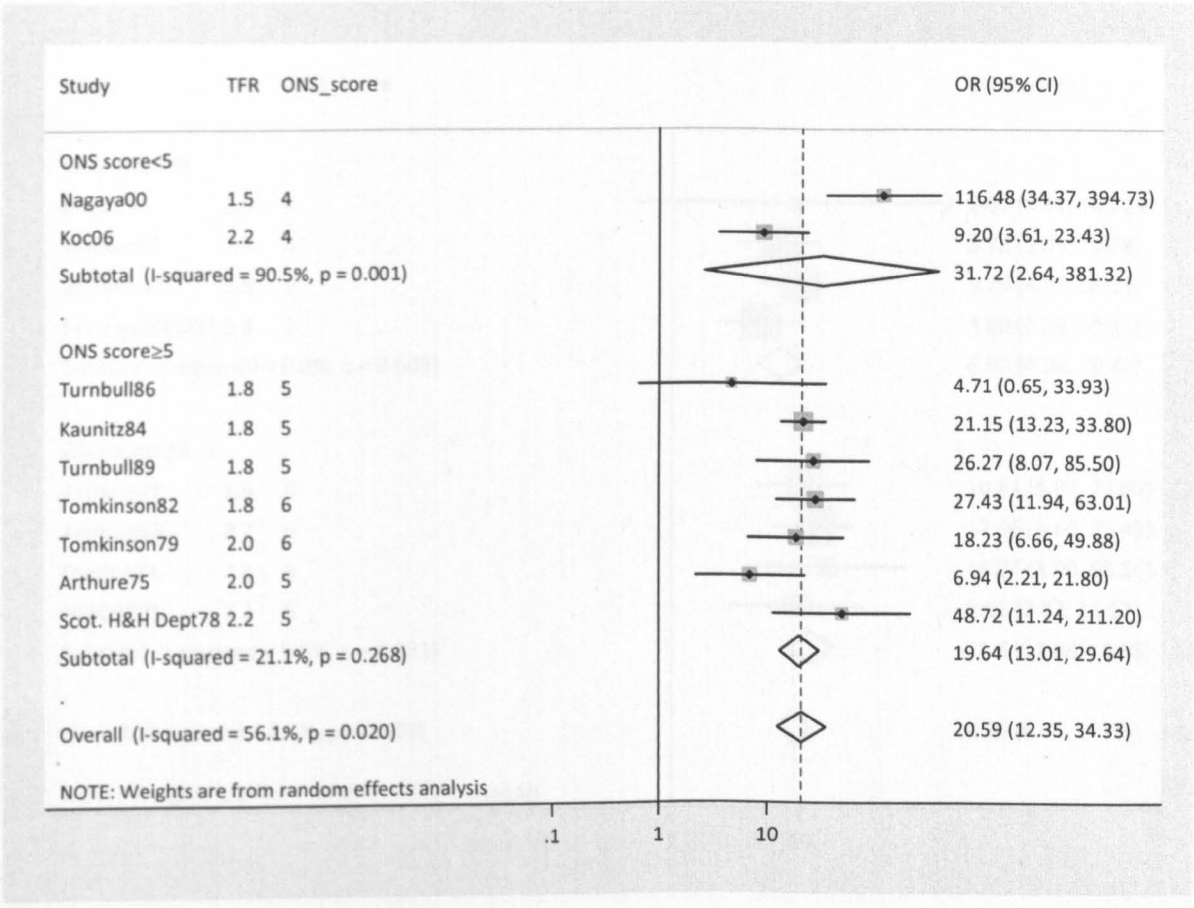

Figure A.45: Crude odds ratios of maternal deaths comparing women aged 45 or older to women aged 20-24 years by study quality in low fertility settings.

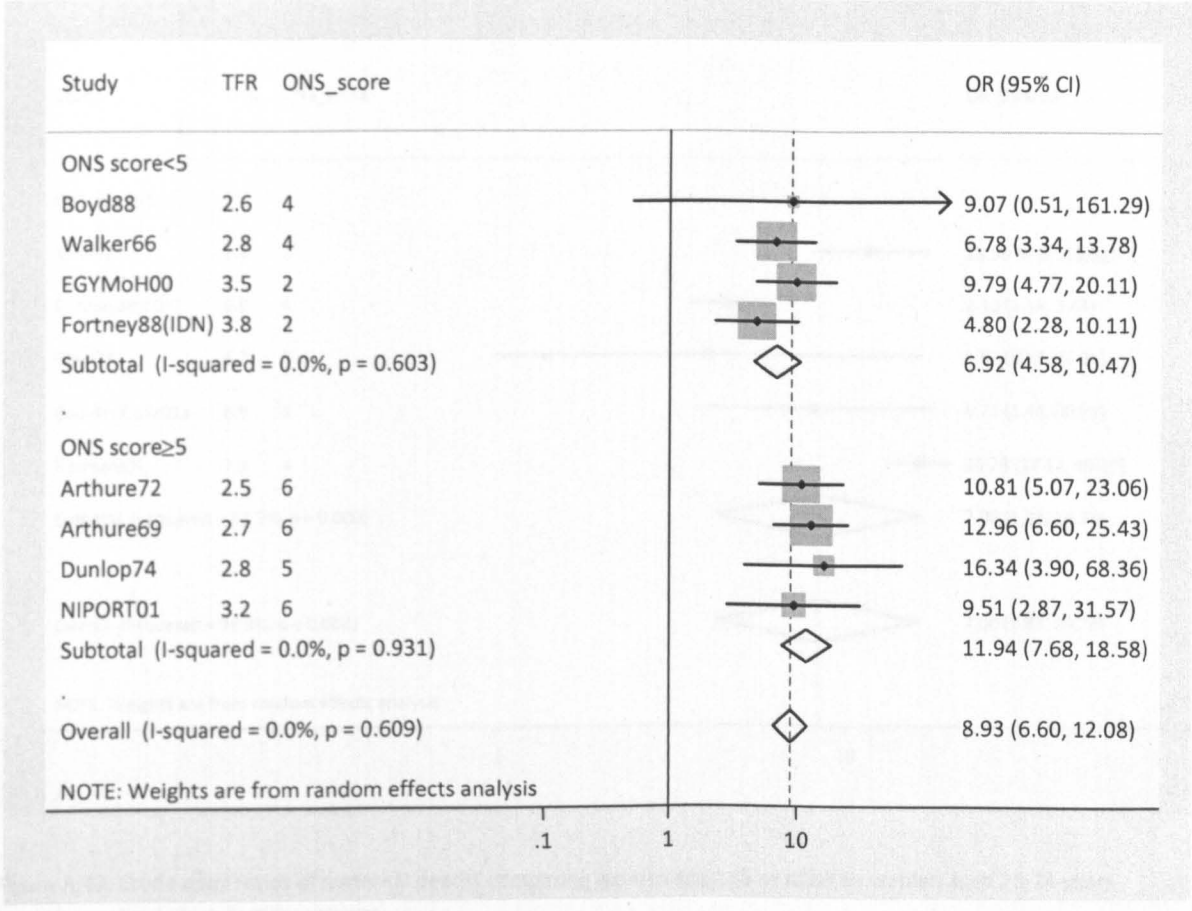

Figure A.46: Crude odds ratios of maternal deaths comparing women aged 45 or older to women aged 20-24 years by study quality in medium fertility settings.

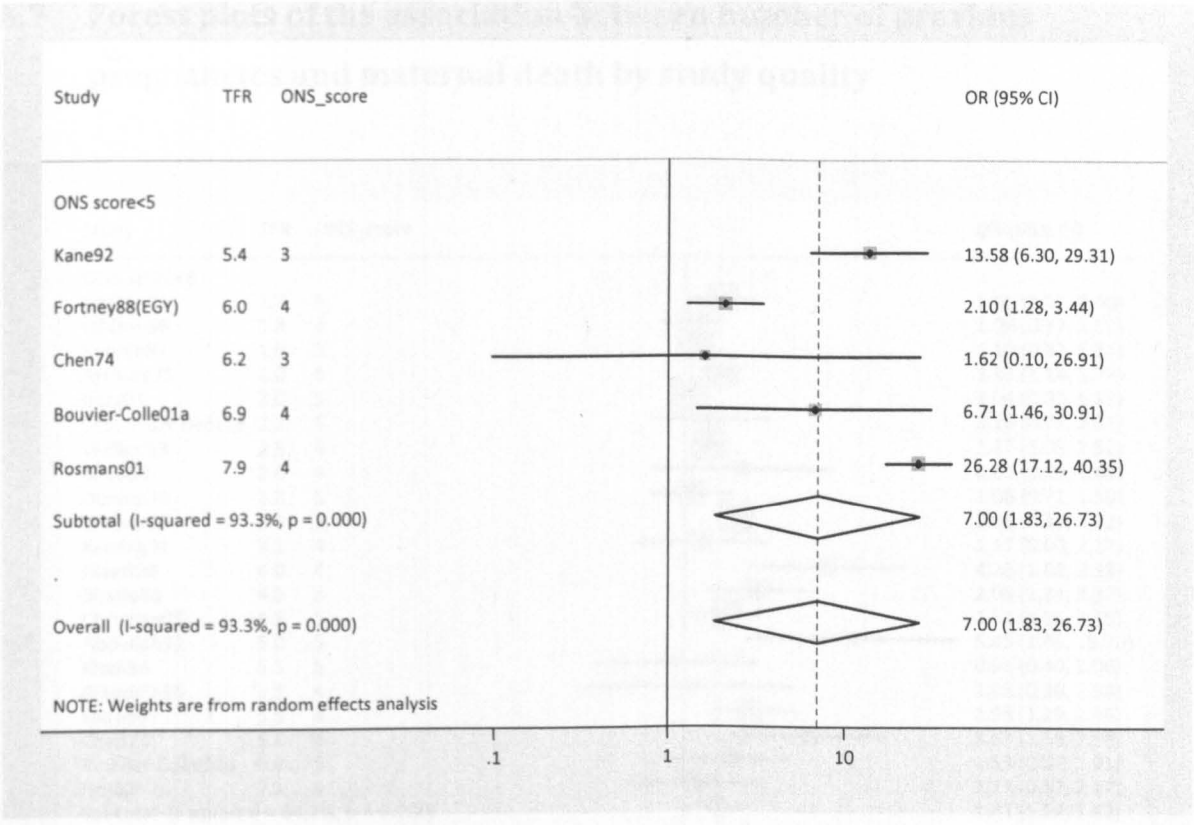

Figure A.47: Crude odds ratios of maternal deaths comparing women aged 45 or older to women aged 20-24 years by study quality in high fertility settings.

A.7 Forest plots of the association between number of previous pregnancies and maternal death by study quality

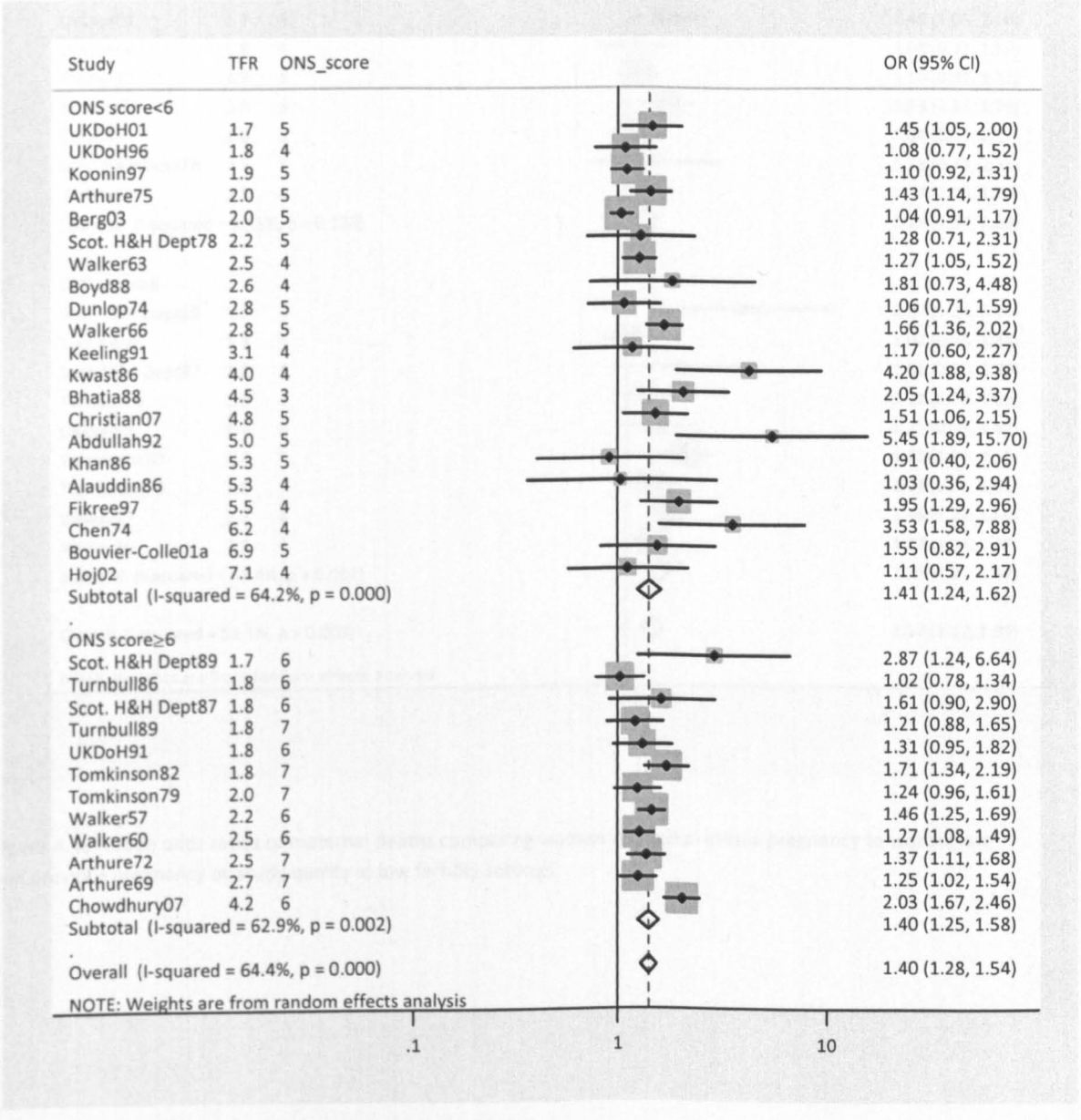

Figure A.48: Crude odds ratios of maternal deaths comparing women with no previous pregnancy to women with one previous pregnancy by study quality.

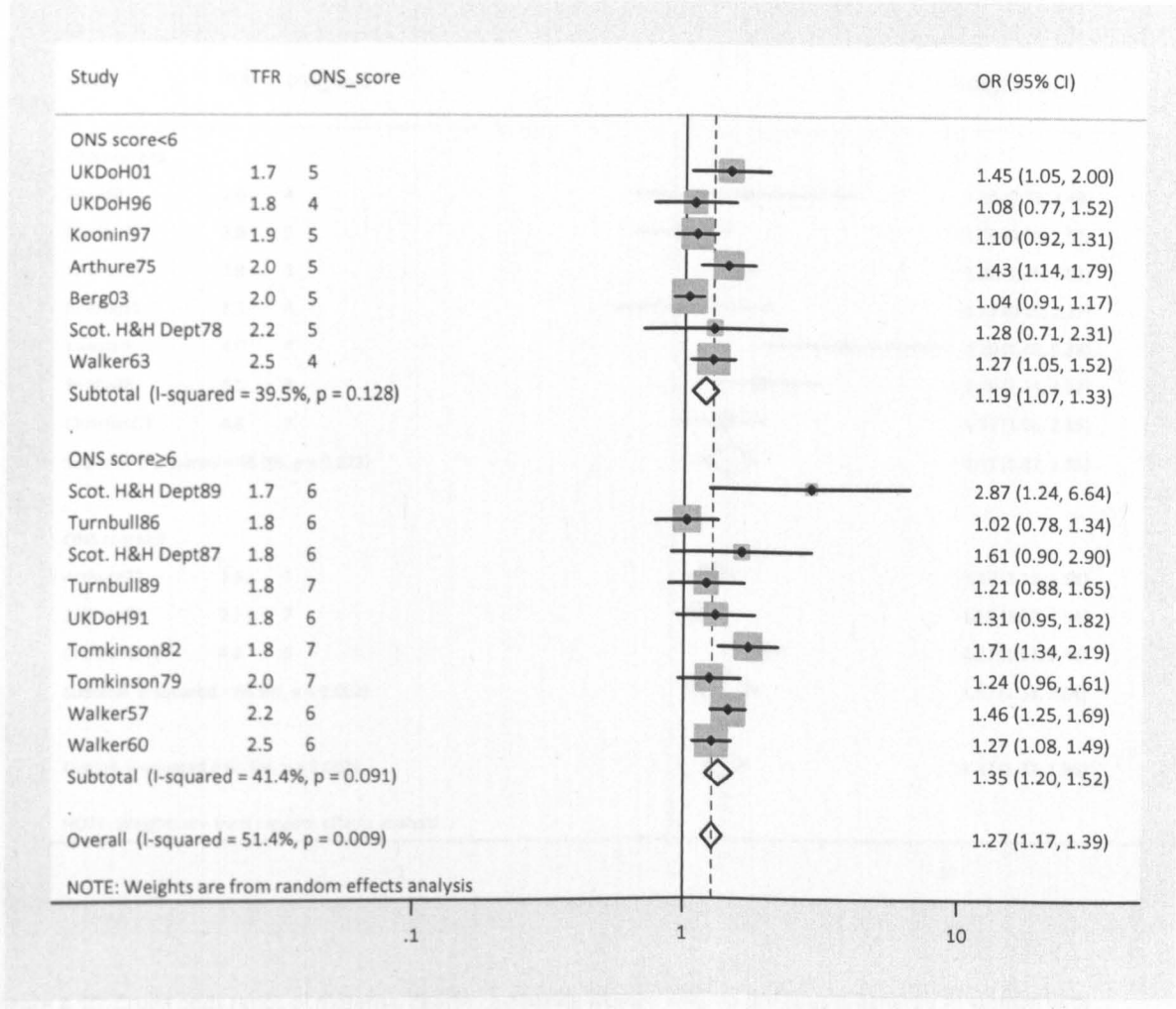

Figure A.49: Crude odds ratios of maternal deaths comparing women with no previous pregnancy to women with one previous pregnancy by study quality in low fertility settings.

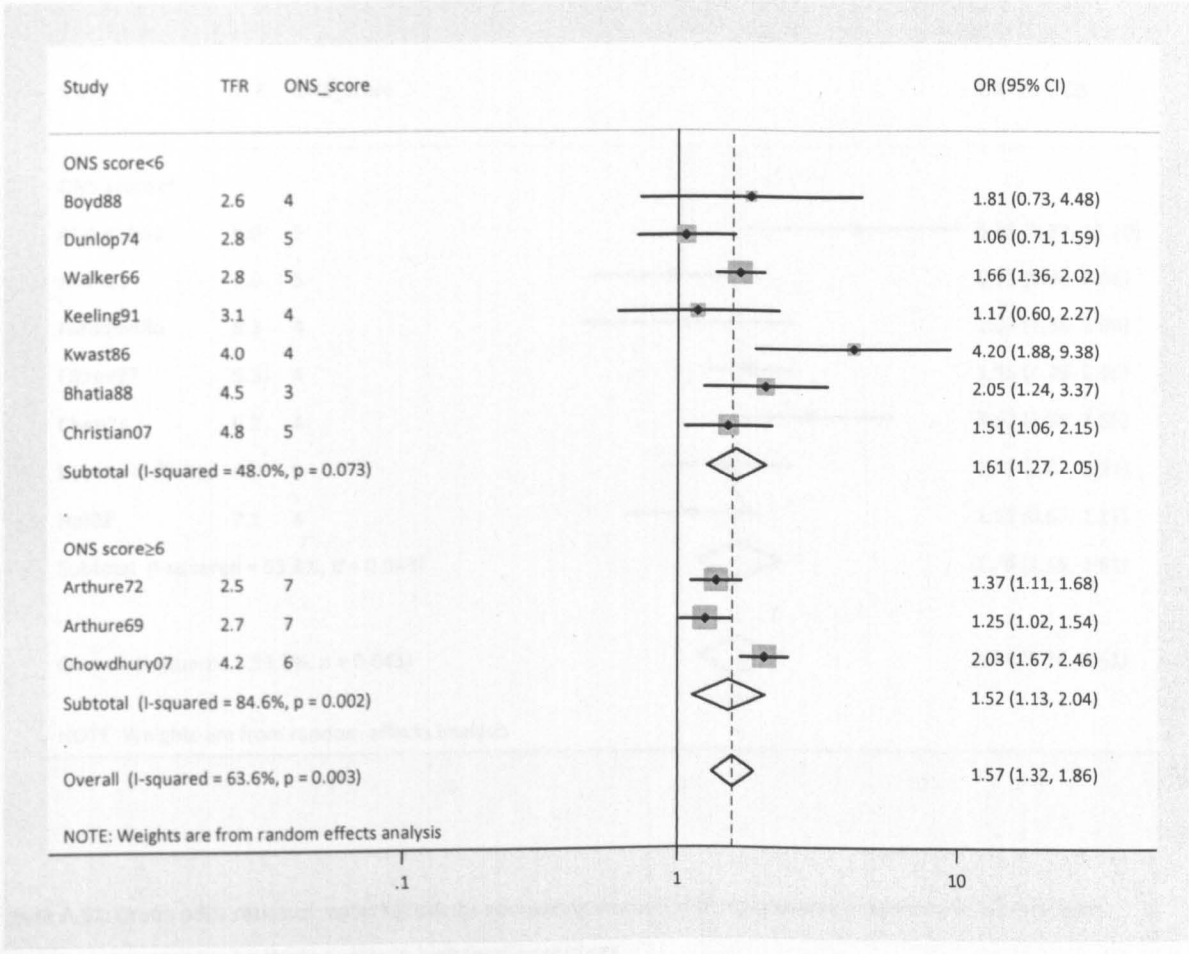

Figure A.50: Crude odds ratios of maternal deaths comparing women with no previous pregnancy to women with one previous pregnancy by study quality in medium fertility settings.

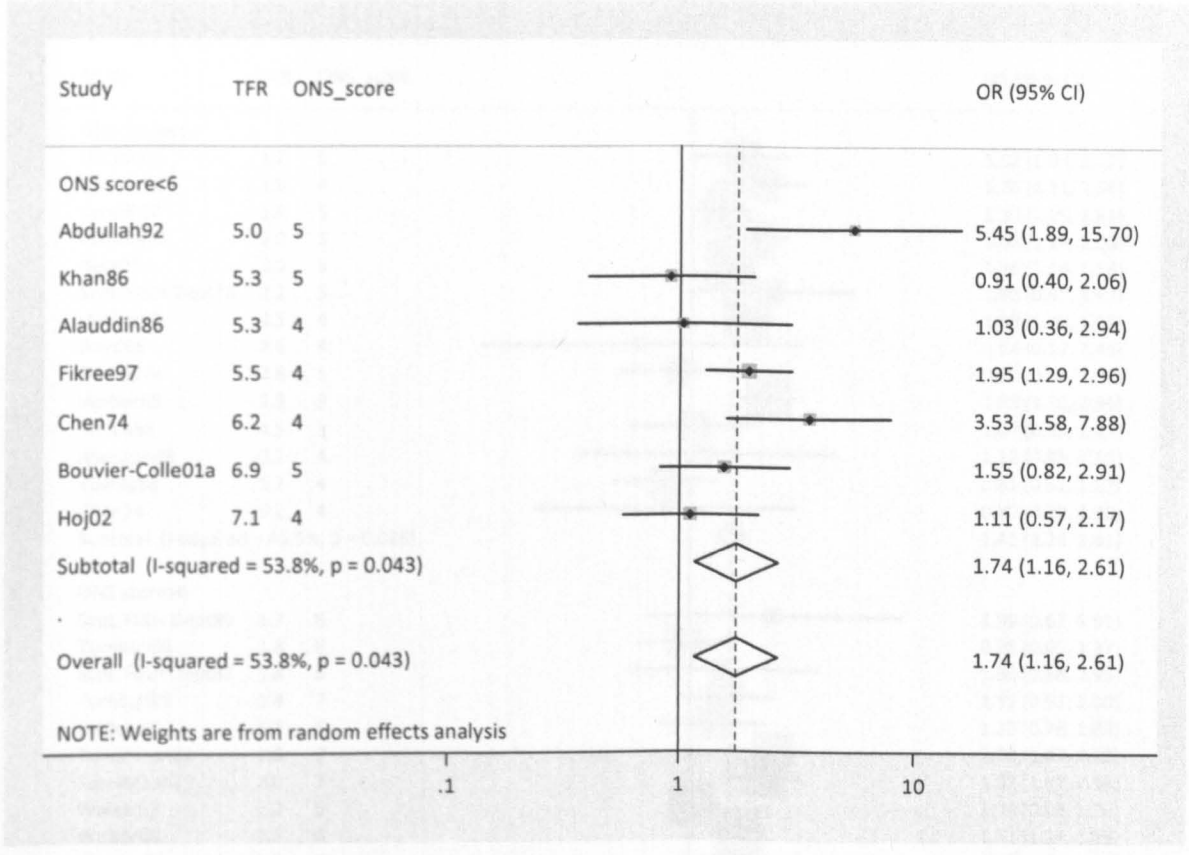

Figure A.51: Crude odds ratios of maternal deaths comparing women with no previous pregnancy to women with one previous pregnancy by study quality in high fertility settings.

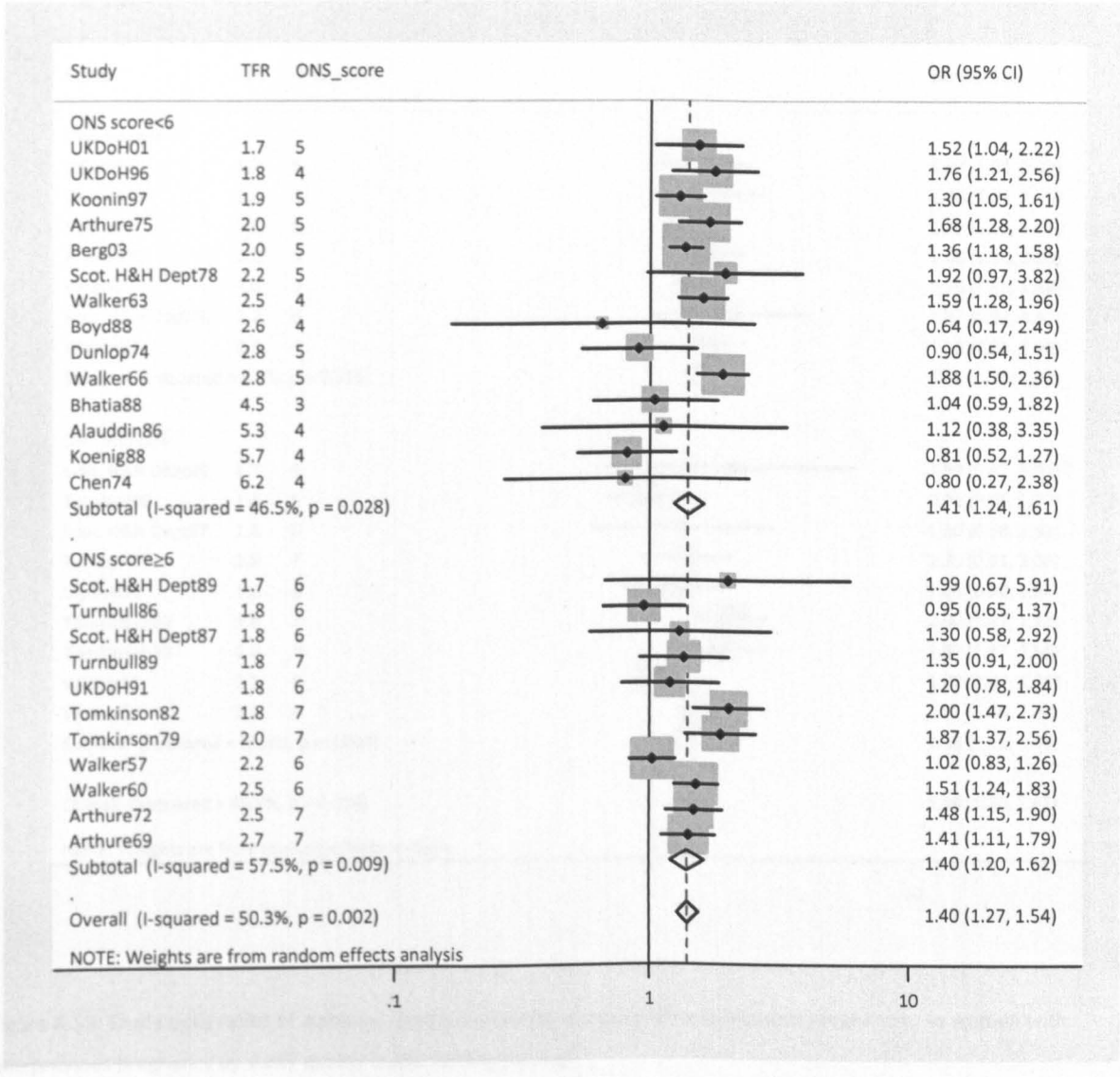

Figure A.52: Crude odds ratios of maternal deaths comparing women with two previous pregnancies to women with one previous pregnancy by study quality.

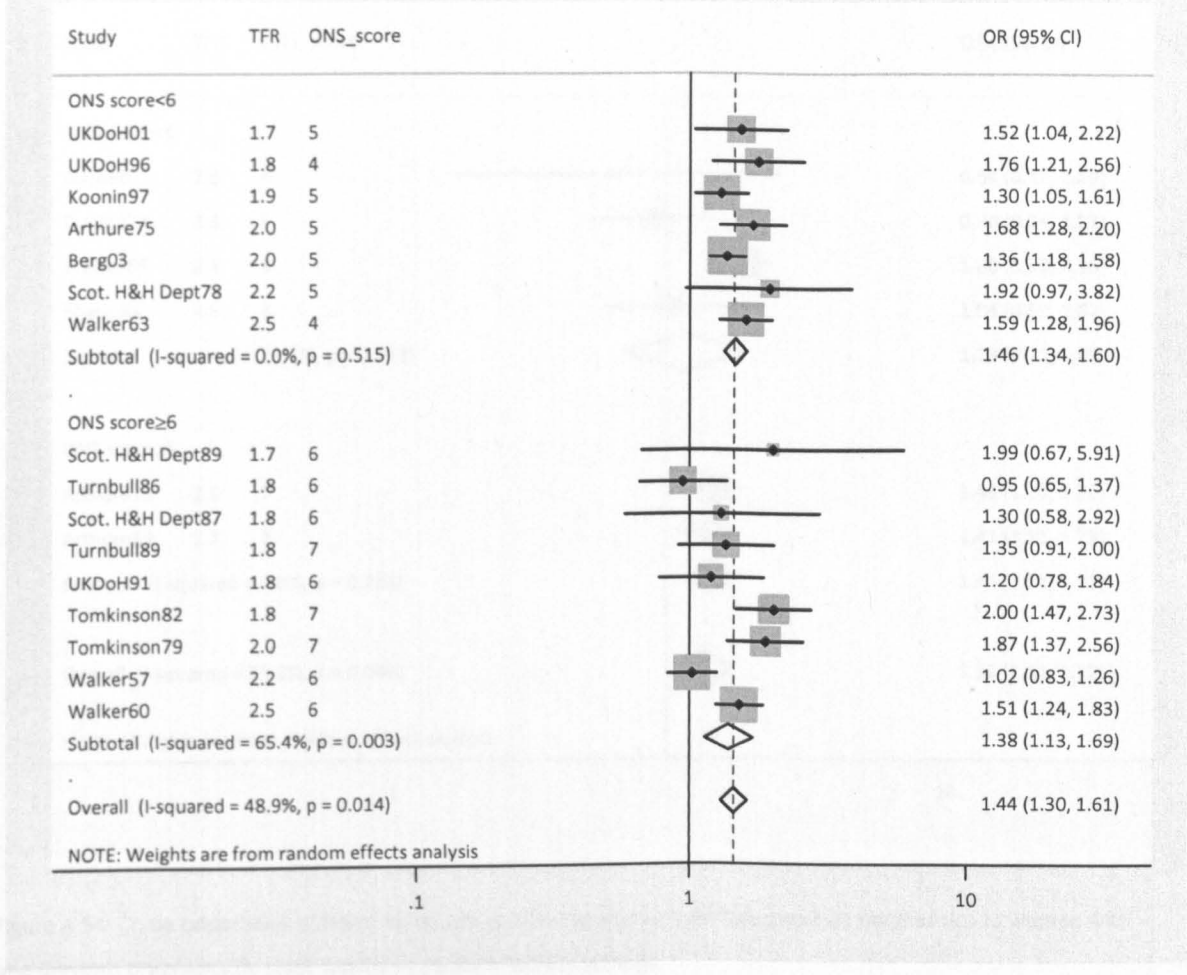

Figure A.53: Crude odds ratios of maternal deaths comparing women with two previous pregnancies to women with one previous pregnancy by study quality in low fertility settings.

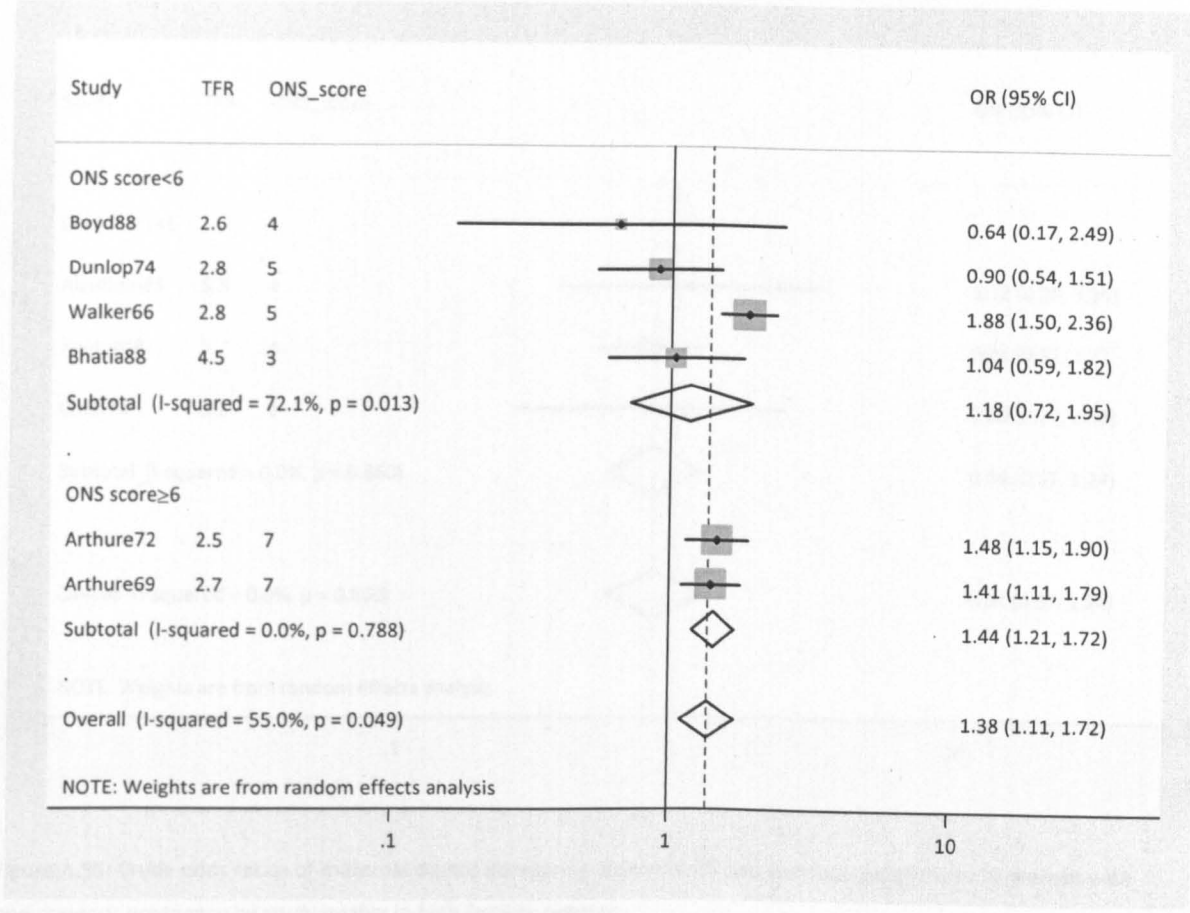

Figure A.54: Crude odds ratios of maternal deaths comparing women with two previous pregnancies to women with one previous pregnancy by study quality in medium fertility settings.

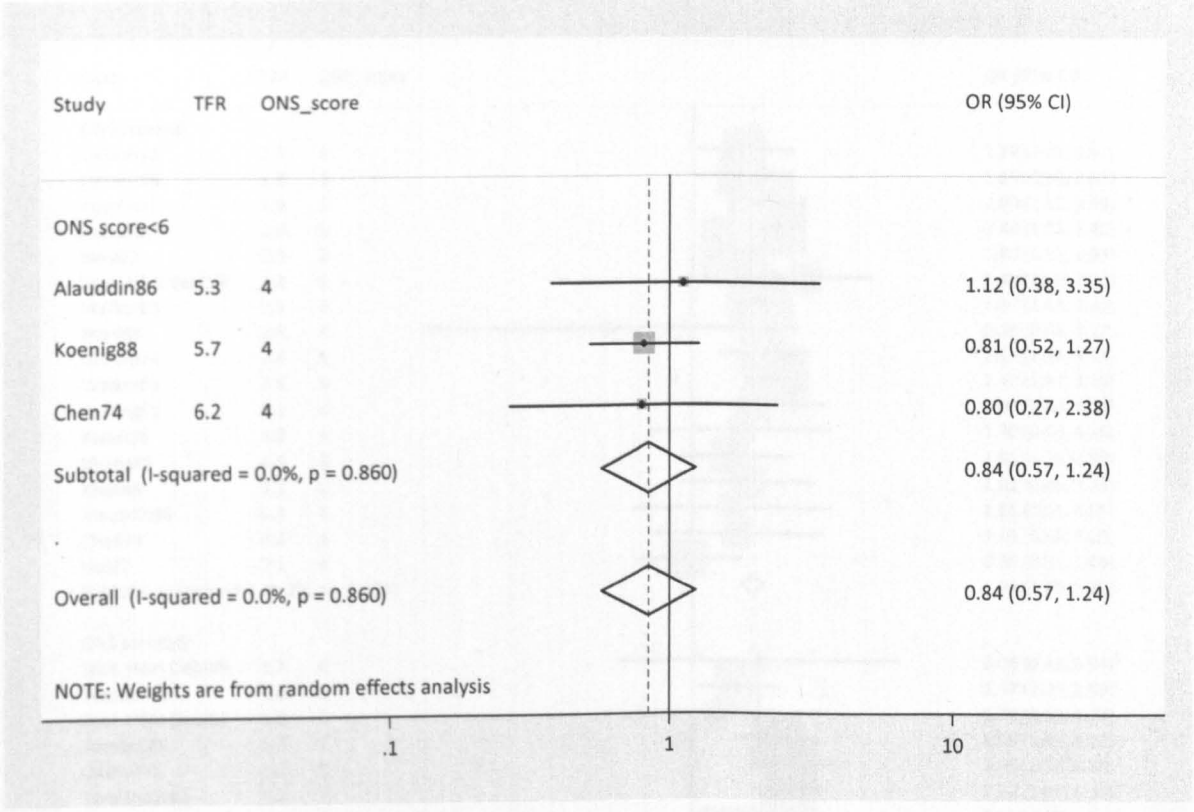

Figure A.55: Crude odds ratios of maternal deaths comparing women with two previous pregnancies to women with one previous pregnancy by study quality in high fertility settings.

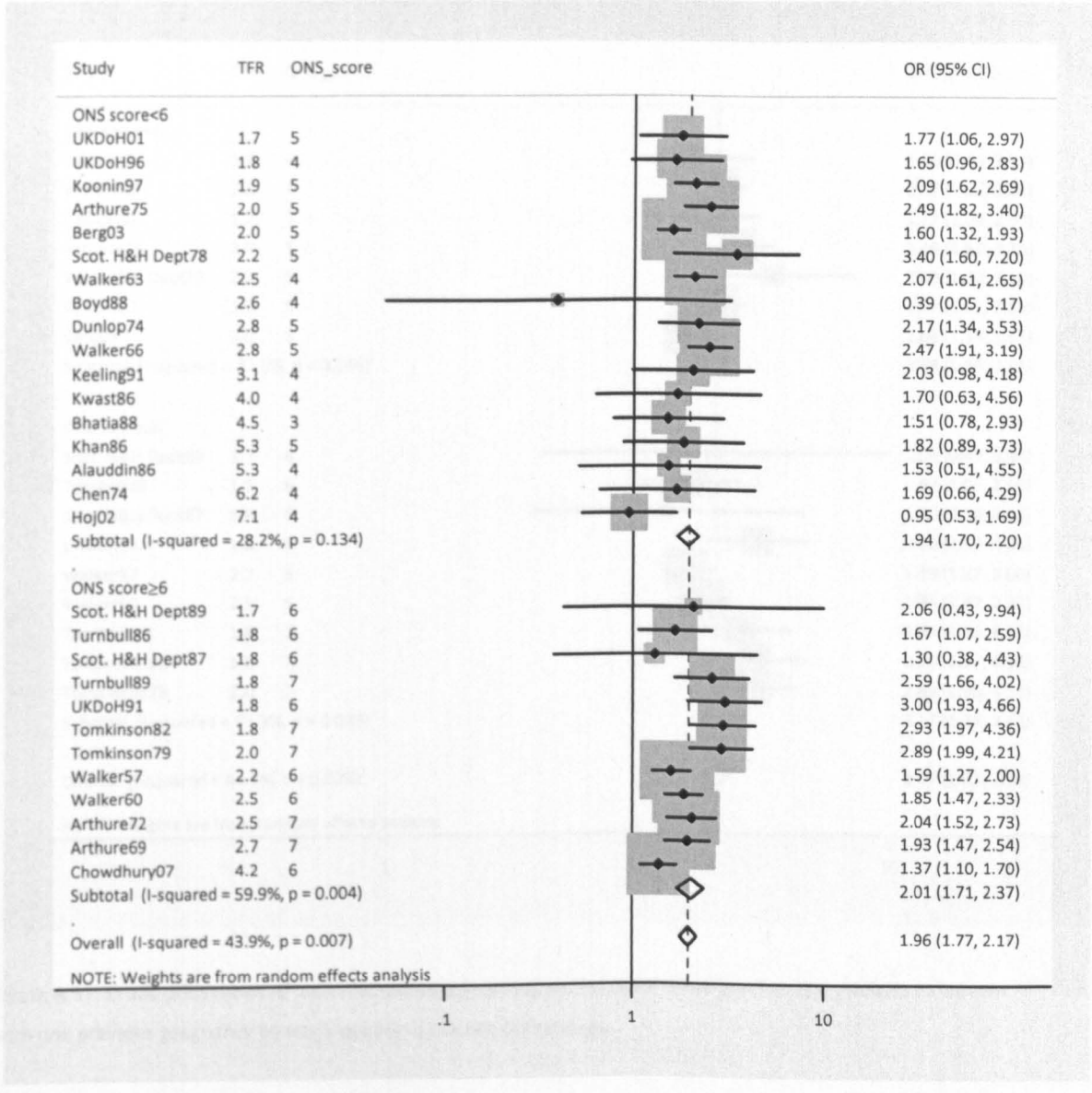

Figure A.56: Crude odds ratios of maternal deaths comparing women with three previous pregnancies to women with one previous pregnancy by study quality.

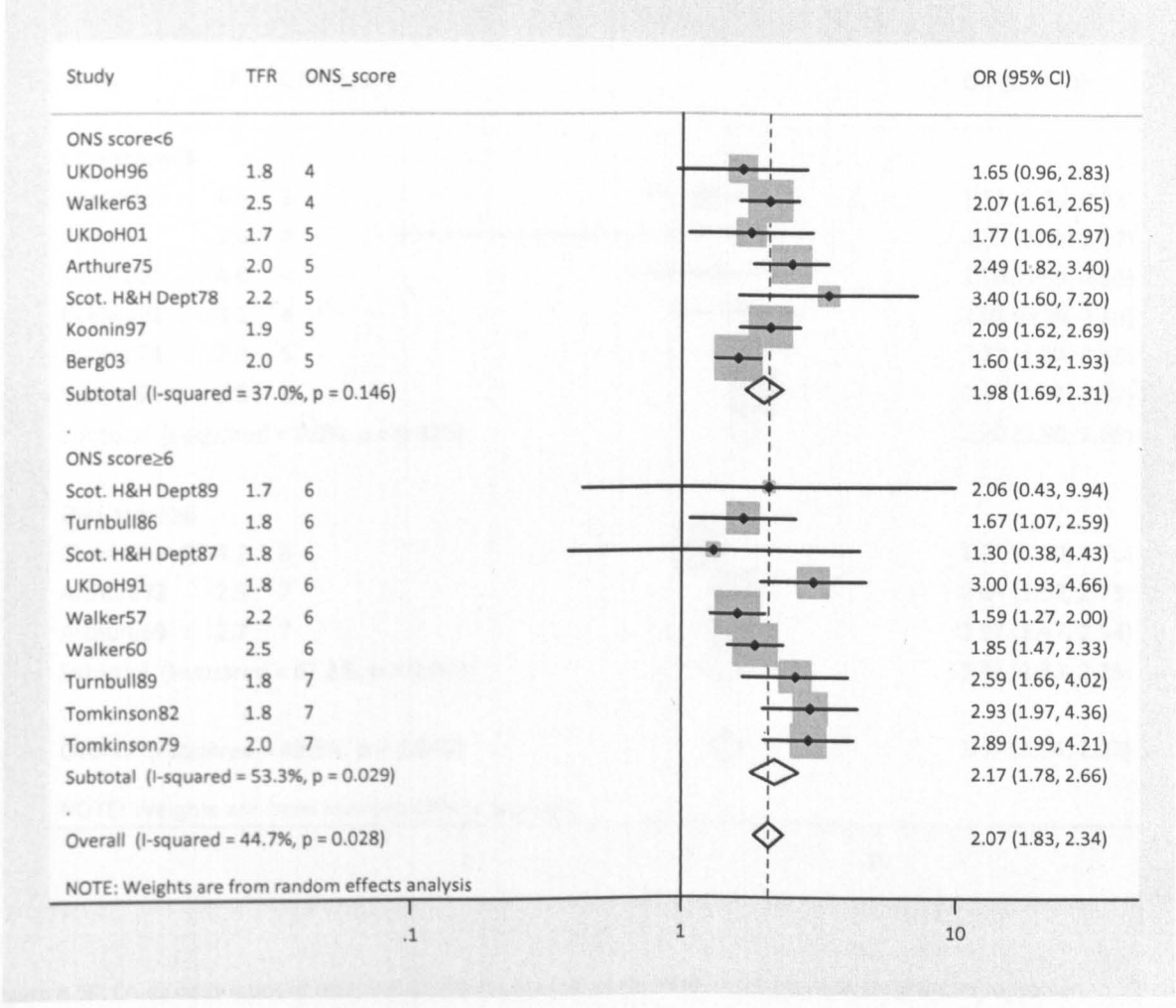

Figure A.57: Crude odds ratios of maternal deaths comparing women with three previous pregnancies to women with one previous pregnancy by study quality in low fertility settings.

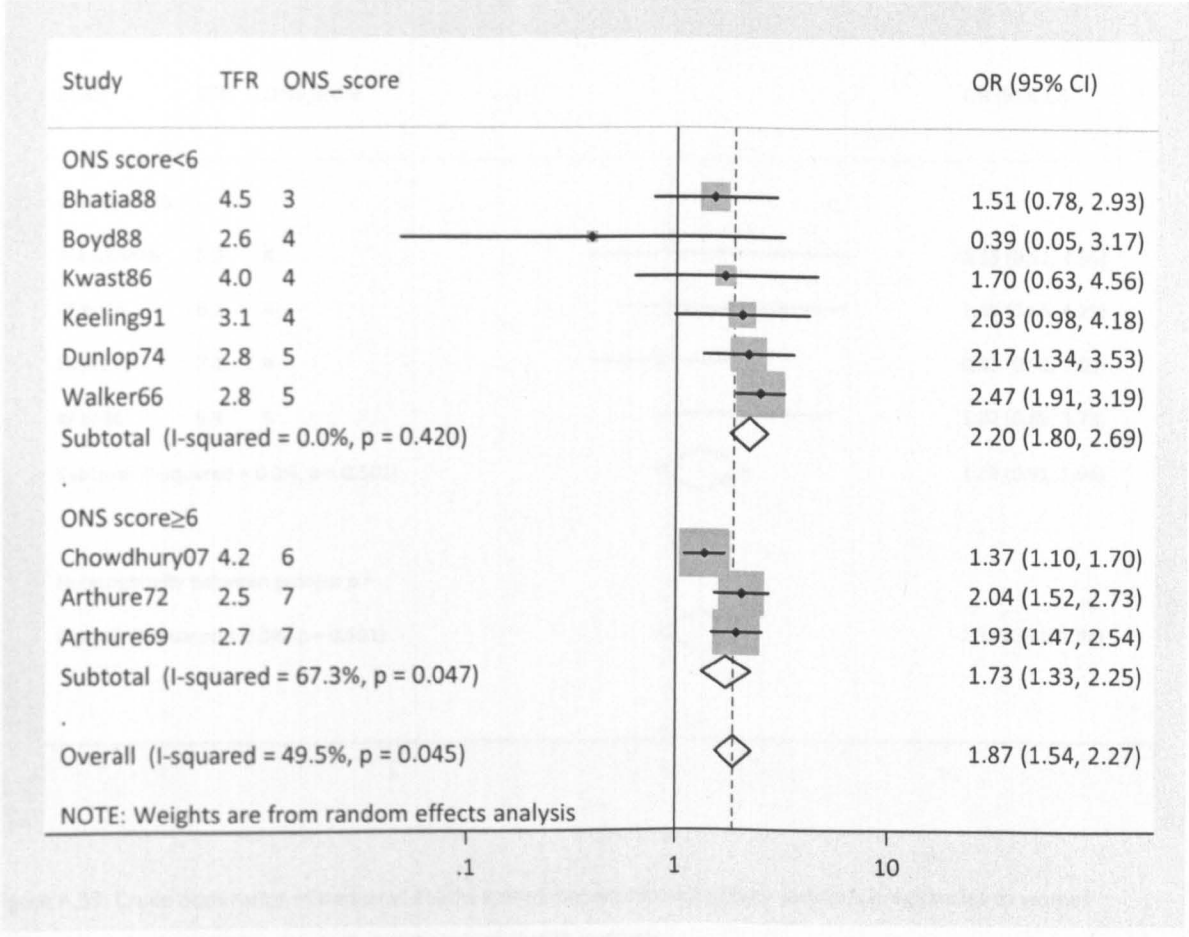

Figure A.58: Crude odds ratios of maternal deaths comparing women with three previous pregnancies to women with one previous pregnancy by study quality in medium fertility settings.

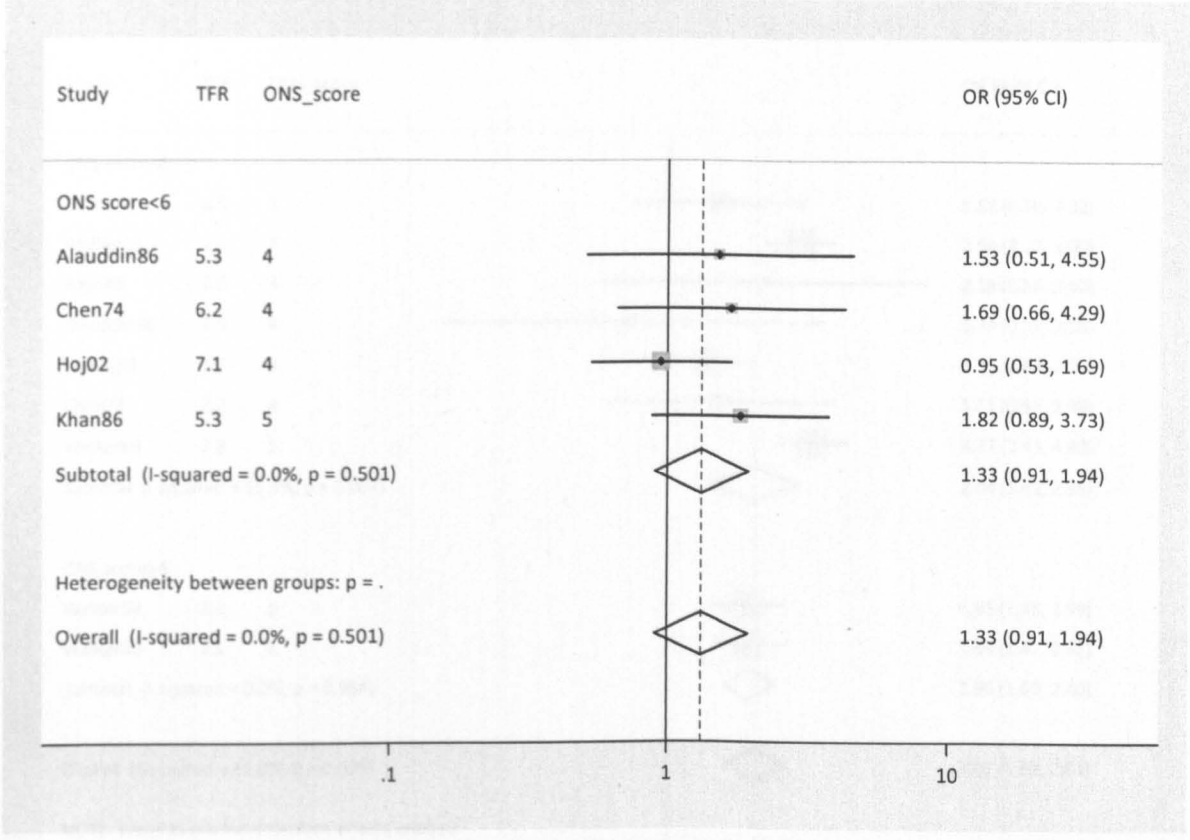

Figure A.59: Crude odds ratios of maternal deaths comparing women with three previous pregnancies to women with one previous pregnancy by study quality in high fertility settings.

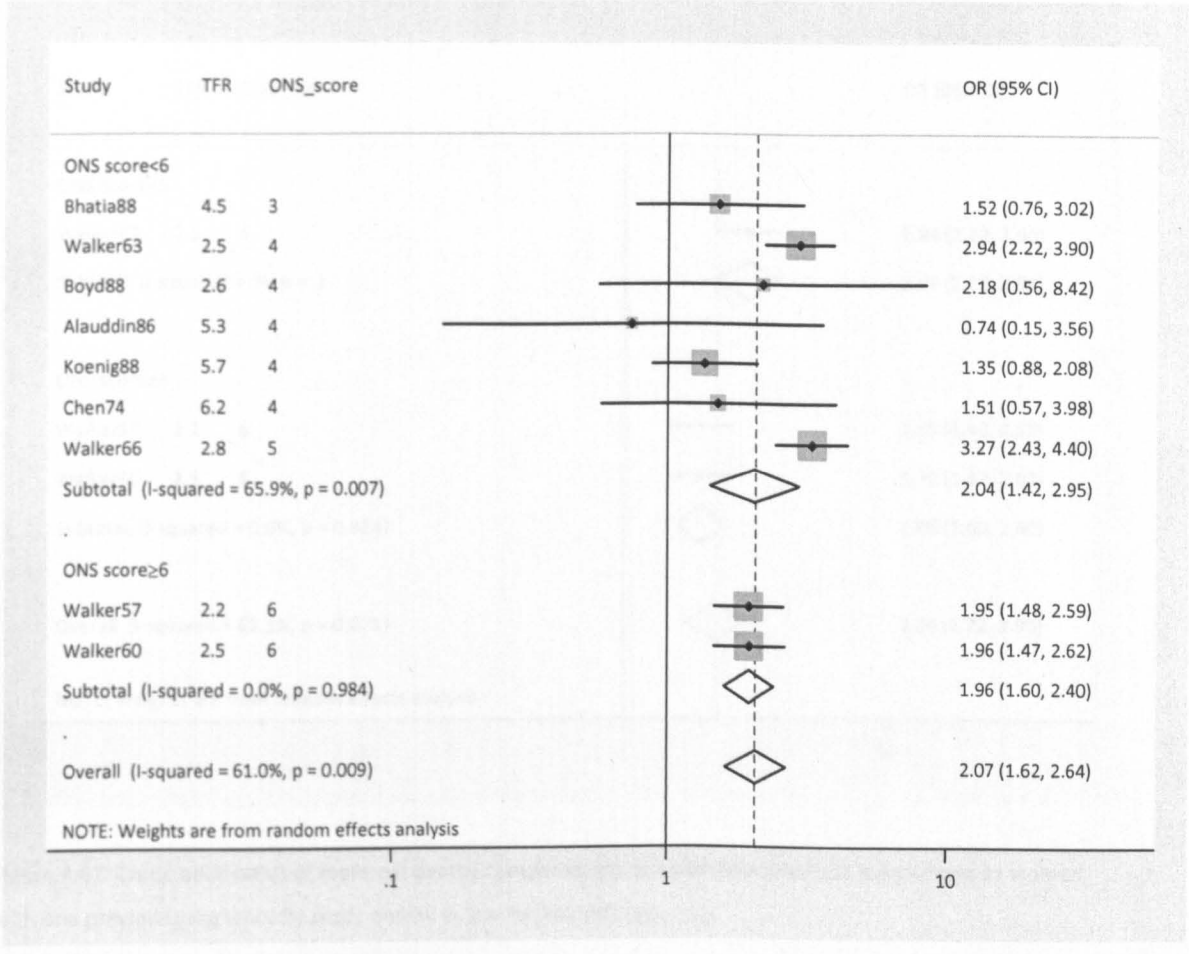

Figure A.60: Crude odds ratios of maternal deaths comparing women with four previous pregnancies to women with one previous pregnancy by study quality.

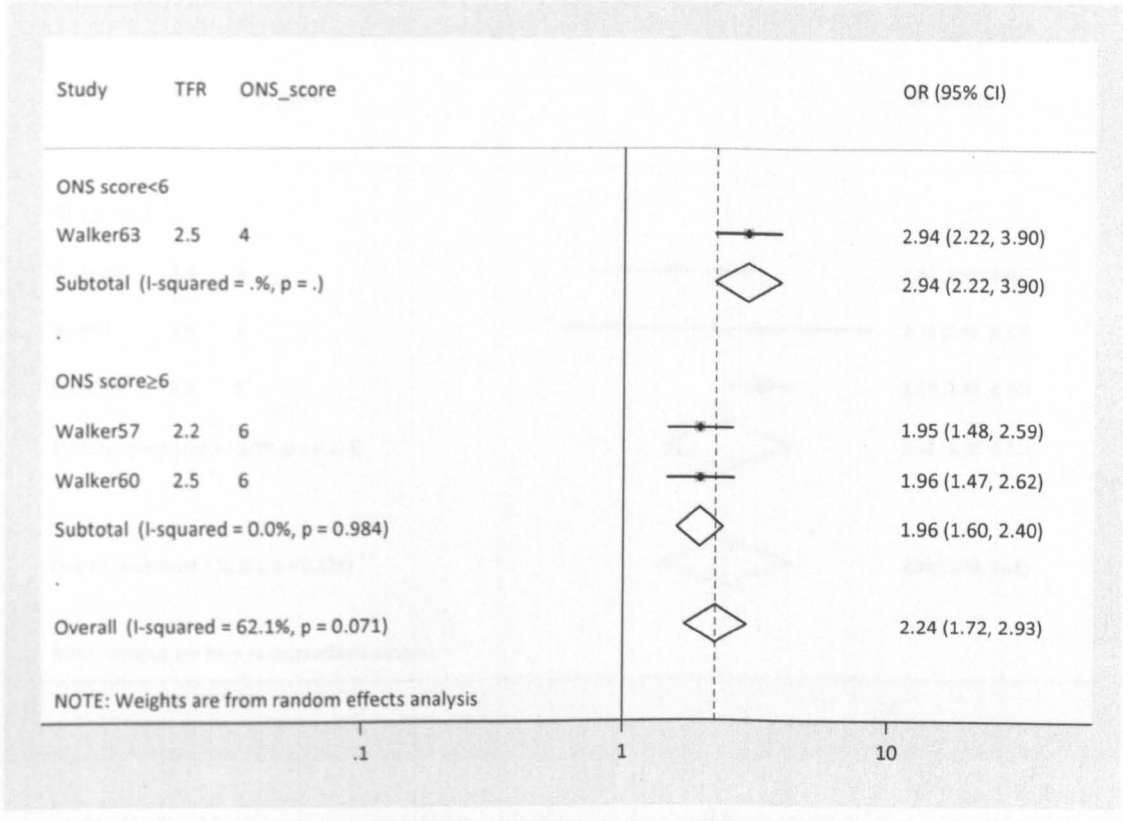

Figure A.61: Crude odds ratios of maternal deaths comparing women with four previous pregnancies to women with one previous pregnancy by study quality in low fertility settings.

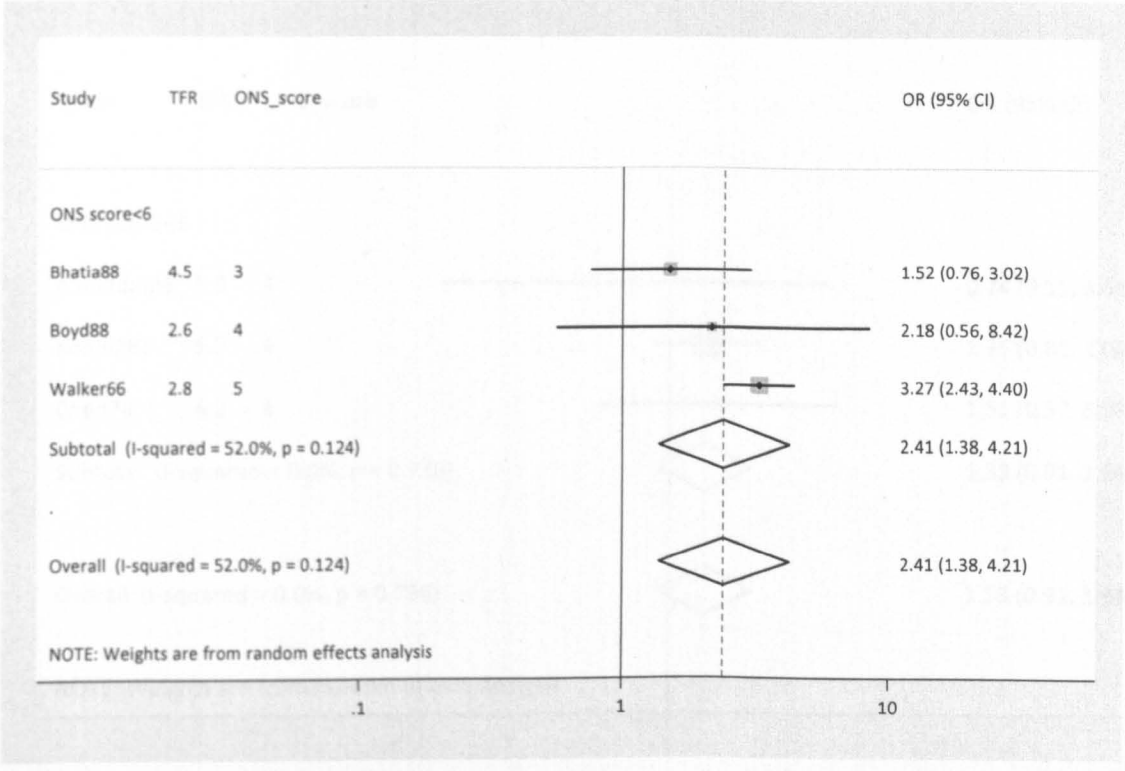

Figure A.62: Crude odds ratios of maternal deaths comparing women with four previous pregnancies to women with one previous pregnancy by study quality in medium fertility settings.

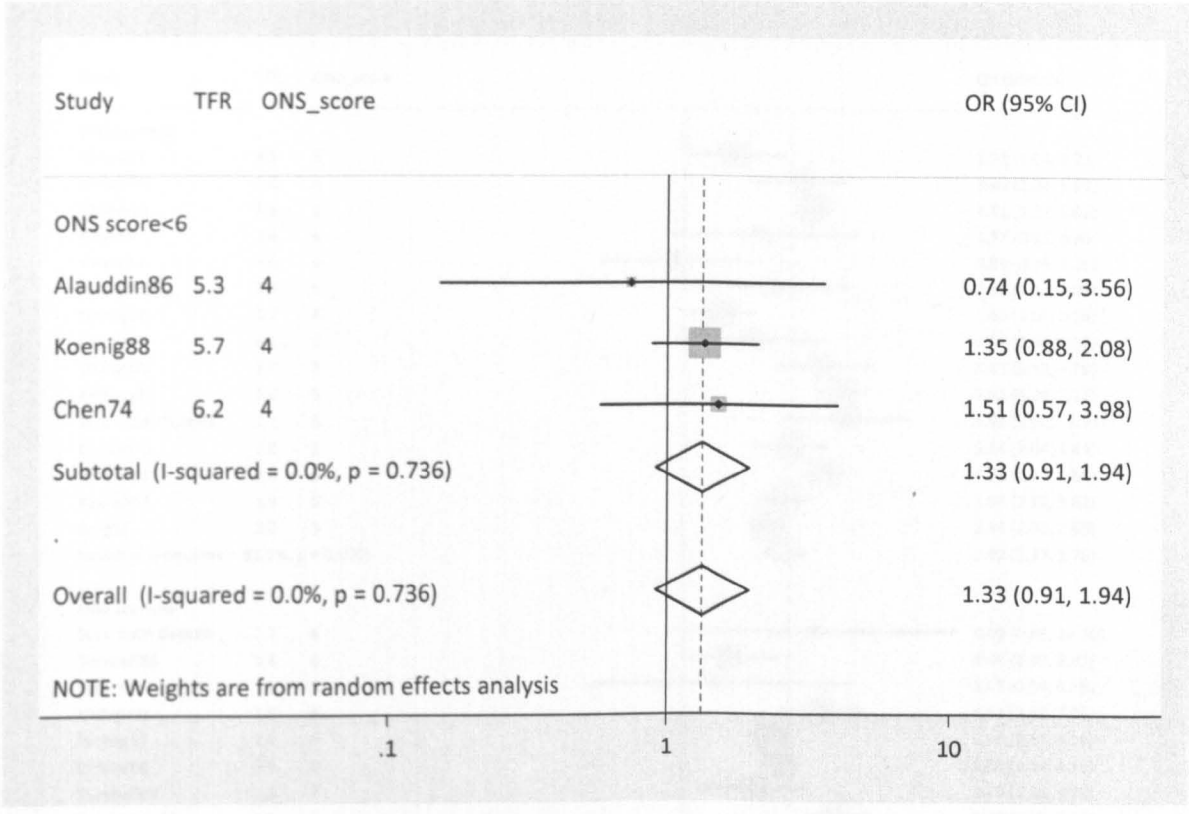

Figure A.63: Crude odds ratios of maternal deaths comparing women with four previous pregnancies to women with one previous pregnancy by study quality in high fertility settings.

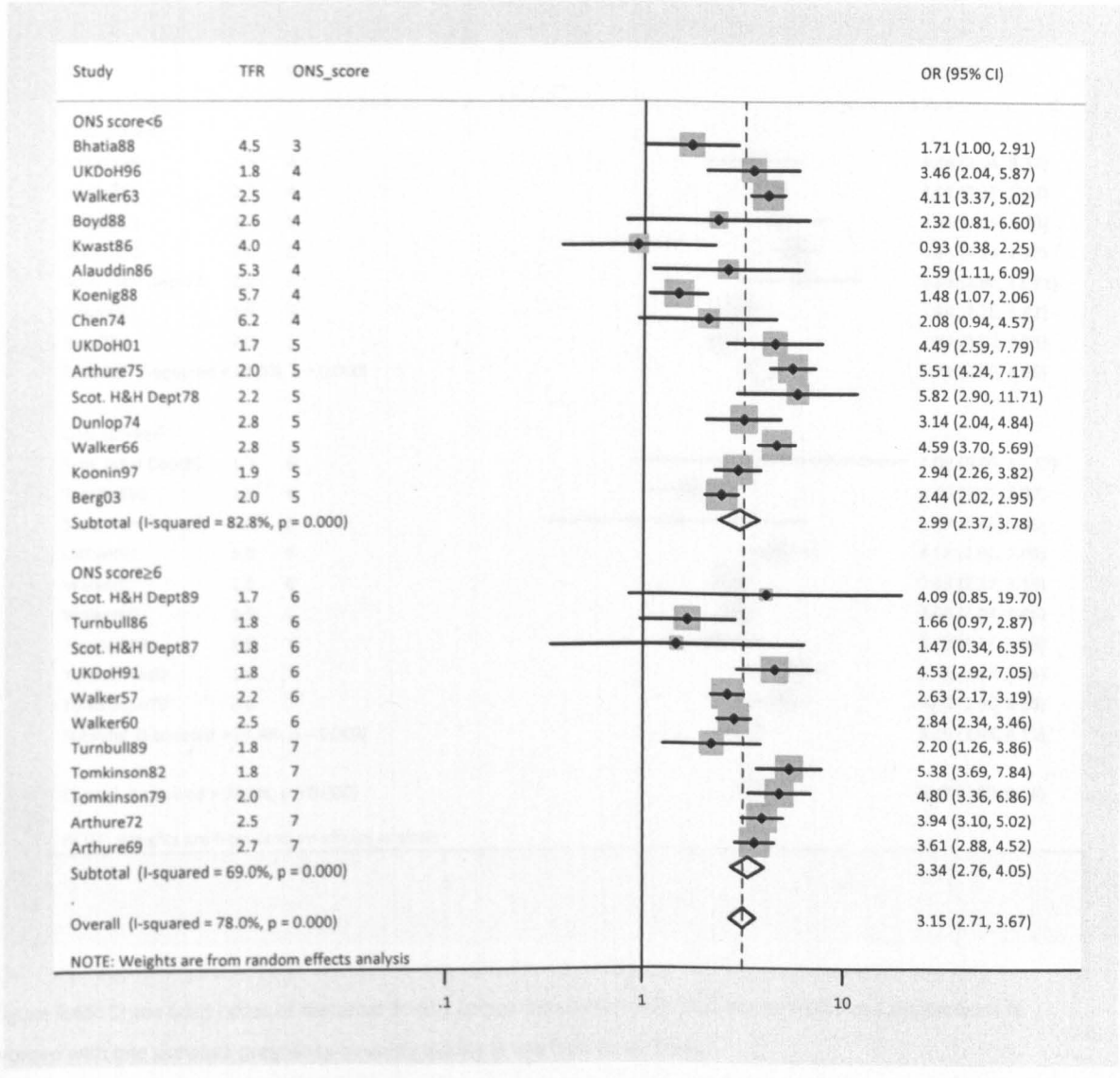

Figure A.64: Crude odds ratios of maternal deaths comparing women with four or more previous pregnancies to women with one previous pregnancy by study quality.

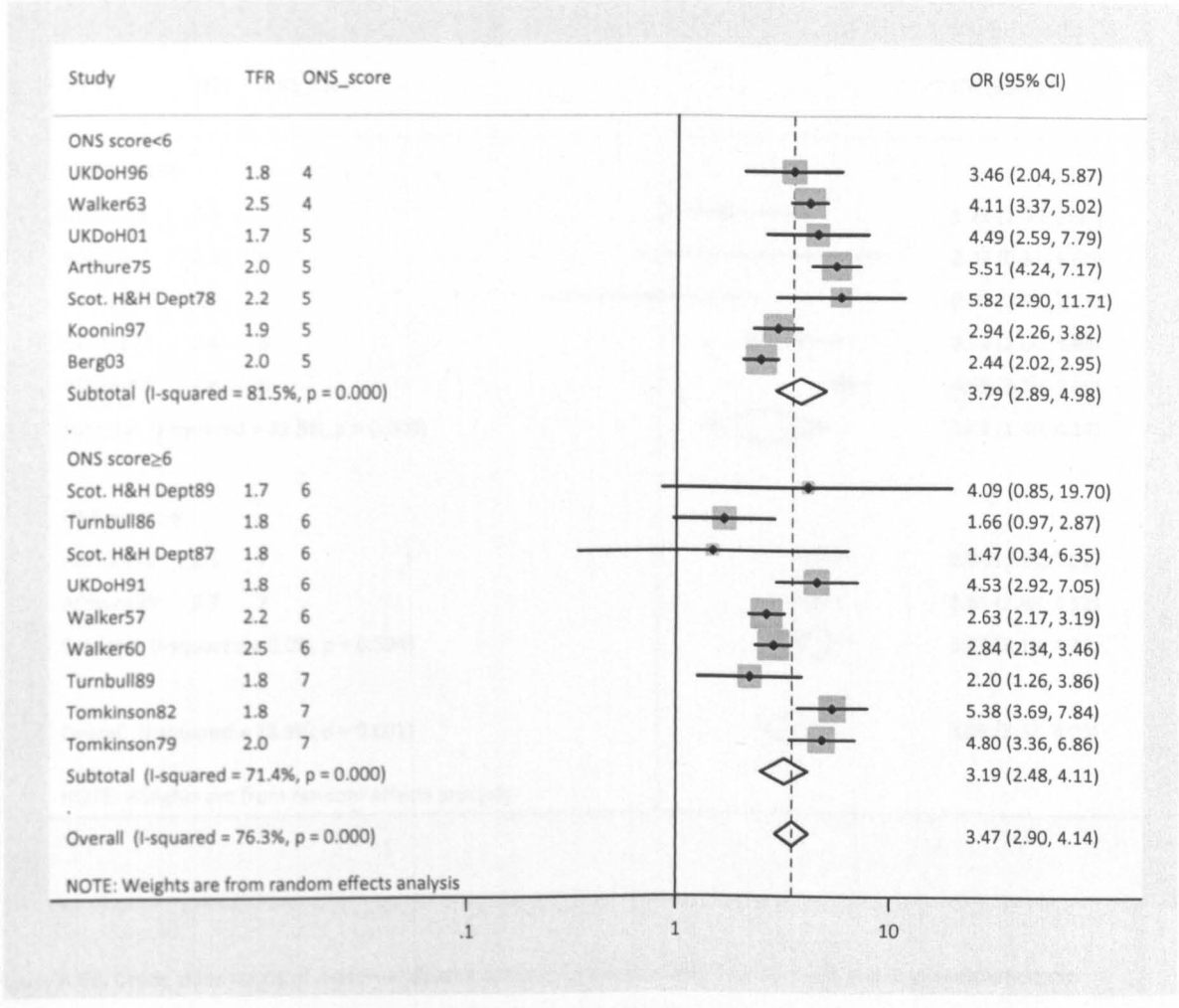

Figure A.65: Crude odds ratios of maternal deaths comparing women with four or more previous pregnancies to women with one previous pregnancy by study quality in low fertility settings.

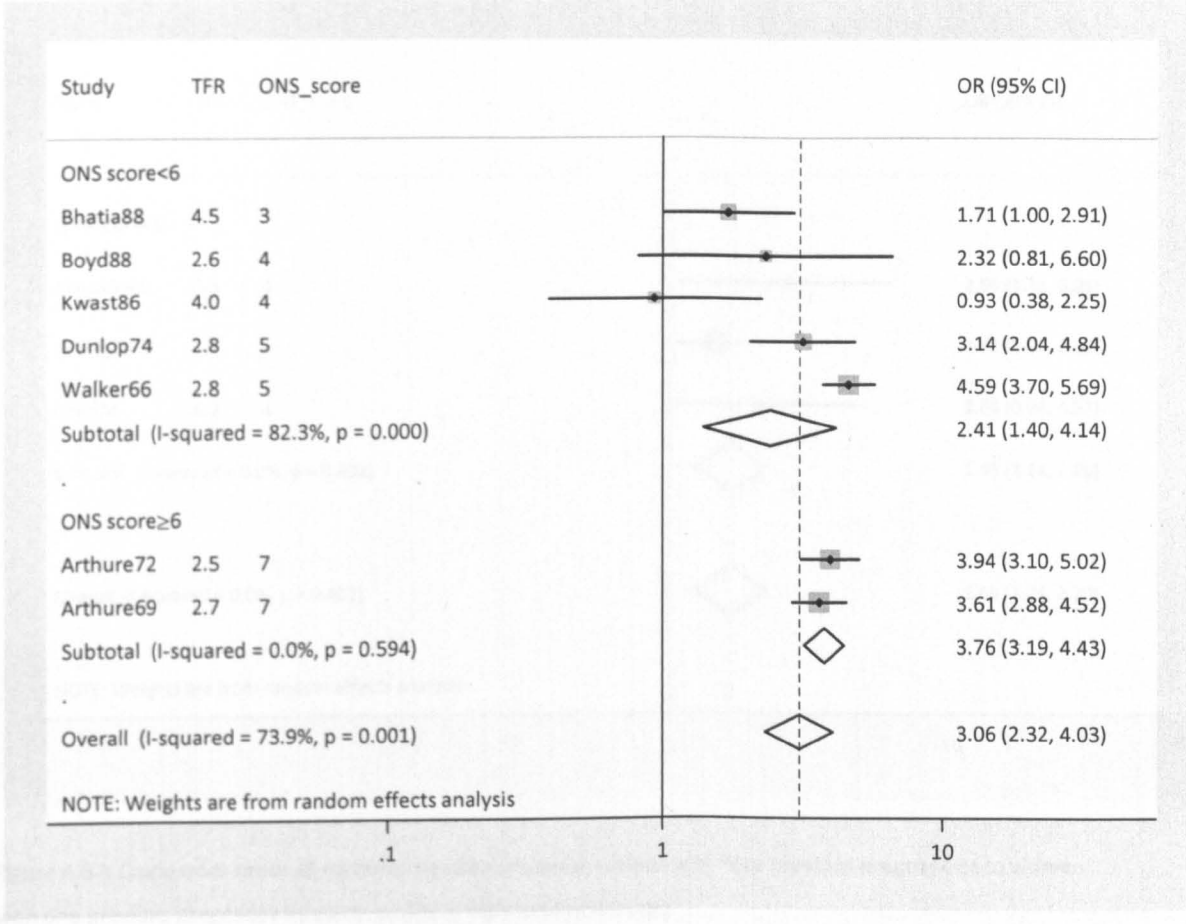

Figure A.66: Crude odds ratios of maternal deaths comparing women with four or more previous pregnancies to women with one previous pregnancy by study quality in medium fertility settings.

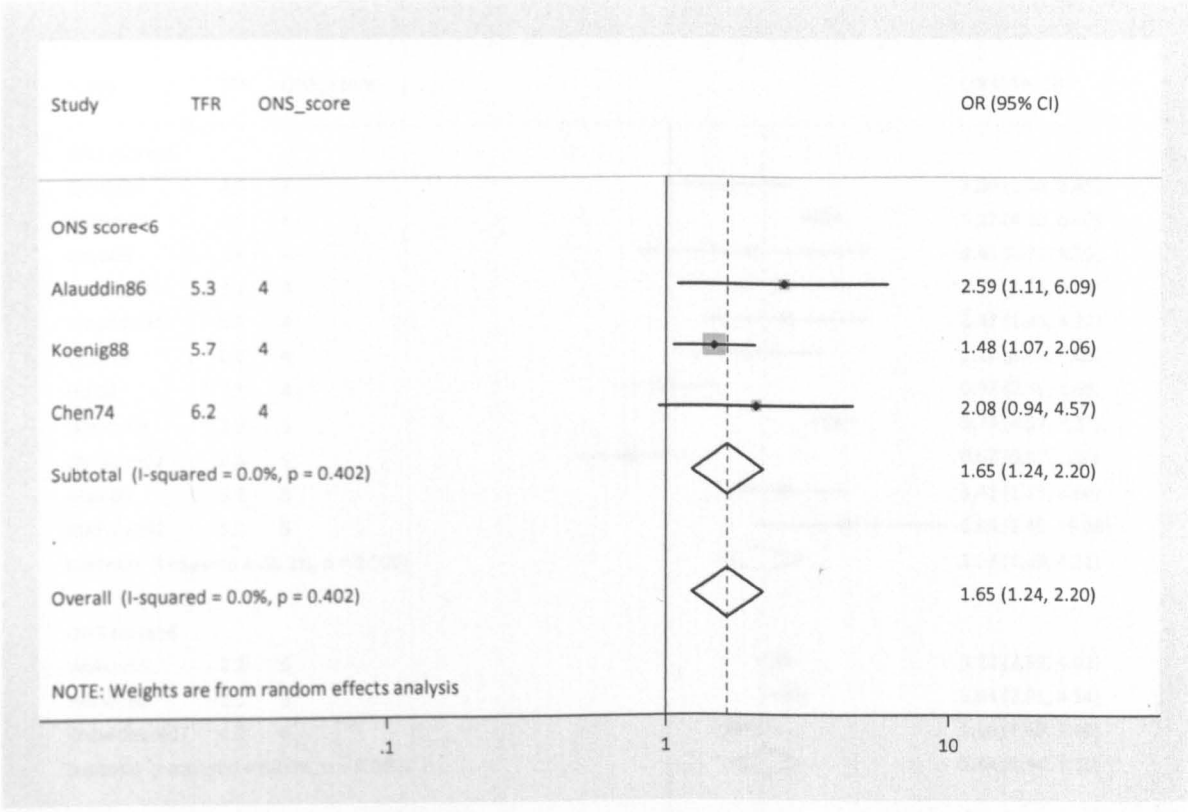

Figure A.67: Crude odds ratios of maternal deaths comparing women with four previous pregnancies to women with one previous pregnancy by study quality in high fertility settings.

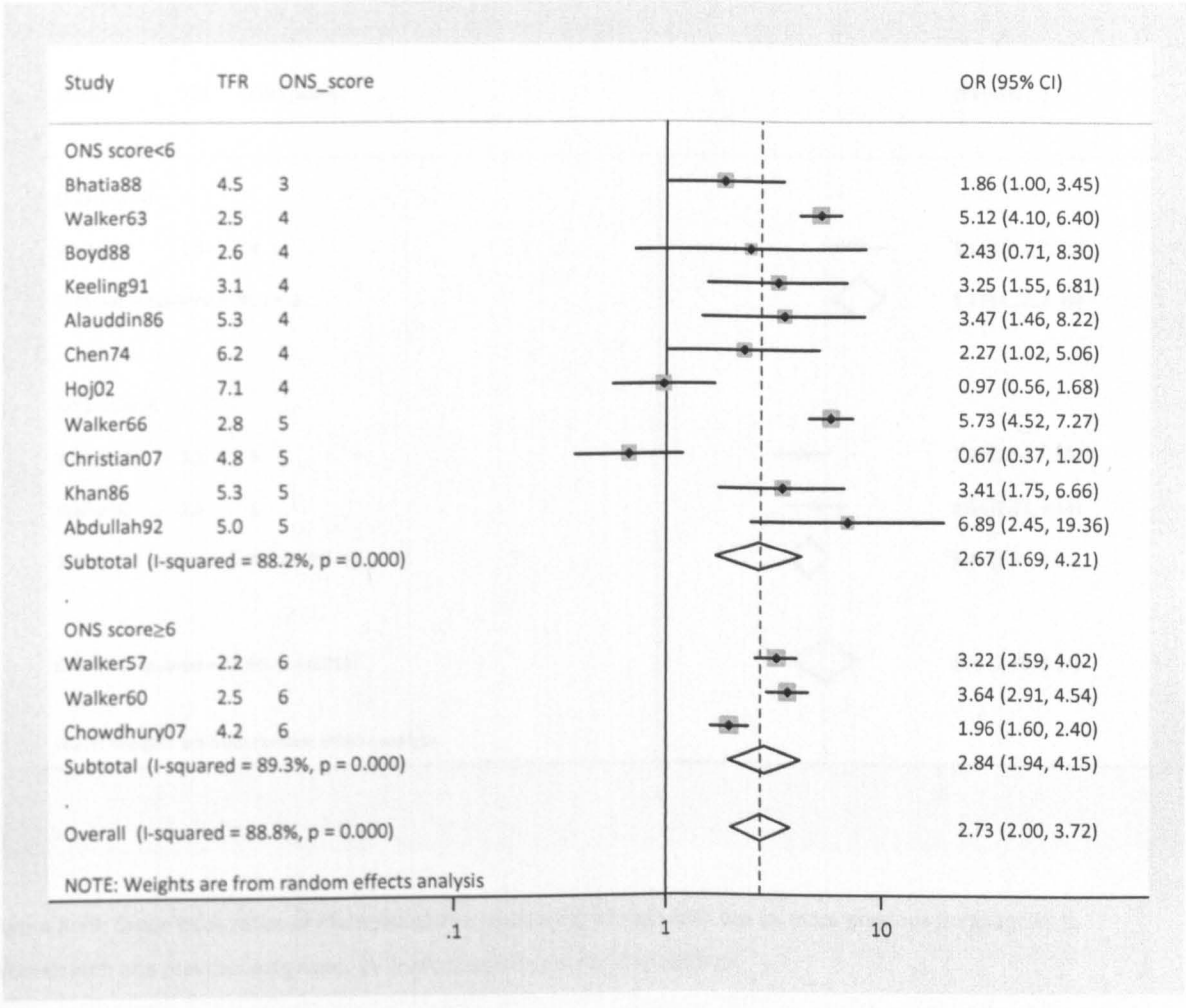

Figure A.68: Crude odds ratios of maternal deaths comparing women with five or more previous pregnancies to women with one previous pregnancy by study quality.

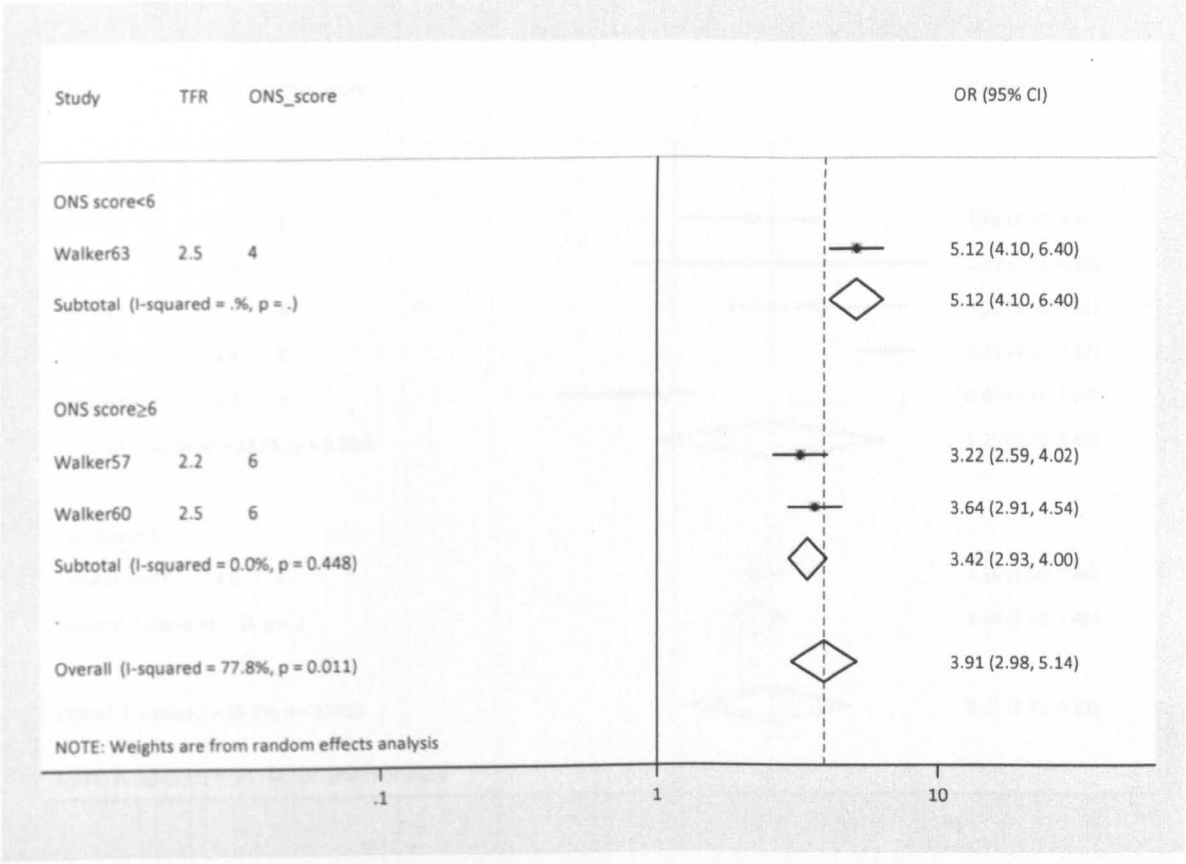

Figure A.69: Crude odds ratios of maternal deaths comparing women with five or more previous pregnancies to women with one previous pregnancy by study quality in low fertility settings.

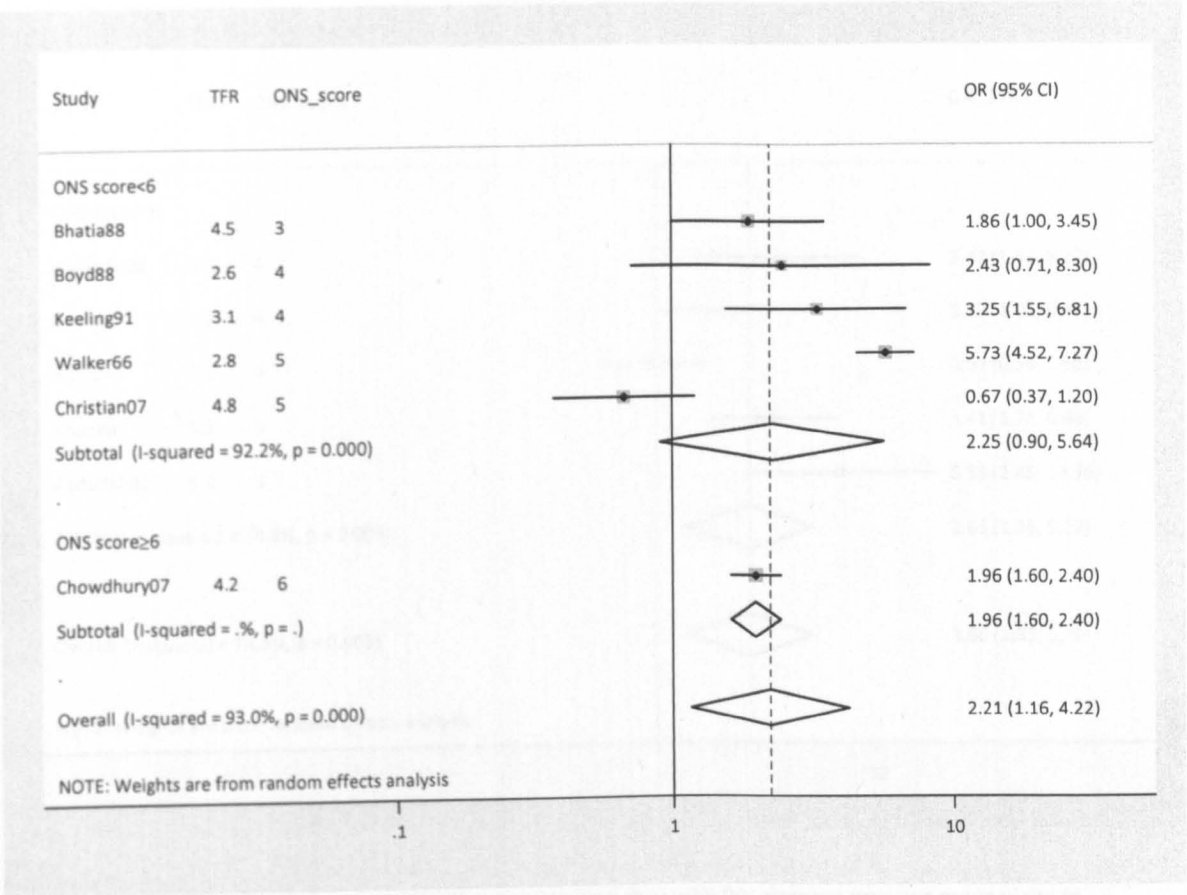

Figure A.70: Crude odds ratios of maternal deaths comparing women with five or more previous pregnancies to women with one previous pregnancy by study quality in medium fertility settings.

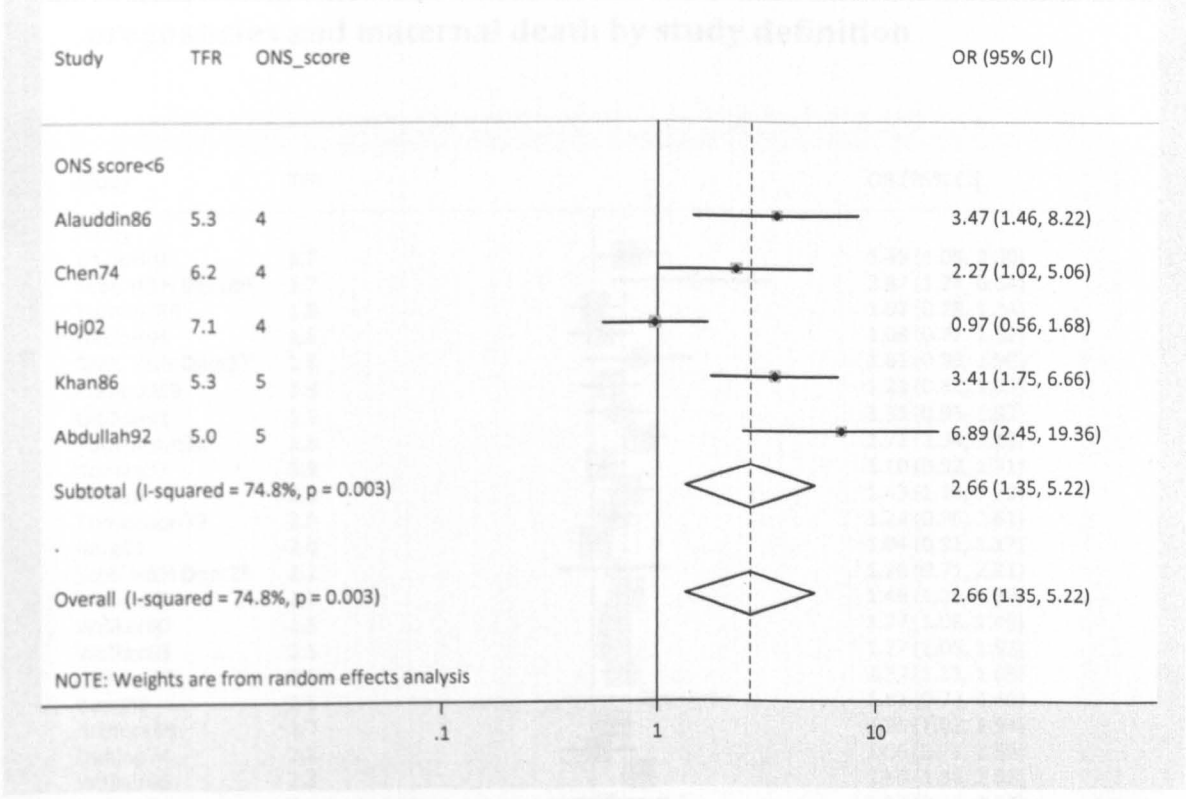

Figure A.71: Crude odds ratios of maternal deaths comparing women with five or more previous pregnancies to women with one previous pregnancy by study quality in high fertility settings.

A.8 Forest plots of the association between number of previous pregnancies and maternal death by study definition

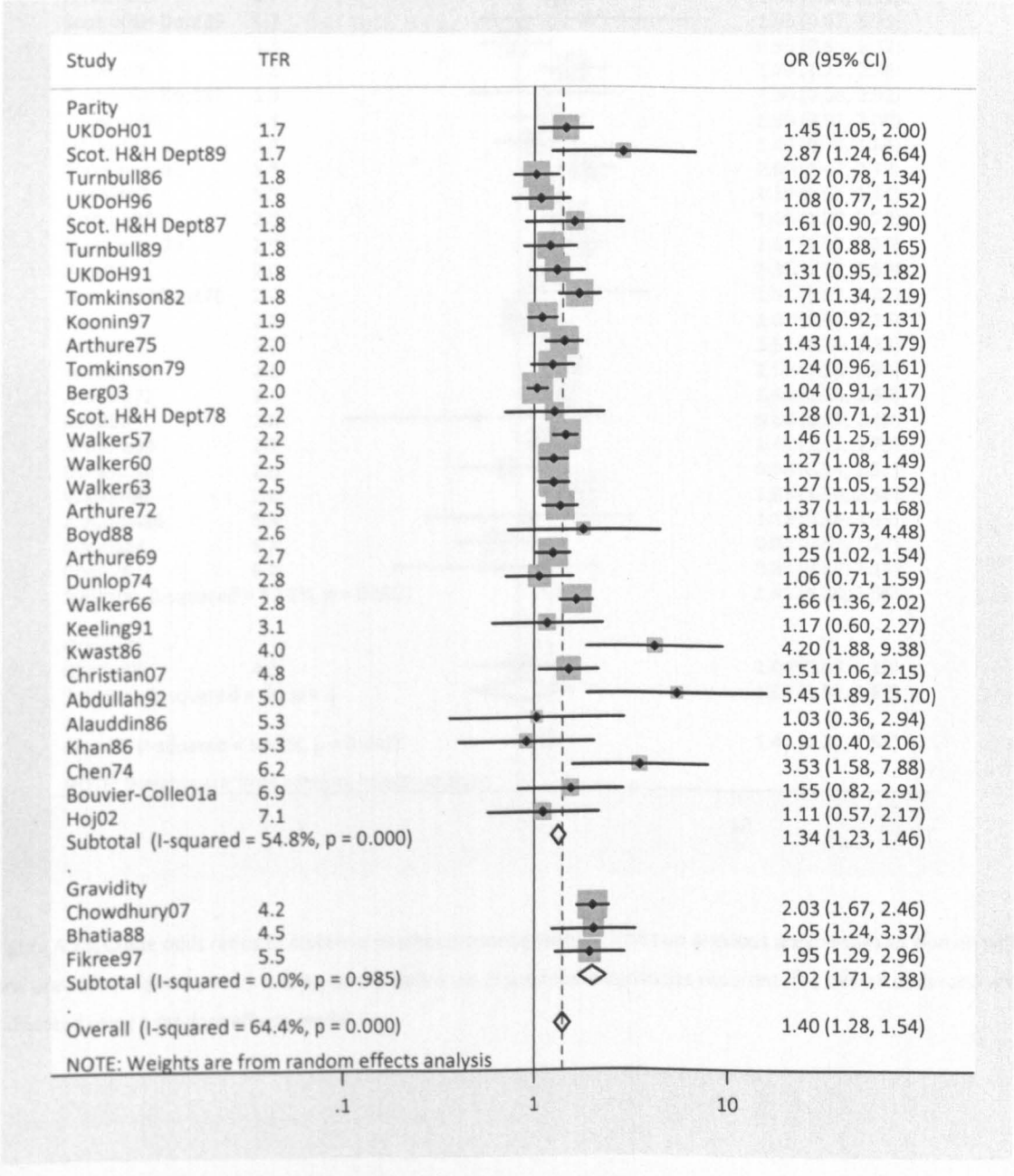

Figure A.72: Crude odds ratios of maternal deaths comparing women with no previous pregnancies to women with one previous pregnancy in 33 studies, by the definition of previous pregnancies reported. The overall odds ratio was calculated using a random effects model

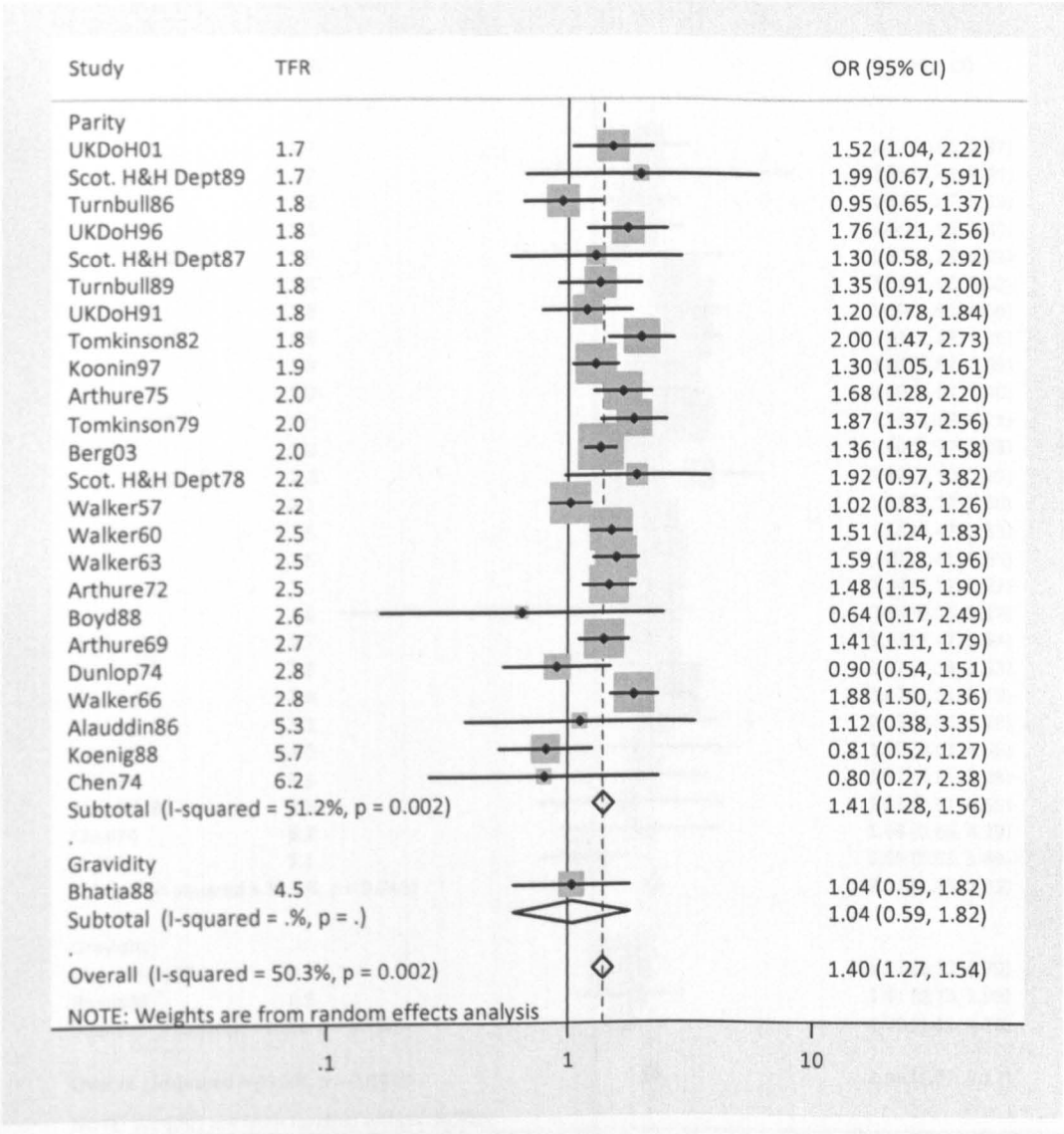

Figure A.73: Crude odds ratios of maternal deaths comparing women with two previous pregnancies to women with one previous pregnancy in 25 studies, by the definition of previous pregnancies reported. The overall odds ratio was calculated using a random effects model.

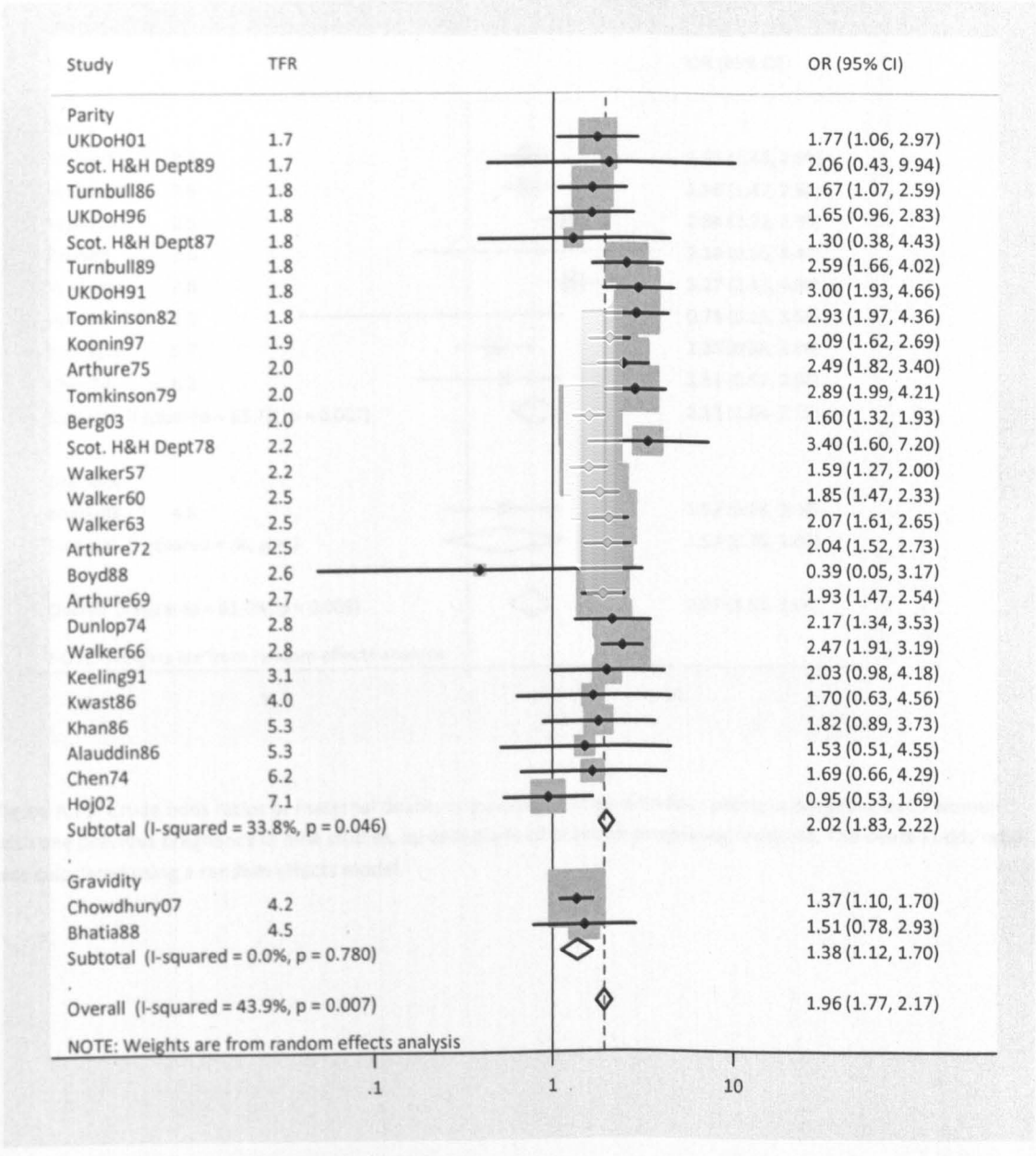

Figure A.74: Crude odds ratios of maternal deaths comparing women with three previous pregnancies to women with one previous pregnancy in 29 studies, by the definition of previous pregnancies reported. The overall odds ratio was calculated using a random effects model.

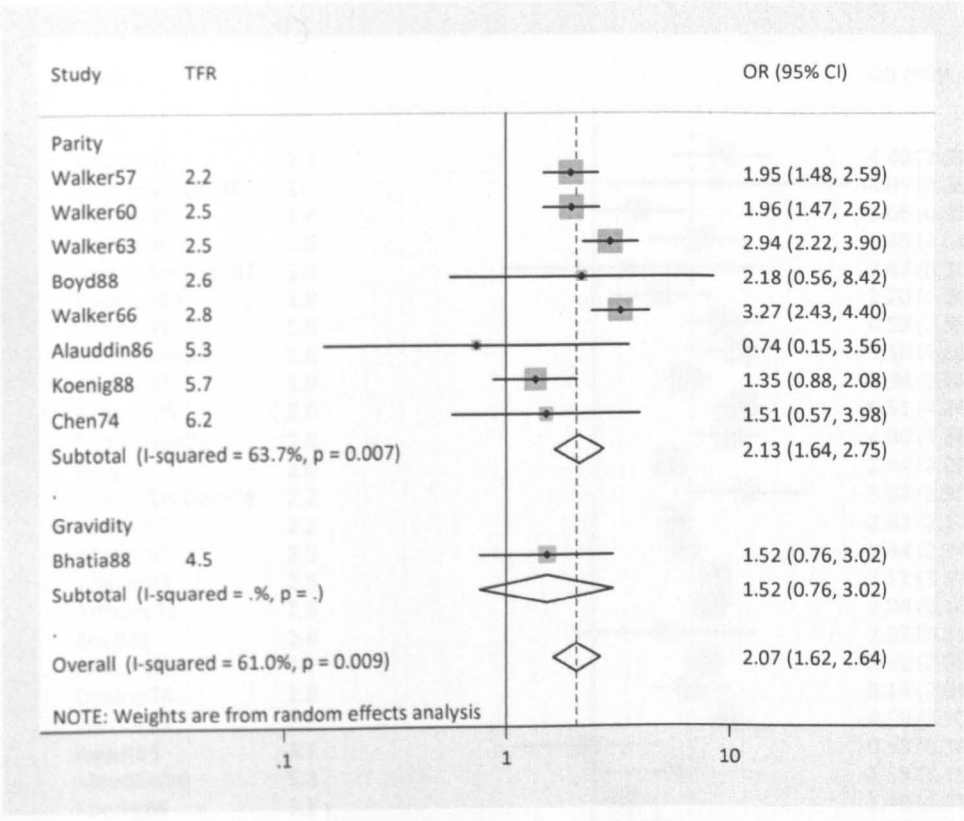

Figure A.75: Crude odds ratios of maternal deaths comparing women with four previous pregnancies to women with one previous pregnancy in nine studies, by definitions of previous pregnancy reported. The overall odds ratio was calculated using a random effects model.

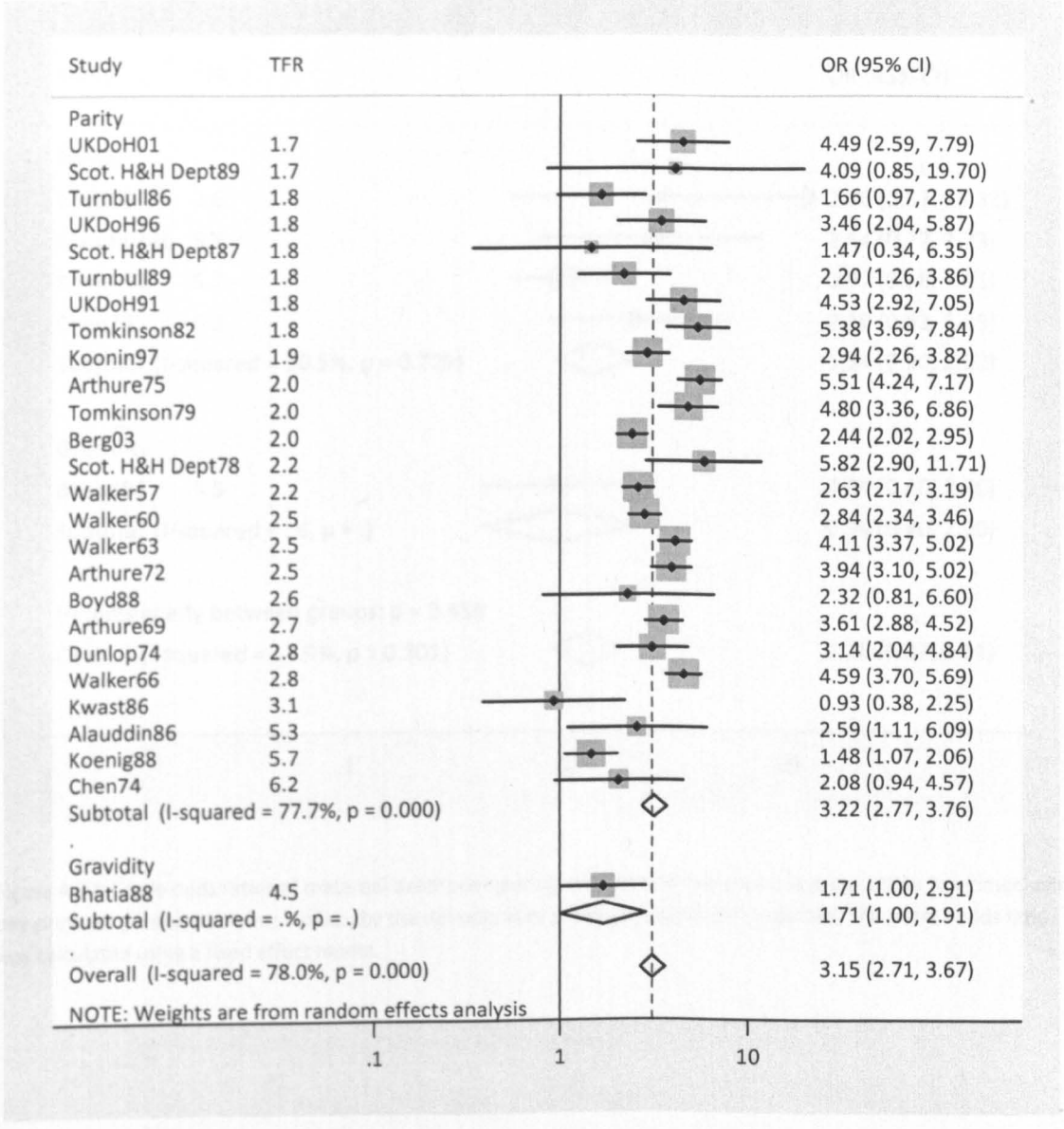

Figure A.76: Crude odds ratios of maternal deaths comparing women with four or more previous pregnancies to women with one previous pregnancy in 26 studies, by the definitions of previous pregnancies reported. The overall odds ratio was calculated using a random effects model.

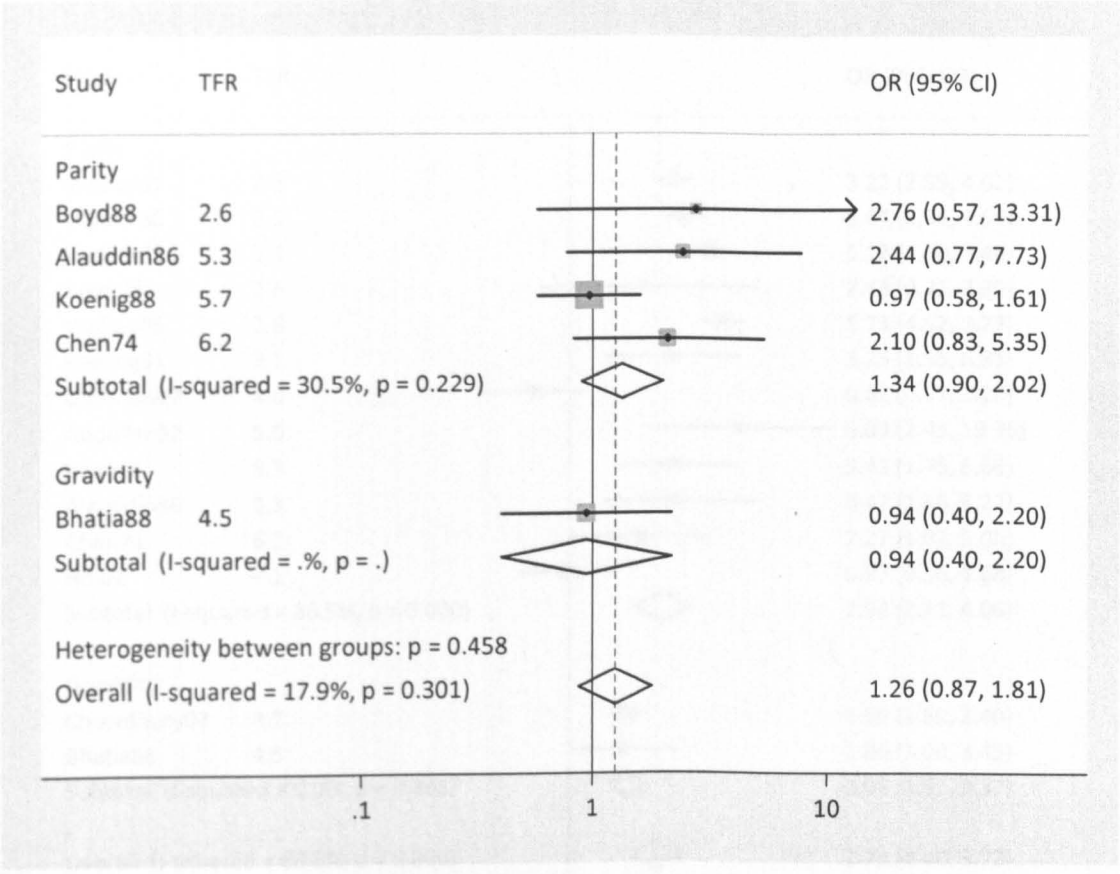

Figure A.77: Crude odds ratios of maternal deaths comparing women with five previous pregnancies to women with one previous pregnancy in five studies, by the definitions of previous pregnancies reported. The overall odds ratio was calculated using a fixed effect model.

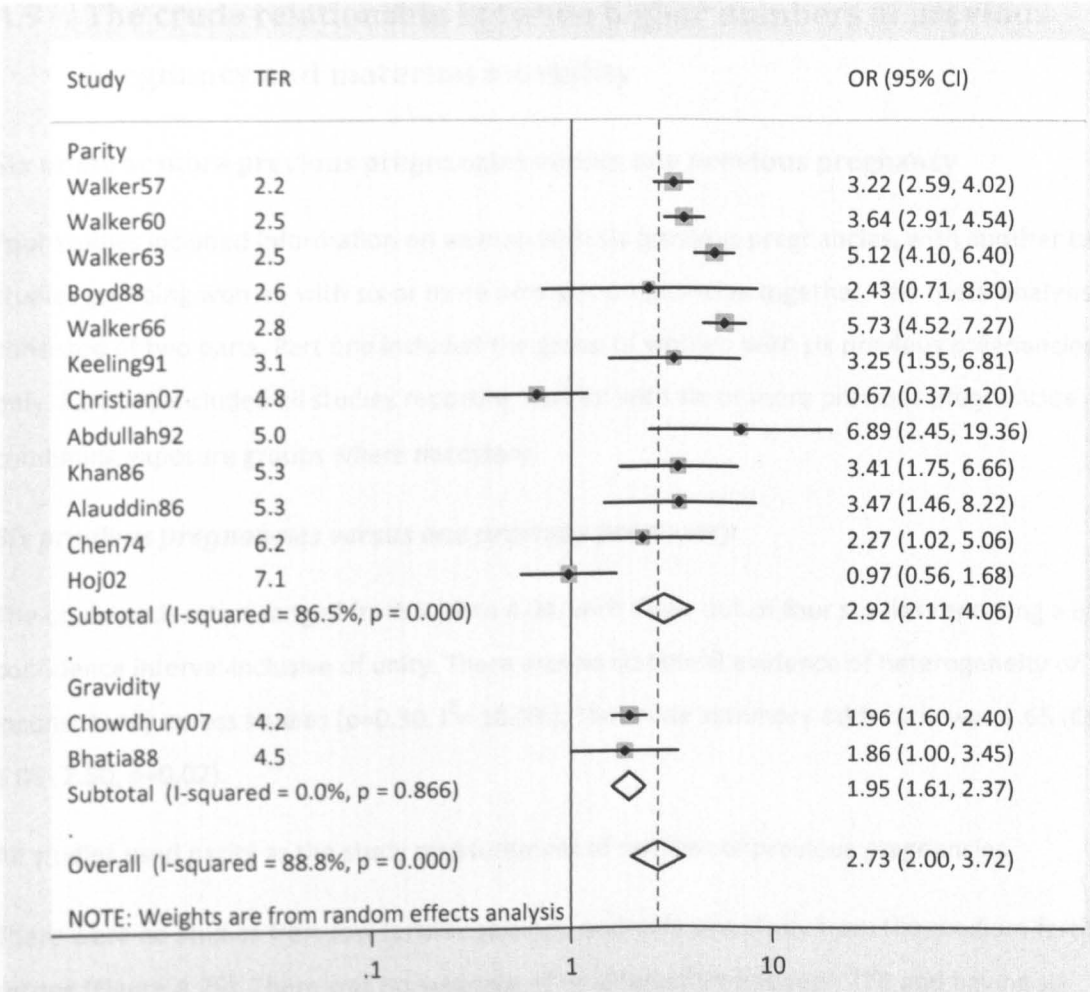

Figure A.78: Crude odds ratios of maternal deaths comparing women with five or more previous pregnancies to women with one previous pregnancy in 14 studies, by the definition of previous pregnancies reported. The overall odds ratio was calculated using a random effects model.

A.9 The crude relationship between higher numbers of previous pregnancy and maternal mortality

Six or six or more previous pregnancies versus one previous pregnancy

Four studies included information on women with six previous pregnancies, with another two studies grouping women with six or more previous pregnancies together. The meta-analysis consisted of two parts. Part one included the group of women with six previous pregnancies only. Part two included all studies reporting women with six or more previous pregnancies combining exposure groups where necessary.

Six previous pregnancies versus one previous pregnancy

The crude odds ratios ranged from 1.29 to 4.04, with three out of four studies reporting a 95% confidence interval inclusive of unity. There was no statistical evidence of heterogeneity or inconsistency across studies (p=0.30, I^2= 18.0%). The crude summary odds ratio was 1.65 (CI: 1.09- 2.50, p=0.02).

All studies used parity as the study measurement of number of previous pregnancies.

There were no studies from low fertility settings, and only one study from the medium fertility setting (Figure A.79). There was no evidence of an interaction between TFR and having six previous pregnancies (p=0.82). The crude summary odds ratio for the high fertility setting was 1.63 (CI: 1.07-2.48, p=0.02). The one study from medium fertility settings reported a crude odds ratio of 2.50 (CI: 0.31-20.29, p=0.39).

All studies used one previous pregnancy as the baseline group, and six previous pregnancies as the exposed group.

There was no statistical evidence to suggest that smaller studies were more likely to report a positive association (Begg's test: p=0.31), thus no evidence of publication bias.

Six or more previous pregnancies versus one previous pregnancy

Six studies with crude odds ratios ranging from 1.29 to 4.03 were included. Three studies reporting a 95% confidence interval inclusive of unity. There was no statistical evidence of heterogeneity or inconsistency across studies (p=0.60, I^2= 0.0%). The crude summary odds ratio was 2.17 (CI: 1.67- 2.81, p<0.0001).

There was no statistical evidence of an interaction between study definitions used and the effect of having six or previous pregnancies (p=0.38). Stratification by definitions did not change the conclusions of the findings (Figure A.80).

. One study reported on gravidity, and the crude odds ratio was 3.15 (CI: 1.44-6.90, p=0.004). The crude summary odds ratio for the parity studies was 2.07 (CI: 1.57- 2.73, p<0.0001).

There was no statistical evidence of an interaction between TFR levels and the effect of having six or previous pregnancies (p=0.42). Stratification by TFR levels did not change the conclusions of the findings. The crude summary odds ratios were 2.93 (CI: 1.45-5.90, p=0.003) and 2.07 (CI: 1.56-2.74, p<0.0001) for medium and high fertility settings respectively (Figure A.81)

Excluding a West African study that used parity 1-5 as the baseline group did not change the overall or subgroup conclusions.

There was no statistical evidence to suggest that smaller studies were more likely to report a positive association (Begg's test: p=0.26), thus no evidence of publication bias.

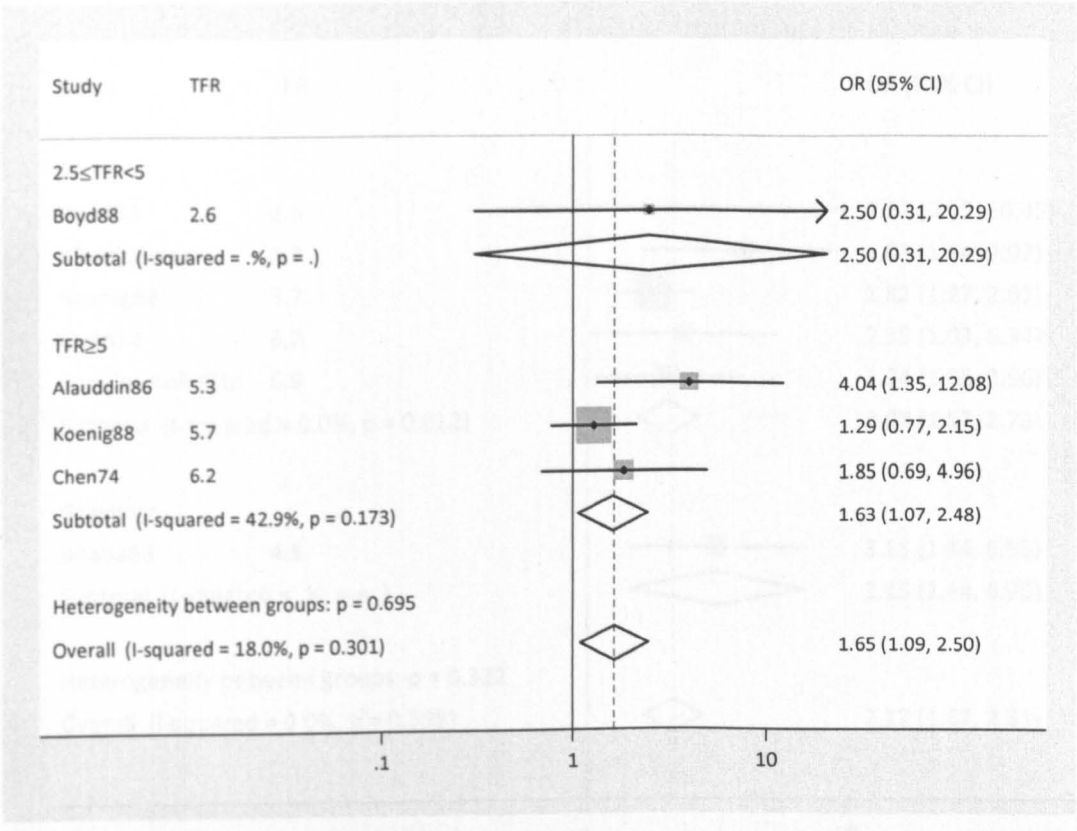

Figure A.79: Crude odds ratios of maternal deaths comparing women with six previous pregnancies to women with one previous pregnancy in four studies, by fertility groups. The overall odds ratio was calculated using a fixed effect model.

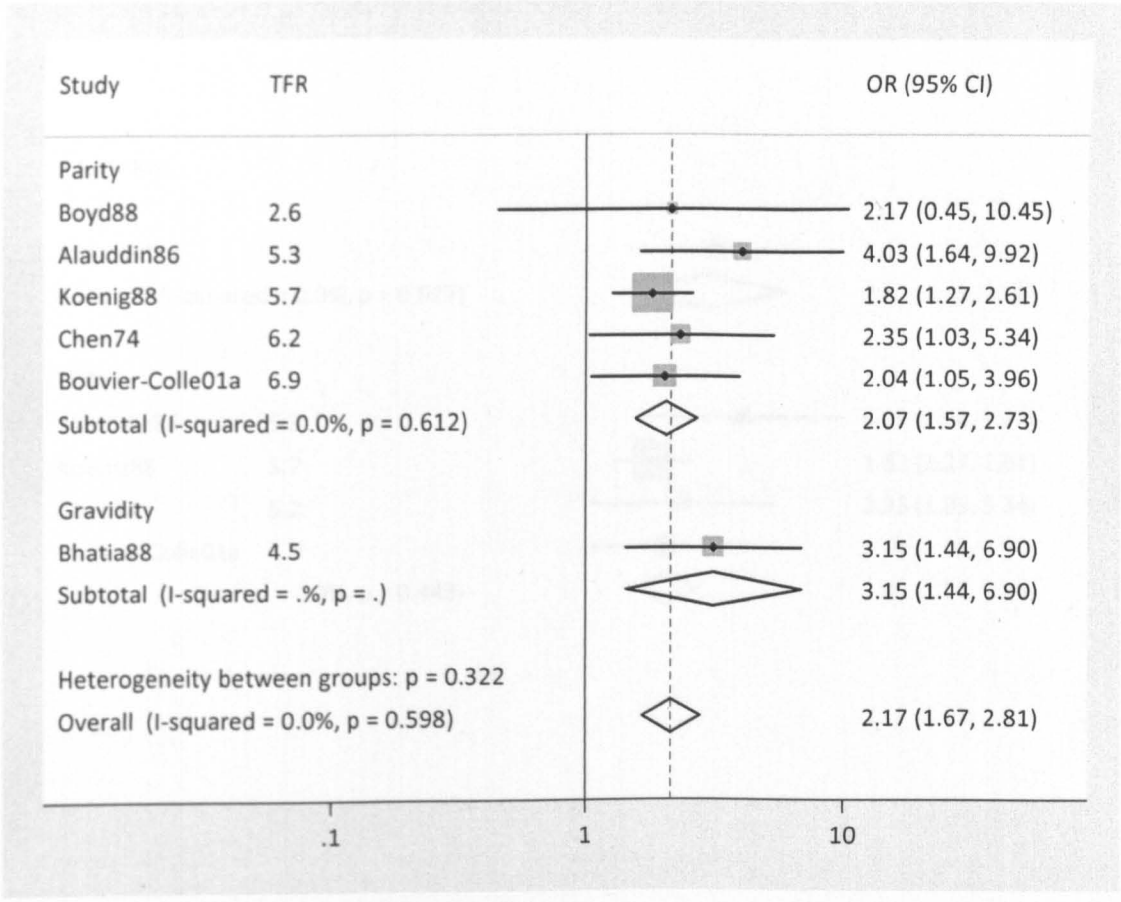

Figure A.80: Crude odds ratios of maternal deaths comparing women with six or more previous pregnancies to women with one previous pregnancy in six studies, by the definition of previous pregnancy reported. The overall odds ratio was calculated using a fixed effect model.

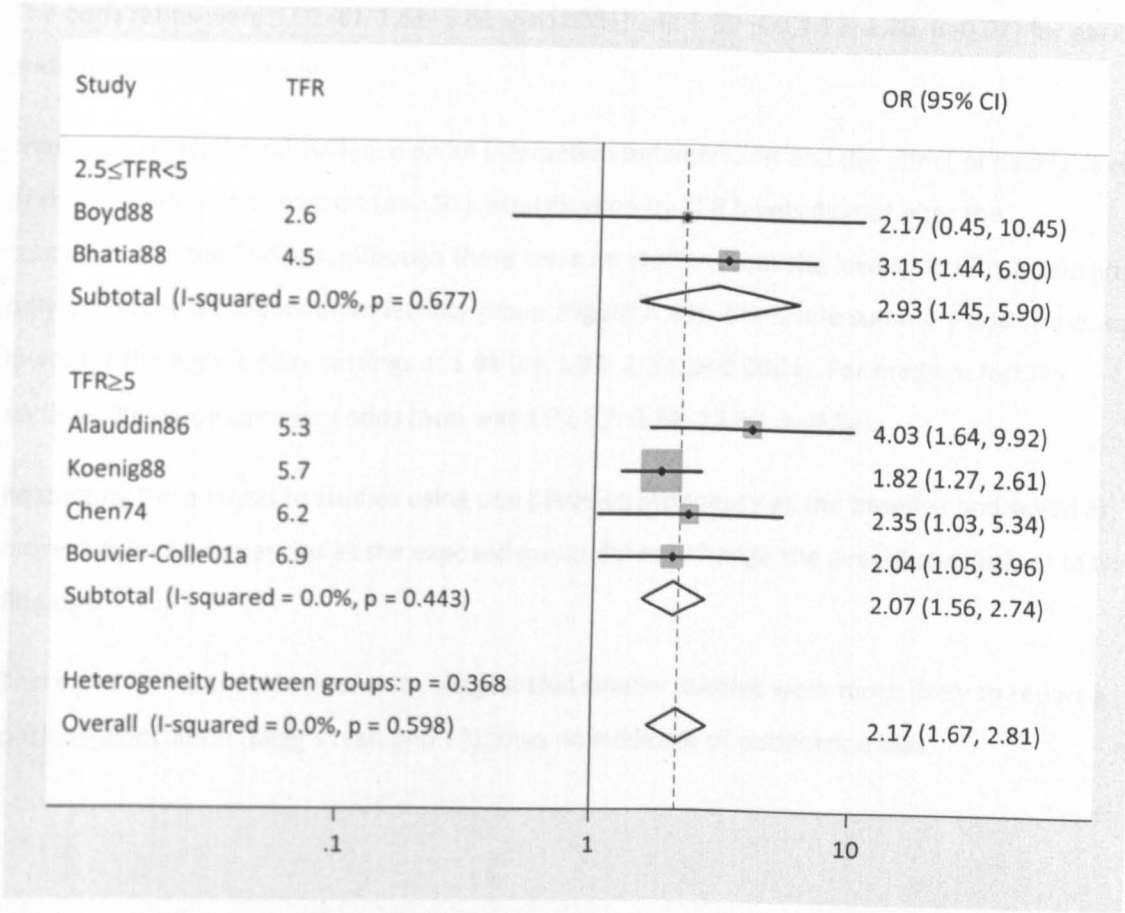

Figure A.81: Crude odds ratios of maternal deaths comparing women with six or more previous pregnancies to women with one previous pregnancy in six studies, by fertility levels. The overall odds ratio was calculated using a fixed effect model.

Seven or more previous pregnancies versus one previous pregnancy

Four studies included information on women with seven or more previous pregnancies, including one study reporting separate categories for women of higher number of previous pregnancies. The crude odds ratios ranged from 1.60 to 4.02 with one study reporting a 95% confidence interval reporting unity. There was little evidence of heterogeneity or inconsistency across studies (p=0.30, I^2= 18.9%). The crude summary odds ratio was 1.86 (CI: 1.38- 2.52, p<0.0001).

There was no statistical evidence on an interaction between the study definition used and the effect of having seven or more previous pregnancies (p=0.22), although there was only one gravidity study. Stratification by definition did not change the conclusions of the findings (Figure A.82). The crude summary odds ratios were higher for parity than for gravidity studies.

The odds ratios were 3.02 (CI: 1.63- 5.61, p<0.0001) and 1.60 (CI: 1.13- 2.26, p=0.01) for parity and gravidity respectively.

There was no statistical evidence on an interaction between TFR and the effect of having seven or more previous pregnancies (p=0.91). Stratification by TFR levels did not alter the conclusions of the findings, although there were no studies from the lowest fertility group and only one study for the medium fertility group (Figure A.83). The crude summary odds ratio was lower for the high fertility settings at 1.86 (CI: 1.37- 2.52, p<0.0001). For medium fertility settings the crude summary odds ratio was 1.92 (CI: 0.24- 15.60, p=0.54).

Restricting the analysis to studies using one previous pregnancy as the baseline and seven or more previous pregnancies as the exposed group did not change the overall conclusions of the findings.

There was no statistical evidence to suggest that smaller studies were more likely to report a positive association (Begg's test: p=0.73), thus no evidence of publication bias.

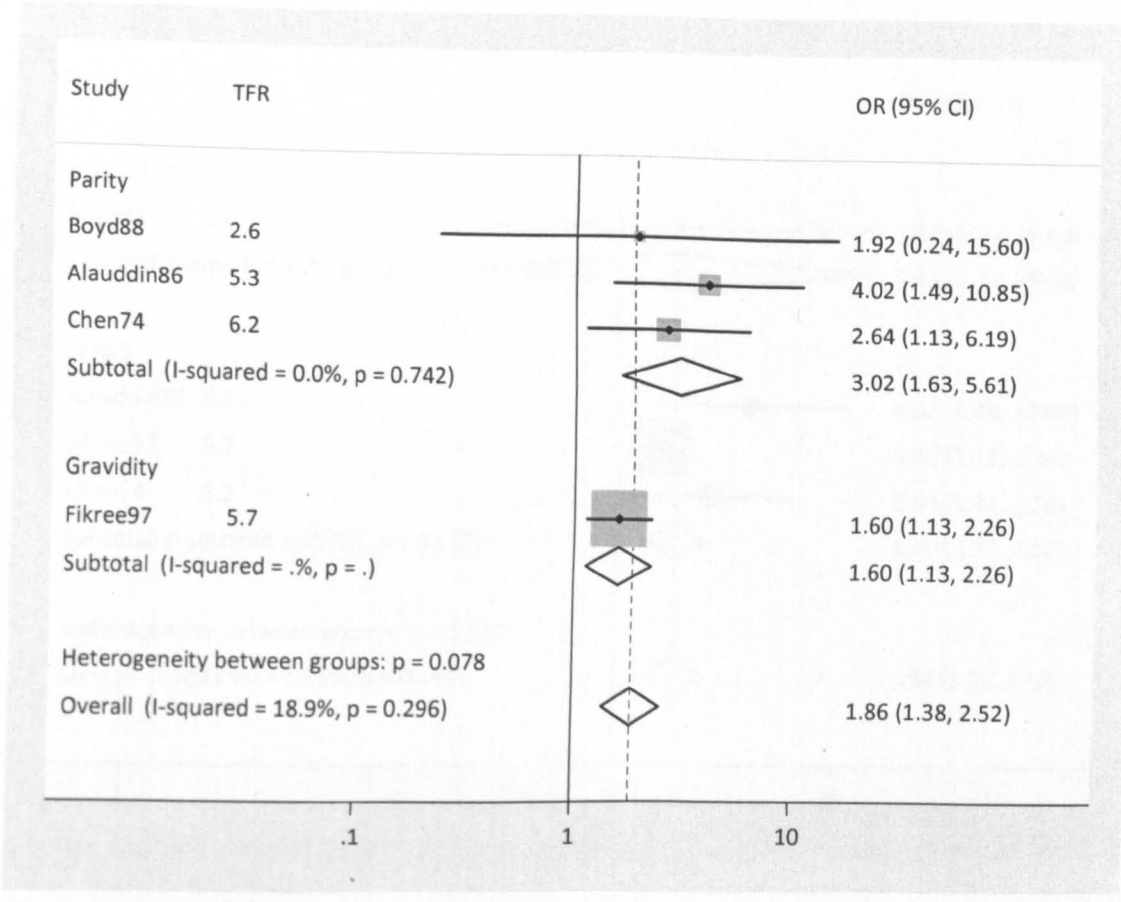

Figure A.82: Crude odds ratios of maternal deaths comparing women with seven or more previous pregnancies to women with one previous pregnancy in four studies, by definitions of previous pregnancies reported. The overall odds ratio was calculated using a fixed effect model.

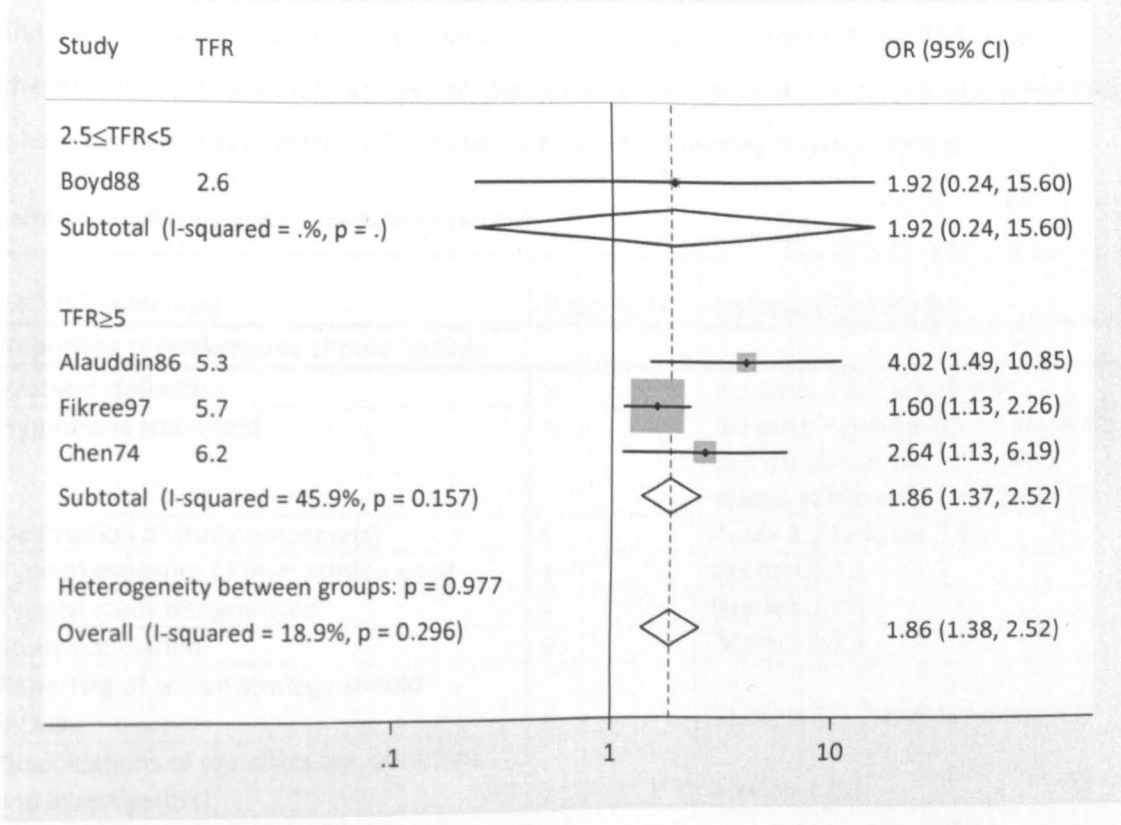

Figure A.83: Crude odds ratios of maternal deaths comparing women with seven or more previous pregnancies/ to women with one previous pregnancy in four studies, by fertility levels. The overall odds ratio was calculated using a fixed effect model.

A.10 MOOSE guidelines

The group on Meta-analysis Of Observational Studies in Epidemiology (MOOSE) presents a check list for reporting meta-analysis of observational studies [334]. The tables below indicate where the item was covered in the thesis, or a comment on why it was no included.

Table A.10.1: MOOSE guideline – background checklist

MOOSE guidelines	Reported?	Location/Comments
Reporting of background should include		
Problem definition	y	Sections 3.1.1 and 3.2.3
Hypothesis statement	n	No prior hypothesis was assumed, but the aim of the review was stated at the start of Chapter 3.
Description of study outcome(s)	y	Table 3.1 to Table 3.14
Type of exposure or intervention used	y	Section 3.1.1
Type of study designs used	y	Section 3.1.1
Study population	y	Section 3.1.1
Reporting of search strategy should include	y	Section 3.1.2 and Appendix A.1
Qualifications of searchers (eg, librarians and investigators)	y	Section 3.1.3
Search strategy, including time period included in the synthesis and keywords	y	Section 3.1.2
Effort to include all available studies, including contact with authors	n	Authors were not contacted due to time constraints. In some cases the studies were also very old, adding to difficulties in contacting the authors.
Databases and registries searched	y	Section 3.1.2
Search software used, name and version, including special features used (eg, explosion)	y	Section 3.1.2
Use of hand searching (eg, reference lists of obtained articles)	y	Section 3.1.2
List of citations located and those excluded, including justification	partial	A summary of selection process can be found on Figure 3.1. A full list can be provided upon request, as the author has a record of all citations found.
Method of addressing articles published in languages other than English	y	Section 3.1.2
Method of handling abstracts and unpublished studies	y	Section 3.1.2
Description of any contact with authors	na	See above

Table A.10.2: MOOSE guideline – method and results checklists

MOOSE guidelines	Reported?	Location/Comments
Reporting of methods should include		
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	y	Section 3.1.1 describes the rationale behind the inclusion criteria, for example, why only certain types of facility based studies were appropriate in estimating population based estimates.
Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	y	See point above
Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability)	partial	Section 3.1.3 and Appendix A.2. The coding used for different types of maternal morbidity is available on request.
Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	y	Section 3.1.3, assessment of confounding was done as part of the study quality assessment.
Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	y	See previous point, and also Section 3.1.3 describes the subgroup analysis planned.
Assessment of heterogeneity	y	Section 3.1.3, heading "Heterogeneity"
Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated)	y	Section 3.1.3, heading "Statistical methods"
Provision of appropriate tables and graphics	y	Section 3.1.3
Reporting of results should include		
Graphic summarizing individual study estimates and overall estimate	y	Sections 3.2.2 and 3.2.3
Table giving descriptive information for each study included	y	Section 3.2.1
Results of sensitivity testing (eg, subgroup analysis)	y	Sections 3.2.2 and 3.2.3
Indication of statistical uncertainty of findings	y	Sections 3.2.2 and 3.2.3

Table A.10.3:MOOSE guideline – discussion and conclusion checklists

MOOSE guidelines	Reported?	Location/Comments
Reporting of discussion should include		
Quantitative assessment of bias (eg, publication bias)	y	Section 3.3.2
Justification for exclusion (eg, exclusion of non–English-language citations)	y	Section 3.3.2, especially "Comprehensiveness of the review"
Assessment of quality of included studies	y	Sections 3.2.2 , 3.2.3 and 3.3.3
Reporting of conclusions should include		
Consideration of alternative explanations for observed results	y	Section 3.3.3
Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	y	Section 3.3.3
Guidelines for future research	y	Section 6.4
Disclosure of funding source	y	In the Acknowledgements

Appendix B RETROSPECTIVE COHORT STUDY

B.1 Timeline of service developments in Matlab, Bangladesh

- 1963
    - First started conducing vaccine field trials.
    - House to house census
    - Field workers went to each house daily to identify cases of cholera.
    - Covered 23 villages with nearly 28,000 people.
- 1966
    - Demographic Surveillance System (DSS) started collecting vital event information - registered births, deaths and migrations.
    - Vital events were registered weekly by local *dais*. *Dais* are traditional birth attendants, typically illiterate, widows with freedom to move around the village. Every six weeks, a Health Assistant (HA) accompanied the dais to record the events on registration forms. Senior Health Assistants (SEAs) were the supervisors.
    - Covered 132 villages, 112,000 people
- 1968
    - An additional 101 villages added to surveillance, 231,000 people living in 233 villages.
- 1975
    - Started to register marriages and divorces.
    - October- Contraceptive Distribution Programme (CDP), intensive door-to-door distribution of oral contraception and condoms in 150 villages (125,000). Another 84 villages served as a comparison group.

- October 1977
    - Surveillance area was reduced from 233 to 149 villages.
    - Maternal and Child Health and Family Planning Programme (MCH-FP) was initiated in 70 villages (88,000 people). The remaining 79 were treated as a government service area, used as comparison group.
        - MCH-FP in 70 villages, half from CDP villages and half from the control villages of the original CDP - 40,000 people belonged to the CDP distribution areas and 40,000 belonged to the CDP control areas.
        - 79 villages (85,000) served as the control, half belonged to original CDP distribution area and half belonged to the original CDP control area.
        - Matlab family planning clinic set up
            - Physician, 2 female family planning visitor (LFPV), record keeper, 2 clinic attendants and a ward cleaner.
            - Service provided: non-clinical contraceptive methods, IUDs, sterilization, menstrual regulation, treat side effects/complications associated with contraceptives/abortions, selected maternity services such as removal of retained placentas.
            - Within Matlab Hospital – 120 beds
        - Four sub-centres, each with one resident LFPV and one male cleaner/messenger.
    - Community Health Workers (CHW) (young married women with secondary education) took over the collection of vital events registration and started collecting data on child and reproductive health. System known as Record Keeping System (RKS). Fortnightly visits were made until about mid 1997, after which monthly visits were made.

- 1979
    - Tetanus immunisation introduced in maternity-care programme area.
- 1987
    - Maternity care programme, outreach services by trained midwives to half of the MCH-FP area.
        - Maternity care clinic at Matlab – no blood transfusion or caesarean section.
        - 2 trained midwives posted at sub-centres in the intervention area (north part of MCH-FP).
            - Prenatal, home-delivery, postpartum care, identifying complications and treating them when possible, if not, referring to clinic in Matlab
            - 24 hour access to speedboat
- 1990
    - Maternity care programme extended to the whole of the MCH-FP area.
    - 2 midwives moved to the southern sub-centres. Each midwife was joined by a paramedic, who received 18 months midwifery training.
        - Equipped for severe obstetric complications
    - Screening tools for CHRWs to detect high-risk pregnancies then refer to midwife/paramedic.
- 1993
    - Household headship and household dissolution recording started.
    - 7 villages disappeared from the Government service area due to river erosion, leaving 142 villages in the HDSS.
    - Geographical Information System (GIS) started

- 1996
    - Previous strategy for providing home-based maternity care services in MCH-FP areas shifted to facility-based care.
    - Community-based midwives and paramedics were withdrawn from the field and assigned to health sub-centres to conduct normal deliveries.
- 1998
    - DSS, RKS and GIS together brought under single administration and collectively known as HDSS.
    - SHAs abolished, former HAs made supervisors with new name of Field Research Assistant (FRAs)
- 2001
    - Microwave link from Matlab to Dhaka allowing data/voice transmission between the two places.
    - Home-based strategy entirely replaced by facility-based strategy for skilled delivery.
- 2003
    - 3 of the 70 villages of ICDDR,B area were transferred to the Government service area.

B.2 Data cleaning and checking

Individual Datasets

Duplication checks

I had three datasets, all with women's unique identifying numbers. The three datasets were pregnancy, birth and the socio-economic status datasets. The pregnancy dataset contained all pregnancies from 1 January 1976 to 31 December 2005. The birth dataset contains all births between 1 January 1976 and 31 December 2003. Finally the socio-economic status dataset

contain the socio-economic status of the household of women who had pregnancies between 1 July 1982 and 31 December 2005. A summary of the number of pregnancies in each datasets and period of data available is shown in Table B.2.1.

To get the maximum amount of information, I merged the three datasets together. Prior to the merging, I removed duplicates from each dataset.

In the pregnancy dataset, each row of data corresponded to one pregnancy. There should be no more than one pregnancy entry for each pregnancy outcome date, even if it was a multiple gestation pregnancy. There were 19 duplicates on pregnancy outcome date to the same women, and thus these were considered to be duplicates and dropped from the dataset.

In both the birth and socio-economic datasets, each row of data should correspond to one birth. Therefore it would be possible to have multiple rows of data for the same pregnancy outcome date due to multiple gestations. Any duplicate birth entries should be dropped, before merging with the pregnancy dataset. There were 2117 entries either for multiple gestations or for duplicates of the same singleton pregnancy which were dropped from birth dataset, and 1729 entries dropped for the similar reasons for the socio-economic dataset.

Table B.2.1: Summary of key information in the original pregnancy, socio-economic and birth datasets and after dropping duplicates.

Dataset	Number of women	Original number of pregnancies	Pregnancies without duplicates	Start Date	End Date
Pregnancy	73,839	215,779	215,760	01 Jan 1976	31 Dec 2005
SES	63,341	165,497	163,768	01 Jul 1982	31 Dec 2005
Birth	69,462	205,257	203,140	01 Jan 1976	31 Dec 2003

Merged dataset

After merging the dataset and correcting for the identification numbers discussed below, there were 216,114 pregnancies to 74,071 women in the merged dataset between 1 January 1976 and 31 December 2005. There 505 pregnancies identified to be in the pregnancy dataset only,

320 pregnancies that were exclusively in the birth dataset and 28 pregnancies identified to be in the socio-economic dataset only.

I have assumed that the extra pregnancies found in the birth and socio-economic datasets do not end in pregnancy related deaths. This applied to 348 pregnancies.

All discrepancies between datasets described below were comparing pregnancies to overlapping periods (for overlapping period, see Table B.2.1)

Identification numbers

Once merged several consistency checks were made. Women who were not matched in the merging process were checked on their birthdays, pregnancy outcome dates, husband's and children's identification numbers (where possible), household, village and various other identification variables to ensure the women's identification numbers were correct, and they were truly extra women who were not already in the other datasets. I only looked at extra women identified between the birth and socio-economic datasets in their overlapping periods, due to the lack of identifying variables in the pregnancy dataset. The pregnancy dataset did not include the husband's or child's identification numbers, and there was no information on the household or village information or the woman's current location. Of the 40 extra women identified between the birth and socio-economic datasets, 16 were found to have different identification numbers between pregnancy and socio-economic datasets but appeared to be of the same woman. They were corrected accordingly and thus there were only 24 extra women identified.

Duplicates

As with the single datasets, the merge dataset was checked for duplicates. Multiple pregnancy entries for the same pregnancy outcome dates to the same woman were considered to be duplicates and dropped; 6 entries were dropped.

An additional pregnancy was dropped due two entries for an infant with the same identification number to the same woman. It was considered to be an entry error since the pregnancy outcome dates were 6 Jan 1982 and 6 Dec 1982 and other key identification variables were the same, with the exception of pregnancy order.

Maternal birth dates

The data were checked to ensure the maternal dates of birth were consistent (or at least very close) between all her pregnancies within each dataset. Only one entry error was found and this was corrected.

There were no differences in the maternal dates of birth between the pregnancy and birth datasets in the overlapping periods. There were 20 women who had different maternal dates of birth between the pregnancy and socio-economic datasets in their overlapping periods.

I took the maternal date of birth in the pregnancy dataset for the main analysis, and sensitivity analyses were done using other date of births given in the other datasets.

Plausibility of maternal ages

Pregnancies to women aged 55 years or older and younger than 10 years old were checked for entry errors since pregnancies to these ages were unlikely, although not impossible. There were 30 pregnancies to 28 women who were under 10 at the time of the pregnancy outcome, and 16 pregnancies to 10 women who were 55 years old or older at the time of the pregnancy outcome. All these pregnancies identified were "extra" women found in birth dataset. Based on the husband's identification number, husband's date of birth, village and household identification numbers, child's identification number, and checking women with similar identification numbers, I was able to redistribute 23 pregnancies to women who were "too old or young" to other women in the dataset. The remaining pregnancies and women were kept in the analysis.

Plausibility of outcome intervals

Inter-outcome intervals of only 14 days or less to the same woman were considered impossible. There were 25 pairs of such pregnancies to 25 women. Any two pregnancies that included the same information on the maternal birth date, sex of infant, pregnancy order, past obstetric history of the woman, maternal exit date(s) and cause where appropriate were considered to be double entries of the same pregnancy. Twenty-three such duplicate pregnancies were dropped. The remaining two pregnancies could be attributed to other women and they were corrected.

The inter-outcome interval to an index live birth was less than 140 days for 27 pregnancies. Twenty-three pregnancies were dropped due to duplications using methods described above. Two pregnancies could be attributed to other women, and the final two were kept in the dataset.

The interval to an abortion was less than 45 days for 4 pregnancies. One pregnancy was attributed to another woman, and one was found to be a duplicate and dropped. The remaining two were kept in the dataset.

Births after death date

There were 42 pregnancies to 34 women after the recorded death of the mother. I was able to attribute 9 pregnancies to other women based on the husband's identification number, husband's date of birth, village and household identification numbers, pregnancy outcome dates and obstetric history information. All such pregnancies had an outcome prior to 1983.

Different information between datasets

Whenever the there was a difference in the information provided by the different datasets, the information from the pregnancy dataset was used for the main analysis (there were some exceptions for the pregnancy order – see discussion below). Sensitivity analyses were carried out for information from the other datasets.

Differences in maternal dates of birth have been discussed previously.

Of all the pregnancies in the dataset, there were 545 pregnancies to 218 women where the gravidity orders do not agree for all three datasets (or two datasets depending on the calendar period). If the pregnancies were unique to a particular dataset the information from that dataset was used. For the rest of the pregnancies, information from the pregnancy dataset was used for the main analysis except when the pregnancy orders were not consecutive for the pregnancy dataset, but was consecutive for another dataset. In this case, the pregnancy order information from an alternative dataset was used. The order of preference was pregnancy, birth, followed by socio-economic dataset.

Correcting pregnancy order

Pregnancy orders within each woman should be observed in ascending orders, and each unique pregnancy order should only be observed once in each woman. The pregnancy orders may not be observed consecutively due to immigration/emigration or pregnancies prior to the study period, but the difference two sequentially observed pregnancy orders should always be greater than zero.

There were 4,220 pregnancies to 3,967 women where the difference between the index and previous pregnancy order was less than zero. Over 98% of 4,220 pregnancies were to pregnancies prior to 1983, and 1% were to pregnancies in 2005. These 3,967 women had a total of 18,541 pregnancies in the period 1 January 1976 and 31 December 2005.

It was known that higher quality data exist for the Matlab from 1 July 1982 onwards. In addition, I have found more inconsistencies in the data such as births after death date, and inconsistent pregnancy orders prior to 1983. Therefore, I decided to limit my analyses to data from 1 January 1983 and 31 December 2005. All subsequent changes and numbers quoted are related to this later period of 1 January 1983 and 31 December 2005

Multiple gestations

Multiple gestations were often counted as multiple gravid events in the dataset. They were corrected if

1) The index pregnancy is a multiple gestation (twin or triplet), and the differences between the index and previous pregnancy order is two for twins or three for triples. Then the index and subsequent pregnancy orders were corrected by subtracting one for twins and two for triplets.
2) If the index pregnancy is a multiple gestation (twin or triplet), and it is the first observed pregnancy to the woman (including if it is the only observed pregnancy). Then the index and subsequent pregnancy orders were corrected by subtracting one for twins and two for triplets.

Pregnancy order changes were made to 3816 pregnancies in total, including all subsequent pregnancies to the original multiple gestation pregnancy.

Inconsistent pregnancy orders

The sequential nature of the pregnancy orders was exploited to correct the inconsistent pregnancy orders. The following rules were carried out sequentially, so that if inconsistencies were corrected in the first rule, then the second rule no longer applies, and so forth.

1) If pregnancy order between the index and previous pregnancies was zero or less, and the differences between the pregnancy order of the previous and next pregnancies was exactly two. Then it follows that the index pregnancy order should be the previous pregnancy order plus one to preserve the previous and next pregnancy orders.
2) If there were three or more pregnancies observed for a woman, and all pregnancy order were consecutive except for the first or last pregnancy then pregnancy order of the last/first pregnancy was changed to follow the order of the rest of the pregnancies if the woman did not immigrate or emigrate from Matlab during the two pregnancy outcomes. There were a couple of cases to consider when changing the first observed pregnancy order:
    a. There was no need to enforce the migration rule if the first observed pregnancy should be pregnancy order one by following the sequence of the rest of the pregnancies.
    b. If the sequence for the later pregnancies suggested that the first pregnancy should be order zero (which is an impossible pregnancy order). Then effort was made to see if there were entry errors, and whether one of the first pregnancies should be attributed to another woman. If there were no obvious errors, then I assumed the first pregnancy should be of order one, and the rest of the pregnancies followed the sequence.
3) If there were only two pregnancies observed for a woman, and there were inconsistency problems, and the first pregnancy observed was pregnancy order one, then the second pregnancy was assumed to be pregnancy order two.
4) If there were only two pregnancies observed for a woman, and there were inconsistency problems, and first pregnancy observed was not pregnancy order one, then I have assumed the first pregnancy order observed was correct, and the second pregnancy order should follow sequentially. Sensitivity analyses were carried out assuming the second pregnancy order was correct, and the first pregnancy order should be second pregnancy order minus one.

Changes were made to 25 pregnancies to 20 women using the above rules. In total there changes made to 3837 pregnancies (2.4%) from the original pregnancy order information in the data.

Pregnancy loss

For the birth dataset, there were nearly 70% missing data for the pregnancy loss variable for pregnancies before 1 January 2004. However, most of the missing data were assumed to represent no pregnancy losses for the woman up to the index pregnancy outcome date. For the socio-economic dataset, there were similar proportions missing for the pregnancy loss variable for all pregnancy between 1 January 1983 and 31 December 2005.

A combined pregnancy loss variable was created using information from the birth dataset for pregnancies prior to 1 January 2004, information from the socio-economic dataset was used for pregnancy after this date,

If the index pregnancy outcome was a pregnancy loss, and the entry of the pregnancy loss variable was missing, then the pregnancy loss variable was corrected to be one. The actual number of pregnancy losses up to that pregnancy outcome may be greater than one and attempts to correct this problem was done in the next few steps outlined below. There 70 changes made to missing pregnancy loss information.

The pregnancy loss numbers were assumed to be the same as previous numbers if the index pregnancy outcome had missing pregnancy losses numbers and the previous pregnancy outcome had non- missing pregnancy losses variable information. Changes were made to 316 pregnancies. All other missing pregnancy losses information were assumed to be mean zero number of pregnancy losses up to the index pregnancy outcome date. This affected 110,360 pregnancies (69.3%) in the dataset.

Similar to pregnancy orders, pregnancy loss numbers up to the index pregnancy outcome date within each woman should be observed in ascending orders. However, the same number of pregnancy losses can be observed more than once. The pregnancy loss numbers may not be observed consecutively due to immigration/emigration, but the difference between the pregnancy losses up to the index and previous pregnancy outcomes should never be negative. In addition if the index pregnancy ended in a pregnancy loss, then the pregnancy loss number should increase by at least one compared to pregnancy loss number recorded for the previous pregnancy for the same woman. Finally, the recorded number of pregnancy losses for each

pregnancy outcome date should be at least as many as the observed number of pregnancy losses up to that pregnancy outcome date. Using these known facts I was able to correct the pregnancy loss variable in the dataset.

The difference between number of pregnancy losses of the index and previous pregnancy outcomes was less than zero for 19 pregnancies. In addition, for 33 index pregnancies that ended in a pregnancy loss, the difference between the number of pregnancy losses between the index and previous pregnancy outcomes was zero. Finally, the observed number of pregnancy losses up to the index pregnancy outcome was greater than the recorded number of pregnancy losses for 62 pregnancies to 38 women.

Rules used to correct these inconsistencies were as follows. If there were negative differences in the number of pregnancy losses, I assumed the index number of pregnancy losses should be the same as the previous pregnancy numbers if the index pregnancy was a live birth. If the index pregnancy outcome was a pregnancy loss, then the index number of pregnancy loss should be one plus the previous number of pregnancy losses. Changes were made to 25 pregnancies, including any changes to subsequent pregnancies within the same woman.

When the index pregnancy outcome was a pregnancy loss, but the difference between the index and previous number of pregnancy losses was zero, then one was added to the index number of pregnancy losses, and any subsequent pregnancies to the same woman updated. This affected 56 pregnancies to 33 women.

Once the first two inconsistencies were corrected, the observed number of pregnancy losses up to the index pregnancy outcome was less than all recorded number of pregnancy losses.

A variable indicating whether a woman has experienced any previous pregnancy losses prior to the index pregnancy was then made using information from the variable containing information regarding the number of pregnancy losses to date.