Association of postnatal severe acute malnutrition with pancreatic exocrine & endocrine function in children and adults: A systematic review

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Abstract

Severe acute malnutrition may lead both concurrently and subsequently to malabsorption and impaired glucose metabolism from pancreatic dysfunction. We conducted a systematic review to investigate the associations of current and prior postnatal wasting malnutrition with pancreatic endocrine and exocrine functions in humans. We searched PubMed, Google Scholar, Web of Science, and reference lists of retrieved articles, limited to articles in English published before February 1, 2022. We included 68 articles, mostly cross-sectional or cohort studies from 29 countries including 592,530 participants, of which 325,998 were from a single study. Many were small clinical studies from decades ago and rated poor quality. Exocrine pancreas function, indicated by duodenal fluid or serum enzymes, or fecal elastase, was generally impaired in malnutrition. Insulin production was usually low in malnourished children and adults. Glucose disappearance during oral and intravenous glucose tolerance tests was variable. Upon treatment of malnutrition, most abnormalities improved but frequently not to control levels. Famine survivors studied decades later showed ongoing impaired glucose tolerance with some evidence of sex differences. The similar findings from anorexia nervosa, famine survivors, and poverty- or infection-associated malnutrition in low- and middle-income countries (LMICs) lend credence to results being due to malnutrition itself. Research using large, well-documented cohorts and considering sexes separately, is needed to improve prevention and treatment of exocrine and endocrine pancreas abnormalities in LMICs with a high burden of malnutrition and diabetes.

Introduction

Wasting malnutrition remains common both for children in low- and middle-income countries (LMICs) and for adults with severe infections, notably HIV or tuberculosis. As treatments for severe acute malnutrition improve [1] and drugs become increasingly available and effective for severe infections, more people survive but the long term consequences of their malnutrition are not fully understood.[2; 3] Acute nutritional deficits during the prenatal period affect the structure and function of organs such as the pancreas which have fundamental roles in metabolism.[2; 4] While there is information from animal models and from human studies of prenatal malnutrition, usually indicated by a proxy of low birth weight,[5] the consequences of postnatal undernutrition on human pancreatic structure and function and later chronic disease development are not well documented.

Both pancreatic endocrine (i.e. production of hormones such as insulin or glucagon) and exocrine (i.e. production of enzymes to aid digestion and subsequent nutrient absorption) functions are critical for nutritional metabolism and chronic diseases including diabetes. A previous systematic review of effects of severe acute malnutrition on pancreatic exocrine function in children concluded that there was evidence of association but could not determine causality.[6] Diabetes mellitus (DM) is one of the most common non-communicable diseases worldwide and is rapidly increasing, particularly in LMICs. [7] While it is established that overweight and obesity in adult life increase the risk of type-2 DM,[8] the contribution of prior malnutrition to the aetiology of DM and its potential interaction with later overweight across the global context remain unclear.

In 1965, a WHO Expert Committee reported that “the evidence that undernutrition protects adult populations from diabetes seems unassailable”. [9] In 1980, they reported that “in some societies, malnutrition is probably a major determinant of diabetes”. [10] In 1985, malnutrition-related diabetes mellitus was included as a classification category of DM divided into 2 subtypes, protein deficiency pancreatic diabetes and fibrocalculous pancreatic diabetes, both commonly reported in tropical countries and usually associated with a history of undernutrition.[11] This classification has since been dropped and the literature is inconsistent in the terms and diagnostic criteria used for these atypical forms of diabetes. As well as the above classifications, other commonly used terms have included “tropical diabetes”, “malnutrition-associated diabetes”, and “African diabetes”. A recent systematic review concluded that, based on currently limited data, two main phenotypes of atypical diabetes emerge, differing in usual age of onset and in requirement for lifelong insulin but both occurring in younger ages than is typical for type-2 DM and in underweight individuals or normal weight/modestly overweight individuals; both phenotypes

have some features similar to type-1 DM.[12] Previous reviews have assessed famine, or malnutrition in a particular age group, and either exocrine function or diabetes as an outcome of endocrine dysfunction but not detailed markers of glucose metabolism.[6; 13] The present study includes detailed glucose metabolism markers and diabetes as well as exocrine pancreas functions in relation to the less studied, postnatal period of exposure to acute malnutrition, not limited to the postnatal period but including childhood and adulthood and from infection-associated malnutrition. Excluding this, most common, type of malnutrition exposure could lead to underestimating the impact on populations which might underlie the large increase in diabetes in populations still experiencing a high burden of infectious diseases. Finally, the decision to include anorexia nervosa as another exposure was to allow the comparison with malnutrition in which diet restriction, rather than infection, has the main causal role.

This systematic review aims to describe the available evidence to determine if severe acute postnatal malnutrition causes persisting changes in pancreatic endocrine and exocrine function and later increased risk of DM.

Methods

Search strategy

An electronic literature search was performed on PubMed, Web of Science, and Google Scholar to identify studies published in English from the earliest available date to 1st February 2022. Detailed search terms are shown in **Supplementary Data 1**. Studies were eligible for inclusion if they reported human pancreatic function in relation to exposure to postnatal malnutrition identified through clinical or anthropometric methods in hospitals, clinics or communities, famine, or eating disorders. Studies were excluded if written in languages other than English, if the full text was unavailable, if study participants had no prior or current malnutrition exposure or only prenatal malnutrition exposure, or if stunting (chronic malnutrition) without wasting (acute malnutrition) was the exposure. We included cross-sectional studies to investigate acute associations between malnutrition and pancreas function and trials, cohort studies or retrospective case-control studies to investigate longer term outcomes. Case-series and case-reports, and studies with ≤10 participants were excluded from the review owing to the high potential for bias. Studies describing abnormal pancreatic function, e.g. due to cystic fibrosis, leading to malnutrition were also excluded. Cancer studies were excluded since, although many cancers may result in malnutrition, the added metabolic complications of cancers and their treatment would make it difficult to determine the effects of malnutrition itself. However, we did include studies of malnutrition secondary to serious infections such as

HIV or tuberculosis with the rationale that infections are virtually always part of severe malnutrition, including classical malnutrition in young children.

Duplicates were identified and removed, and the titles and abstracts reviewed to determine possible eligibility by a single reviewer (FF). Additional studies were identified by manually searching the reference lists of included papers and previous reviews or meta-analyses. The full texts of the relevant articles were obtained and independently reviewed for final selection according to the eligibility criteria by at least two of the authors. Any differences in judgment were discussed with all authors to reach consensus.

Quality assessment

A quality assessment checklist was developed based upon the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)[14] and Consolidating Reporting of Clinical Trials (CONSORT) checklists.[15] The quality assessment checklist comprised 16 items for cross-sectional studies, 19 items for cohort studies, 20 items for case-control studies and 22 items for clinical trials where scores for each question item ranged from 0 to 2. Scores were assigned as follows: '0' for no information/unlikely or not reported/poor or inappropriate description; '1' for partially or possibly reported/satisfactory and '2' meaningfully reported/good. Using these checklists, three authors (FF, SC, NBS) independently evaluated the included articles. Scores and decisions were then discussed before assigning an overall quality rating of each study with each article's quality rated as 'high' if score ≥80%; 'medium' if score 60-79%; 'low' if score < 45-59% or very low if score<45%.

Data extraction

Details of the included studies were extracted into an Excel file under the following headings: first author, year of publication, study design, country, quality category, age when participants were malnourished, number of participants, participant inclusion/exclusion criteria, diagnostic criteria or definition of malnutrition used, pancreatic outcomes assessed, a description of any interventions or treatment/nutritional rehabilitation received, the type, timing and frequency of pancreatic function outcome assessments conducted, and the main or most salient results; plus a column for further comments.

Results

Articles included and excluded

After the removal of duplicates, 8,108 articles were identified. After screening of abstracts, full texts of 259 papers were obtained (**Figure 1**). An additional 30 articles meeting the study inclusion criteria were obtained from a manual screening of article reference lists. Of the 289 articles, 221 articles were excluded due to not meeting the inclusion criteria, leaving 68 articles. The list of excluded studies with reasons is provided in **Supplementary Data 2.**

The included articles represent results from 29 countries and a total of 592,530 participants. Results are presented divided into 3 tables based on the nature of the malnutrition exposure and then split into exocrine and endocrine outcomes. **Table 1** includes studies reporting the association between malnutrition in young children and exocrine (n=13),[16-28] or endocrine (n=19),[29-47] pancreatic function either concurrently or after follow-up, most of which was short-term. **Table 2** includes studies reporting the association between malnutrition in older children or adults, mainly anorexia nervosa patients, and exocrine (n=3)[48-50] or endocrine (n=15)[51-65] pancreatic function. **Table 3** includes studies reporting the association between famine exposure in infancy to young adulthood and glucose metabolism or endocrine (n=18)[66-83] pancreatic function; there were no papers describing exocrine pancreas function after childhood famine exposure.

Study design and participants characteristics

There were 32 cross-sectional studies,[18; 22; 24; 27; 29; 32; 34-36; 39; 42; 43; 48; 51; 53; 54; 57; 58; 60; 66-68; 71; 72; 75-79; 81-83], 27 cohort studies,[17; 19-21; 28; 30; 31; 33; 37; 41; 46; 47; 49; 50; 52; 55; 56; 59; 61; 63-65; 69; 70; 73; 74; 80], of which 19 were clinical cohorts, mostly comprising short-term follow-up of inpatient malnourished children or adults; 3 case-control studies, [44; 45; 62] and 6 intervention trials,[16; 23; 25; 26; 38; 40], not all randomized. Of the total 592,530 participants, most were from the famine studies including one nationwide study with 325,998 participants, mostly non-famine-exposed controls.[73] Most other studies had fewer than 100 participants and addressed malnutrition in young children.

Study quality assessment

Individual studies' quality scores are shown in **Supplementary Data 3**. Twelve studies had an overall quality rating considered to be high,[16; 59; 67-69; 72-76; 78] 15 studies were rated as medium, [39; 44; 45; 55; 58; 62; 65; 66; 70; 71; 77; 79; 80; 82; 83] 17 studies were rated as low, [17; 18; 23-25; 27; 29; 30; 35; 40; 43; 46; 52; 53; 57; 60; 81] and the remaining 24 as very low. [19-22; 26; 28; 31-34; 36-38; 41; 42; 47-51; 54; 56; 61; 63; 64] The main problems resulting in a poor score were not clearly stated study design, undefined sampling strategy, unclear study inclusion and exclusion criteria, low sample size, unclear or absent statistical methods or investigation of confounders, or lack of appropriate

control/healthy comparison groups. These problems were mainly found in older studies done at a time of different expectations for study design and presentation but many of these studies appear otherwise carefully conducted and contain valuable information for this review. It should be noted that similar data found in some of these studies is unlikely to be collected in future since the studies used invasive techniques in children which would not be approved by most modern ethics committees.

Definition of the malnutrition exposure

The definition of childhood severe malnutrition has varied over the publication dates of included studies from clinical definitions of kwashiorkor and marasmus, comparison with various different child growth standards, and more recently the current WHO definition of severe acute malnutrition (SAM) based on the 2005 growth standards or edema.[84] While there may be minor differences between definitions, we believe these likely reflect broadly the same clinical conditions across time and have therefore considered the definitions of childhood clinical malnutrition together. The more important difference for effects on the pancreas appears to be whether or not the SAM involved edema, i.e. kwashiorkor. Adult malnutrition in the included papers has generally been by low body mass index (BMI) and/or a clinical diagnosis of anorexia nervosa. For the studies of long-term consequences of childhood famine exposure there were no assessments of malnutrition at the time so exposure was defined by date and place of residence at the time.

Definitions of exocrine and endocrine pancreas outcomes

Tests used in the included studies of exocrine pancreas function fit into two main groups. Some earlier work measured enzymes in duodenal juice collected with a catheter, both basally and after stimulation with secretin or cholecystokinin, whereas recent studies were less invasive and collected only feces or serum; this makes it hard to compare results. Studies using catheters and collecting duodenal fluid before and after simulation measured various enzymes, including amylase, lipase, phospholipase, trypsin, and chymotrypsin, as well as bicarbonate and electrolytes.[19; 22-26; 28; 48; 49] Recent studies assessed fecal elastase, which is low in pancreatic insufficiency, [16; 17; 27; 50] or blood levels of enzymes such as trypsinogen, amylase or lipase which may be either high or low in pancreatic disorders. [18; 20; 21] One study measured pancreas head size in children using ultrasound [21] and another measured d-xylose and triglyceride absorption.[50]

As for exocrine pancreas tests, the older and more recent literature generally use different tests for endocrine function, although this is partly driven by the fact that much of the more recent literature is from post-famine studies which, with their very large sample sizes, use mostly simple tests or diagnoses from

clinical databases. In some studies, the main outcome was fasting blood or plasma glucose.[29; 38; 44-46; 72; 76; 77; 79; 80; 82; 83] One study had only random plasma glucose.[67] Hemoglobin A1c (HbA1c) was measured mainly but not exclusively in the large famine studies.[29; 65; 72; 75-78] Some of these large studies used previously clinically diagnosed diabetes from national or other large databases.[59; 69; 70; 73; 74; 80-83] Oral glucose tolerance tests (OGTT) [30; 31; 33; 35; 39; 40; 43-45; 58; 64-66; 68; 71; 80; 83] were frequently conducted as were intravenous glucose tolerance tests (IVGTT).[30-34; 36; 37; 41; 42; 47; 51; 60; 63] These generally followed similar standard protocols. Some researchers measured insulin as well as glucose in these tests. Researchers rarely used these tolerance tests to diagnose diabetes but were interested in various glucose metabolism indicators calculated from the glucose and insulin levels during the tests, including areas under the curves (AUC), insulin : glucose ratios, and glucose disappearance rate. Homeostatic model assessment (HOMA) indices were rarely calculated. [46; 75] Several studies investigated glucose metabolism after injection or perfusion with glucagon, [43; 47; 56] insulin [46; 55] or arginine. [51; 54; 55] There were single studies using each of the following methods: a standard meal as the glucose challenge; [57] a euglycemic hyperinsulinemic clamp method; [61] and only 24-hour C-peptide excretion. [53]

Exocrine pancreas function during and after malnutrition in children and adults

Most papers addressing exocrine pancreas function were from hospital-based studies of acute malnutrition in young children, at admission, during treatment, or at hospital discharge; two papers[24; 28] also included some children longer after discharge (**Table 1**). Among the 7 studies which measured duodenal enzymes, most both before and after pancreas stimulation,[19; 22-26; 28] all but one[22] found decreases in several enzymes (amylase, lipase, trypsin, chymotrypsin). Short term nutritional therapy in hospital usually increased enzyme levels but not always to levels of well-nourished controls. Discrepancies among studies may be due to small sample sizes, differences in patient populations, and the duration and type of nutritional or other therapy.

Three studies,[16; 17; 27] two from the same research group, used fecal elastase as the exocrine pancreas marker. The study in Indonesia,[27] which was concerned mainly with diarrhea and did not clearly define malnutrition, found no differences in elastase between malnourished children at hospital admission and well-nourished children. The studies in Malawi[16; 17] included no well-nourished children but investigated changes over time during therapy among malnourished children; children with edematous malnutrition had lower fecal elastase than those with non-edematous and generally did not recover within a month of nutritional therapy. In all these studies there is a concern that diarrhea, which is common among children

hospitalized with malnutrition, could interfere with the use of fecal elastase as a marker of pancreas function.

Four studies, all with fairly large sample sizes, measured pancreatic enzymes in blood or serum.[17; 18; 20; 21]. Circulating trypsinogen was higher in children with edematous compared to non-edematous malnutrition,[17] and in malnourished children than in healthy controls.[20] In one study, serum trypsinogen was not associated with malnutrition but was increased in children with gastroenteritis[18]. Serum amylase and lipase, as well as pancreas head size, were low in malnourished children at hospital admission compared with healthy controls and increased during treatment.[21]

There is limited information about exocrine pancreas function during or after malnutrition occurring in adulthood (**Table 2**). There was no difference in fecal elastase among 10 anorexia nervosa patients before and after nutritional recovery; this study also found normal D-xylose and triglyceride absorption.[50] Two papers from the same group in India studied possibly overlapping small numbers of malnourished adults and controls.[48; 49] Before nutritional therapy, malnourished adults had steatorrhea and low duodenal juice contents of trypsin and lipase basally and post-stimulation with cholecystokinin (pancreozymin) and secretin; amylase content was low only post-stimulation. After nutritional therapy, lipase and amylase differed little from values in healthy controls both before and after stimulation while trypsin remained low.

Endocrine pancreas function

1. Studies in young children

This group comprises the bulk of the included papers but only one was scored as medium quality[39] and the rest were rated as low or very low quality. Fasting blood or plasma glucose (not always distinguished in the papers and referred to here as FBG), was generally unaffected by acute malnutrition[33-35; 37; 38; 47] but decreased FBG was also reported.[29; 36; 46] HbA1c was higher in children with kwashiorkor or marasmus compared with controls and FBG and HbA1c were inversely associated.[29] Altered fluid balance, especially among children with edematous malnutrition, and the more acute time frame represented by FBG than by HbA1c may have contributed to an apparently anomalous negative correlation between FBG and HbA1c.

Slow glucose disappearance rates during OGTT or IVGTT were commonly seen at hospital admission in malnourished children, especially those with kwashiorkor[32-34; 37; 41] but not always in those with marasmus.[33] One study[32] suggested that lack of insulin was not the reason for slow glucose disappearance since insulin infusion in 4 children with kwashiorkor did not increase the glucose

disappearance rate. Another study[33] found glucose disappearance rate in kwashiorkor patients was negatively correlated with blood fatty acids which suggests a role for insulin resistance. However, a small study which used stable isotopes to investigate glucose metabolism found no evidence for hepatic or peripheral insulin resistance but did note that glucose clearance was positively correlated with plasma albumin.[39] Nutritional therapy generally normalised glucose disappearance rate [33; 37; 41] although one study found this was still slow in children 6-12 years post-hospitalisation for kwashiorkor.[42]

Fasting plasma insulin in different studies of kwashiorkor or marasmus was variable, likely reflecting variable populations and small sample sizes.[33; 35; 38] Insulin release during an OGTT or IVGTT, measured either as plasma levels or in relation to glucose, was generally low for children admitted to hospital mainly with kwashiorkor but sometimes also with non-edematous malnutrition,[30; 31; 34; 39-41] although one study found high peak insulin during an OGTT in malnourished children.[35] Insulin levels increased in the short term with nutritional therapy but were not always restored to normal even months after admission,[30; 33; 34; 37; 38] although the overall patterns of response normalized.[31] Interestingly, in a series of studies by the same research group with overlapping patient populations,[30; 31; 40] insulin/glucose AUC was more reduced and patterns of response more abnormal compared with controls during an OGTT than in an IVGTT, and a pattern of delayed insulin secretion in malnutrition was common; both these could indicate that part of the impaired insulin response was due to factors in the intestine. One study measured plasma glucagon and found low fasting levels in children admitted to hospital for malnutrition.[38]

Five studies investigated endocrine pancreas function using OGTT or IVGTT in participants several years after they were hospitalised for malnutrition in early childhood.[30; 42-45] Ten years post-kwashiorkor there was no difference compared with sibling controls in peak insulin or insulin/glucose AUC in an IVGTT.[30] There were two small studies from the same malnutrition unit in Uganda of children about ten years after they recovered from kwashiorkor. One found a slower glucose disposal rate during an IVGTT in recovered malnourished children compared to controls.[42] The other study found lower fasting insulin in recovered kwashiorkor patients but normal insulin response in an OGTT and with a glucagon stimulus to elicit maximal insulin release.[43] More recent studies with larger sample sizes found larger differences in glucose metabolism of malnutrition survivors compared with controls. Jamaican adults who had experienced marasmus in early childhood had lower insulin secretion and poorer glucose tolerance in an OGTT compared with kwashiorkor survivors or not previously malnourished controls.[44] Among young adult Mexican male survivors of childhood malnutrition, plasma glucose concentration and area under the curve in an OGTT were higher than in not previously malnourished controls only after controlling for BMI, age and

birth weight whereas plasma insulin was higher both with and without controlling for these variables and the difference between cases and controls was greater in those with higher BMI.[45] A recent study in 1,080 Chilean adults found higher glycemia at age 22-28 years in those who were wasted or at risk of wasting at 12 months (WLZ score <-2 or <-1), including after adjustment for confounders including birth weight and gestational age. Those who were underweight (WAZ-score <-2) at 12 months had evidence of increased glycaemia in unadjusted but not adjusted analysis but increased insulin sensitivity when assessed using single point insulin sensitivity estimate but not HOMA-IR.[46]

2. Endocrine pancreas function after malnutrition in later life

Of 15 papers on endocrine pancreas function after malnutrition experienced in later childhood or adulthood, 12 are about anorexia nervosa (AN) patients, only one of which included males,[59] two are about Indian adults, and one is about African adults (**Table 2**). The quality scores for the majority in this group were classified as low or very low, with the exception of a study in Sweden[59] which utilized a national register with long-term follow-up and was rated as high quality, plus 4 studies rated as medium quality: one from the USA,[58] a case control study in malnourished Indian adults,[62] a cohort study in African malnourished adults,[65] and a study in Japanese women with AN before and 5 months after treatment.[55] When patients were admitted to hospital with AN, there was a fairly consistent finding of abnormal, that is, low or delayed, insulin production during OGTT, IVGTT, arginine or glucagon infusion, or after a meal.[51; 52; 54-56; 61; 64] Glucose metabolism during these tests was more variable: there was often poor glucose tolerance, as might be expected from the low insulin production,[51; 52; 64] but others found normal responses.[55] Plasma glucagon was generally not different between AN patients and controls[51; 54] although one study found abnormal patterns of glucagon changes during an OGTT, [52] and another found low glucagon after insulin-induced hypoglycemia but not after arginine infusion.[55] One study found that 24-hour urinary excretion of C-peptide did not differ between AN patients and controls.[53]

Several studies examined AN patients after weight recovery either just before discharge from care or several years later. Not all studies included controls so it is difficult to determine whether normal pancreas endocrine function was achieved following weight regain. Insulin production and glucose tolerance often improved compared to admission results by the time, usually after several months, AN patients had gained sufficient weight to be discharged,[61; 64] but did not always reach normal levels.[52; 56] A study of AN patients who had recovered weight, but which provided no information on time since diagnosis, found continued impairments in insulin production but heightened insulin sensitivity resulting in similar glucose responses following a test meal.[57] Insulin production remained low and glucose tolerance impaired 8-10 years after

AN diagnosis in those who remained low weight but not in those who had achieved normal weight.[58] The incidence of diabetes diagnoses on a Swedish national register was lower among former AN patients than among the general population but not different from sibling controls; the low incidence among those with prior AN may have been related to their very low incidence of overweight as adults but the study was not designed to control for this.[59]

In a study of malnourished Indian adults, in which malnutrition duration and severity was not well-defined and there were no well-nourished controls, insulin increase was slow but prolonged in an IVGTT, glucose disposal rate was low, and both glucose and insulin responses to arginine infusion were blunted; all responses improved after 2-4 months of nutritional therapy.[63] A case-control study of tropical pancreatitis in Indian adults found that 13.5% of the patients had diabetes, based on fasting and postprandial blood glucose levels, and that weight loss appeared a consequence, not a cause, of the impaired pancreas function.[62] A cohort study in African adults reported that malnutrition associated mainly with HIV or tuberculosis infection 7-12 years previously was later associated with lower insulin levels in an OGTT in men but not in women.[65]

3. Studies in adults exposed to famine in childhood

The famine follow-up studies (Table 3) represent the largest amount of information on long term outcomes of childhood malnutrition, with by far the largest sample sizes, with generally robust statistics, and when participants were in middle age when diabetes is more common than at younger ages. The famine studies were the majority of studies rated good or medium in the quality assessments. The drawback of the famine studies is that the diagnosis of prior malnutrition is based on date and place of birth so cannot generally account for local differences in famine exposure or individual or family response to famine, although one study asked participants what they recalled of their famine experience.[74; 81] Another concern is that, particularly in the Chinese famine of 1959-61 which was prolonged and had high mortality, there is likely to be a survivor bias, and this may have had a sex difference, that is, boys may have had higher mortality than girls.[72; 78; 80-83]

Eleven of the 18 included studies were from China, were done by different research teams and together included data from 6 representative cohorts (one with two publications from the same group with different purposes,[75; 76] and another one with two publications by different research groups[72; 77]). Methods were similar in that famine exposure was determined by birth location and date with respect to the 1959-61 famine. Most studies also examined fetal famine exposure which is not the concern here. There were

differences among studies regarding the sex and postnatal age for which famine exposure carried greatest risk of hyperglycemia (assessed by fasting blood glucose and/or HbA1c) or diabetes: all ages from early to late childhood,[75; 76; 80; 82; 83] all ages but only in women,[72; 78] early childhood in women only,[79] infancy only,[77] or late childhood only.[68; 81] Although both men and women were at increased risk of high fasting plasma glucose or HbA1c, if exposed prenatally, β-cell function, indicated by homeostatic model assessment (HOMA)-β, seemed to be the major problem in men whereas it was insulin resistance (IR), indicated by HOMA-IR, in women.[75] Women exposed to famine at any stage of childhood had increased prevalence of hyperglycemia but not of diabetes whereas men in the study had no difference in hyperglycemia but lower prevalence of diabetes.[72] In another study that examined sex differences, this was only observed for risk of composite metabolic syndrome, with similar risks among men and women for hyperglycemia.[82] There appears to be an interaction between famine exposure and diet or BMI at the time of glucose assessment: being overweight or currently eating a Western style rather than traditional Chinese diet increased the risk of hyperglycemia or diabetes after childhood famine exposure.[68; 77; 83] One cohort study investigated incidence of clinically diagnosed diabetes over about 7 years in middle age.[69] The incidence was increased among those exposed to famine in utero but not those exposed in childhood and was aggravated by adult abdominal obesity; however, about three times as many cases of prevalent diabetes were excluded from the study as were found to have incident diabetes so it is difficult to determine the overall effect of famine exposure.

The Dutch famine of 1944-45 has been greatly studied for long-term effects of in utero exposure but less so for postnatal exposure. Famine exposure during adolescence, and to a borderline extent earlier in childhood, increased risk of a later diabetes diagnosis in women but not in men.[70] A study which included only women[74] found increased risk of later diabetes by self-report or clinical diagnosis if exposed to famine at any time during childhood and the risk was increased if women reported their famine exposure as severe versus moderate.

Famines in Bangladesh, Hong Kong (on Chinese population), Nigeria, Russia and Austria are represented by one paper each. Early childhood famine exposure in Bangladesh did not affect fasting glucose or glucose response in an OGTT.[66] In Nigeria, childhood famine exposure had no effect on random blood glucose; unfortunately the study's recruitment method precluded use of other tests of glucose metabolism.[67] In Hong Kong, self-reported childhood famine exposure was not associated with DM risk.[81] Childhood famine in Russia was not associated with glucose, insulin, proinsulin or C-peptide in adulthood.[71] Analysis of a large Austrian national database which included people of a wide age range covering fetal or childhood

exposure to several 20th century famines found clear evidence of increased risk of fetal famine exposure but not of childhood exposure.[73] It is unclear why these studies from other countries differ from the general findings of ongoing impaired endocrine pancreas function seen in the Chinese and Dutch famine studies but differences in famine experience and mortality and in later environment and diet could be important.

Discussion

There is considerably more research on how postnatal malnutrition affects endocrine than exocrine pancreas function. This likely reflects the high prevalence of diabetes globally and its serious health consequences but is in part because there are fewer non-invasive tests of exocrine than endocrine pancreas function available. Some earlier work on exocrine pancreas function used catheters to collect duodenal juice but such tests are unlikely now to be considered ethically justified for research and the earlier work was of generally poor quality due to low participant numbers, inadequate statistics and consideration of confounding and high risk of selection bias.

Overall, while there are differences among studies of exocrine pancreas function, it seems that secretion of many pancreatic enzymes is reduced in acute childhood malnutrition. The several papers reporting steatorrhea suggest that this reduced enzyme secretion may have important functional consequences which, through impaired nutrient absorption, could have contributed to the malnutrition in the first place and would very likely exacerbate it. In most cases, nutritional therapy improved enzyme secretion although not always to control levels, possibly because of varying durations and quality of the therapy. One trial which investigated adding enzyme therapy to nutrition[16] found no additional benefits; this was a recent study using current WHO nutritional therapy guidelines which likely provide better nutritional support than was available in earlier studies. Our results are consistent with a previous review[6] which found an association between malnutrition and decreased exocrine pancreas function but could not determine causality.

Regarding endocrine pancreas function, there seem to be prolonged impairments in insulin production among people severely malnourished in childhood or adulthood but these are most profound in people who remain malnourished.[46; 47] Adults in LMICs recruited when malnourished may have been so through much of their lives[48; 49] and long-term impairments in AN patients are greatest in those who remain malnourished.[55; 57] It would be interesting to investigate insulin in people in LMICs of previously good adult nutritional status who first became malnourished in adulthood. However, adult-onset malnutrition often

follows serious infections, for example, with HIV or tuberculosis, or cancers so these factors confound the situation. AN remains the most common cause of severe malnutrition resulting mainly from low dietary intake. Since there appear similarities between observations in AN patients, people exposed to famine in childhood[74; 78], and adults in LMICs, this suggests that it is malnutrition itself, rather than only the accompanying infections, environmental enteropathy and other aspects of living in poverty, that influence pancreatic insulin production.[55; 64; 65; 70; 74] Furthermore, since AN normally occurs in people who were previously adequately nourished in high-income countries, the results from AN patients suggest that the direction of causality is from malnutrition to impaired pancreas function, although the opposite direction of causality, with pancreas disease causing malnutrition, may also contribute.[62]

The mechanisms whereby malnutrition may result in long-term effects on the pancreas are unclear and the studies included in this review provide little information, in part because the more recent and high quality studies have been mainly large ones investigating the epidemiology of glucose metabolism in famine survivors. Some studies in India have investigated pancreas calcification as the mechanism of the impaired function; such reports contributed to the earlier WHO classification of fibrocalculus pancreatic diabetes [11] but most such studies in the present review were excluded because the main exposure was not prior nutritional status. Environmental enteropathy, which is common in low-income countries and often associated with malnutrition,[85] may have contributed to impaired glucose tolerance in studies of acute malnutrition. Evidence for this comes from studies showing delayed insulin responses or larger effects on the insulin response to OGTT than to IVGTT which bypasses the gut. Possible mechanisms of intestinal epithelial involvement include delayed or reduced glucose absorption[86] during an OGTT and reduced insulin production because of low incretin production by enterocytes.[87]

Most abnormalities in endocrine pancreas function of severely malnourished people seem to improve in the short term with treatment of the malnutrition; recovery of exocrine pancreas functions after malnutrition has been less studied. There is limited information about long-term pancreas function outside the famine studies. Several of those studies suggest early insults may interact with later diet and illness. [68; 77] This is in keeping with the capacity-load model of chronic disease [88] in which damage to a physiological capacity, e.g. pancreas functions, earlier in life is most likely to result in health problems if in later life there is a greater load on the system, e.g. due to overweight or consumption of a diet high in sugar. Differing prevalence of adult obesity in men and women, in addition to potential sex differences in survival from malnutrition, may contribute to the variable sex differences seen in some of the famine follow-up studies.

Strengths and limitations of the review

A strength of the review is that it included a large number of studies from many countries of varying income levels and with multiple study designs and participant characteristics. The overall similarity in results from very different studies, i.e. clinical malnutrition in young children, AN in older children and adults, and follow-up of famine studies, lends credence to the findings. At least two of the authors reviewed all the included studies. The review has limitations resulting from the heterogeneity of data from varying methodologies, settings, and populations enrolled which also precluded being able to conduct any meaningful meta-analyses. Many of the included studies were poor quality with small sample sizes, poorly defined populations, and unclear statistics. We did not analyse the findings of only good quality studies separately since this would have excluded too many which provided data not available elsewhere. Many of the early studies were conducted to define the aetiology and biology of kwashiorkor versus marasmus so were not addressing our interests specifically. Similarly, much research on AN was not specifically investigating pancreas function. The techniques used in older compared with newer studies differed and were not always validated so results are hard to compare. Authors of some of the famine studies were interested in prenatal famine exposure so included postnatal exposure as a control for that. The absence of an original aim to investigate postnatal malnutrition and pancreas function could have meant that, even if the study contained data relevant to our search, the title and abstract may not have mentioned it so would have been missed at the first level of the search; this may explain why a large proportion of the included studies were actually located from the reference lists of other articles found. In addition, we did not include studies where the population was selected based on diabetes because this could have resulted in bias in relation to our aims; for example, studies looking at malnutrition as one of many risk factors for diabetes in a population may have included it in the abstract only if the association was statistically significant., e.g. Fekadu et al.[89]

Conclusion

Much of the world is currently facing a double burden of under- and over-nutrition in which there is an increasing prevalence of overweight, diabetes and other chronic diseases but an ongoing high prevalence of malnutrition, both in young children and in older individuals with severe infections. There is a need for better understanding of how these conditions interact in order to improve prevention and treatment of chronic conditions. This review suggests that malnutrition at any postnatal age can have both acute and long-term adverse effects on pancreas function so that diabetes treatments should consider insulin production as well as insulin resistance. Currently the common first line pharmacological treatment for diabetes in many settings, including low-income ones where detailed metabolic investigations are often not

possible, is metformin which acts primarily on insulin resistance; however, it may not be the best treatment in populations where low insulin production is a major concern.[90] The similarity of findings from very different populations, including children living in poor environments, adults with malnutrition secondary to severe infections, anorexia nervosa patients, and famine survivors, suggests that it is malnutrition itself which can result in impaired pancreas functions. If infection-mediated malnutrition has life-long impacts on diabetes risk, this provides added impetus to prevent and treat this malnutrition, beyond achieving favorable outcomes of the original infection, e.g. tuberculosis or HIV. More well-designed research with clearly defined populations, adequate sample sizes, consideration of the sexes separately, and using robust current techniques to determine the contribution of low insulin production or increased insulin resistance, is needed in order to understand both the epidemiology and mechanisms of interactions between malnutrition and pancreas functions.

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Table 1. Association between concurrent/short-term outcome of childhood malnutrition and pancreatic function.

Author & reference	Study design	Country/ Quality assessment	Age when malnourished	No of participants	Inclusion/ exclusion criteria	Definitions of MN	Pancreatic function times and tests	Intervention or Nutritional Rehabilitation (NR)	Main relevant findings	Comments
Exocrine Pancreatic Function										
Barbezat et al., 1967[28]	Clinical cohort	South Africa V. Low	mean age 18.3 m	• 21 MN inc: • 14 KK • 7 MS • 10 treated for KK 5 yrs before (5-Yr FU) 7 non-MN controls	Inclusion unclear • similar age & population group non-MN controls Exclusion criteria not specified	• KK by clinical criteria • MS: <61% expected weight (Boston ref) without edema	• 1 d after admission and after acute recovery (KK, n=11, day not specified) • duodenal juice volume, pH amylase, lipase, trypsin, chymotrypsin before and after SST	NR: K-Cl daily supplements, after stabilization , full cream milk, them mixed diet	• low amylase both basal and after SST in MN but increased after acute recovery • basal lipase low in only KK, improved on acute recovery • slightly decreased trypsin in MN which improved on acute recovery • both basal and after SST chymotrypsin v low in MN; improved after acute recovery but ↓ in 5-yr FU group. • Vol/kg and pH not affected by MN	• Unclear MN definitions (post KK group all "underweight for age") • Small sample size • Enzymes improved after acute recovery, but not to control levels • Enzymes correlated with baseline plasma albumin more than patient groups

Author & reference	Study design	Country/ Quality assessment	Age when malnourished	No of participants	Inclusion/ exclusion criteria	Definitions of MN	Pancreatic function times and tests	Intervention or Nutritional Rehabilitation (NR)	Main relevant findings	Comments
Bartels et al., 2017[16]	RCT - single blind	Malawi High	6-60 m	90 MN	Inclusion: hospitalized with SAM Exclusion: malaria or severe infections	• SAM: WHO criteria[91]	• Admission, d14, d28 • Fecal elastase (FE) • exocrine pancreatic insufficiency (EPI): EPI: FE <200 µg/g Severe EPI: FE <100 µg/g	Pancreatic enzyme replacement therapy vs standard care	• At admission, EPI =83.1%; severe EPI=69% & median FE lower in edematous vs non-edematous MN • After treatment, FE increased in all children unrelated to enzyme therapy and more in those with non-edematous MN • Most with edema at baseline remained with EPI or severe EPI at d28.	• RCT 1º outcome of weight gain not affected but ↓ time to discharge and lower mortality in enzyme therapy group • Nutritional status of children after intervention not clear. • No modifying effects of HIV or diarrhea
Bartels et al., 2016[17]	Clinical cohort	Malawi Low	IQR 16 - 27 m	89 MN, incl 56 with edema	Inclusion: 6-60 m, hospital with SAM +/- HIV Exclusion: previous admission within 1 y, severe neurological or hemodynamic illness	• SAM: WHO criteria[91]	• Admission & 3d post-stabilization • Fecal elastase (FE) • EPI: FE <200 µg/g • Severe EPI: FE<100 µg/g • Serum trypsinogen & amylase	NR carried out according to WHO[1]	• At admission, EPI=92.2%; severe EPI=76.6%. • Severe EPI more common in edematous than non-edematous MN (88% vs 59%); • d3 vs d0, FE modestly ↑ in all children but 83% still EPI at d3; • Higher trypsinogen but not amylase in edematous MN; • No association between trypsinogen & FE.	• No modifying effects of age, sex, HIV
Briars	Cross-	Australi	0-3 y	2 groups	Aboriginal	• Severe	• Hospital	None	• No difference in	• Non-standard

Author & reference	Study design	Country/ Quality assessment	Age when malnourished	No of participants	Inclusion/ exclusion criteria	Definitions of MN	Pancreatic function times and tests	Intervention or Nutritional Rehabilitation (NR)	Main relevant findings	Comments
et al., 1998[18]	sectional	a Low	& 6m – 15y	in 2 sites • 472 0-3 y; • 187 0.5-<16 y;	children admitted to hospital	MN: WAZ<-2.0 • Mod MN: WAZ -1.0 to -2.0 • Control: WAZ >-1.0	admission • Whole blood trypsinogen		trypsinogen concentration between MN groups; • inverse correlation between trypsinogen and WAZ; • Higher trypsinogen in admissions associated with gastroenteritis	categories of MN; • Not all statistics reported
Danus et al., 1970[19]	Clinical cohort	Chile V. Low	<2 y	• 10 MN, • 7 non-MN hospital controls	Not specified	• Marasmic: grade-3 MN • Well nourished not defined.	• Admission, d4, d30 of NR • Pancreatic secretion volume, duodenal bicarbonate, amylase, lipase before and after SST (stimulation with secretin, cholecystokinin)	NR but no details given	• Comparable pancreas secretion volume in MN & controls before and after SST • bicarbonate increased 5-6-fold after stimulation in all children; • Amylase & lipase, basal and after SST ↓ in MN at admission and after NR compared to controls	• unclear definitions of nutritional status • Formal statistics not reported.
Durie et al., 1985[20]	Clinical cohort	Canada V. Low	0.1-3.8 y (MN) 0.1-5y healthy controls	• 25 severe MN • 23 Moderate MN • 2 Mild-MN	Inclusion: • Hospital with wasting Exclusion criteria unclear	• Severe MN: <=75% of ideal weight-for-height (WfH)	• Admission and after NR • Serum trypsinogen.	Oral or intravenous NR but no details given	• Trypsinogen positively associated with severity of MN & ↑ compared to controls at admission • After NR, trypsinogen tended to revert toward normal, especially in those with greatest nutritional	• Unclear definition of MN • Reasons for hospitalization missing • Various primary clinical causes

Author & reference	Study design	Country/ Quality assessment	Age when malnourished	No of participants	Inclusion/ exclusion criteria	Definitions of MN	Pancreatic function times and tests	Intervention or Nutritional Rehabilitation (NR)	Main relevant findings	Comments
				• 38 healthy controls		• Moderate MN: 75 - 85% of WfH • Mild-MN: 85 - 90% of WfH			improvement • Fat malabsorption documented in 17/43 MN	of MN • No details of healthy controls • No details of NR • No renal impairment which could ↑ trypsinogen
El-Hodhod et al., 2005[21]	Clinical cohort	Egypt V. Low	Mean for MN 11.8 m, Control mean 14.8 m	• 33 MN: 10 KK, 15 MS,8 marasmic-KK • 12 age- & sex-matched healthy controls	Inclusion: hospital with MN Exclusion unclear	• Wellcome 1970[92]	• Admission & after 3-6 m NR • Pancreatic head size by ultrasonography; • Serum amylase and lipase	NR carried out according to the WHO	• ↓ serum amylase, lipase & pancreas head size in all MN groups compared to controls, before NR • Pancreas head size, amylase, lipase ↑ in all MN groups after NR, increasing with duration of treatment	• Multiple statistical tests with limited sample size • Controls assessed once only so age-associated changes not accounted for in post-NR comparisons
Keni et al., 1995[22]	Cross-sectional	India V. Low	9 m - 9 y	• 23 MN of varying severity inc 12 marasmic-KK • 5 non-MN	Inclusion: 9 m - 9 y, MN hospitalized with recurrent diarrhoea; Exclusion: cystic fibrosis	• NCHS WfH • 4 MN grades	• Admission • Pancreatic water electrolytes & trypsin output (units/kg/hr) during SST, assessed in duodenal fluid	Not reported	• No consistent effect on trypsinogen across MN grades. • water output increased in MN with bicarbonate relative to water output but decreased in severe MN associated with loss of K+ in severe MN	• Results may not be applicable to non-persistent diarrhea cases • Multiple statistical tests with limited sample size

Author & reference	Study design	Country/ Quality assessment	Age when malnourished	No of participants	Inclusion/ exclusion criteria	Definitions of MN	Pancreatic function times and tests	Intervention or Nutritional Rehabilitation (NR)	Main relevant findings	Comments
				controls						
Mehta et al.,1984[23]	Non-randomised 3-arm trial in MN plus controls	India Low	9 - 42 m	56 MN 15 age-matched Not controls	Inclusion: Hospitalized with MS Exclusion: no major infection	• MN weight <60% of median Boston standards • Controls weight >80% of Boston median	• Admission & after 2 w of NR • Duodenal amylase, lipase and trypsin activity, duodenal pH after pancreatic stimulation (milk).	• High protein diet (n=16): • High fat diet (n=20); • High carbohydrate diet (n=20): • Each diet also sub-divided into further different compositions	• ↓ pH, duodenal amylase, lipase and trypsin activity in MN compared to controls before NR; • High protein diet ↑ pH and all enzyme activities compared to baseline; • High fat diet ↑ lipase activity only compared to baseline	• Selection of controls • Reports enzyme activities/dL not amounts • No comparisons with controls post NR • No report of degree of nutritional recovery
Saunier et al., 1986[24]	Cross-sectional	France & Ivory Coast Low	1-8 y	• 15 Ivorian MN (KK) • 10 recovered KK; • 73 hospital controls (62 French, 11 Ivorian)	Inclusion • Current KK • recovered KK; • recurrent KK; • Non-MN control from acute conditions or trauma Exclusion criteria not specified.	KK by clinical criteria	• Current MN at admission or after recovery from KK • Pancreatic amylase, lipase, phospholipase trypsin, chymotrypsin electrolytes in duodenal fluid volume after SST	Not reported	• ↓ lipase, trypsin & phospholipase in MN compared to controls • recovered MN not different from controls • ↓bicarbonate, Cl^-, lipase, phospholipase in African control vs European control	• Europeans and Africans differed non-consistently across tests attributed to diet not ethnicity • Statistical tests unclear • Small sample size for MN, especially for recurrent MN
Saunie	RCT in	Senegal	1-3 y	• 28 MN	• Specific	KK by	• Admission and	• NR locally	• Secretion of enzymes &	• Different NR in

Author & reference	Study design	Country/ Quality assessment	Age when malnourished	No of participants	Inclusion/ exclusion criteria	Definitions of MN	Pancreatic function times and tests	Intervention or Nutritional Rehabilitation (NR)	Main relevant findings	Comments
re et al., 1988[25]	MN plus controls	, Ivory Coast, France Low		(KK) • 21 African controls • 31 French controls	inclusion & exclusion criteria not described • Controls mix of relatives of MN, hospital controls with no medical or surgical disease, or French	clinical criteria	after 5d (Ivory Coast) or 28d (Senegal) of NR • Pancreatic secretion volume, duodenal pH, electrolytes, amylase, chymotrypsin, lipase, phospholipase and trypsin after SST	sourced diet • Random assignment to pancreatic enzyme replacement therapy (porcine pancreas powder)	electrolytes ↓ in African controls (esp Senegalese) than French controls (inc when adjusted for body weight) • In Ivory Coast MN had ↓pancreas enzyme secretion than controls which significantly improved after 5 d of NR but not to French or African control levels. • In Senegal MN, severe pancreas enzyme deficiency not improved by 28 d NR • No effects of pancreatic enzyme replacement therapy	2 countries with v different outcomes. • Pancreatic assessments standardized across sites • Multiple testing across many small groups • Low pancreas enzymes in African controls compared to French suggest other environmental factors than MN are key
Thompson et al., 1952[26]	Non-randomized multiple arm trial	Uganda V. Low	9 - 58 m	59 MN (KK) , 24 non-MN hospital control	Inclusion: pitting edema, hair changes, low weight Controls: normal hair, no edema, hospitalized for other conditions Exclusion	• KK by clinical diagnosis	• At admission to hospital (1-5 d) & discharge after NR (7-51 d) (N=40) • Duodenal amylase and lipase	• NR: hospital diet with comparisons of groups assigned to extra milk or other protein supplements	• At admission, ↓ amylase & lipase in KK vs control • At discharge, lipase ↑ similar to controls, & amylase ↑ > controls • No differences in change of amylase/lipase between NR interventions.	• Statistical analysis details missing • Little information about the non-MN controls, e.g. weight not given

Author & reference	Study design	Country/ Quality assessment	Age when malnourished	No of participants	Inclusion/ exclusion criteria	Definitions of MN	Pancreatic function times and tests	Intervention or Nutritional Rehabilitation (NR)	Main relevant findings	Comments
					criteria not specified					
Widodo et al., 2016[27]	Cross-sectional	Indonesia Low	6 - 60 m	• 31 MN • 120 non-MN apparently healthy hospital controls	Inclusion: 6-60m at 2 hospitals in- & outpatient clinics Exclusion: • EPI at birth, • inflammatory bowel disease or other chronic diarrhea • recent medications	(moderate or severe MN not defined	• Fecal elastase (FE)	None	• No difference in FE in MN vs controls	• Study also recruited children with persistent diarrhea – data not included here • Group with persistent diarrhea and MN had lowest FE
Endocrine pancreas function										
Adegbenro et al., 1991[29]	Cross-sectional	Nigeria/ Low	1 - 5 y	25 KK, 25 MS, 25 non-MN healthy controls	Inclusion: not specified Controls same age group, well nourished, clinically stable; Exclusion: Marasmic-KK	• MN by Wellcome Trust[92]	• FBG & HbA1c	None	• ↑ HbA1c in KK vs controls but comparable in MS vs controls • ↓ FBG in all MN vs controls; • In MN, HbA1c inversely associated with to FBG	• Relatively small sample size, in relation to observed variability in FBG and HbA1c. • Only 1 KK had hypoglycemia • MN children did not require hospitalization
Becker	Clinica	South	8 - 38 m	Acute MN	Inclusion:	• KK	• Admission,	• Locally	• Insulin & insulin/glucose	• abnormal

Author & reference	Study design	Country/ Quality assessment	Age when malnourished	No of participants	Inclusion/ exclusion criteria	Definitions of MN	Pancreatic function times and tests	Intervention or Nutritional Rehabilitation (NR)	Main relevant findings	Comments
et al., 1971[30]	l cohort acutely and long-term follow-up	Africa Low	acutely; 7-12 y at follow-up	• 38 KK • 16 MS • 10 age-matched non-MN controls Follow-up • 10 recovered MN • 10 closest siblings as controls	MS or KK Controls with wt >3rd Boston percentile Exclusion: obvious infection, anemia, or gross diarrhoea Follow-up: Hospitalized for KK 10 y earlier	defined clinically MS: <=60% WfA without oedema	recovery (3-6 wks of NR), 2-10 m of NR (in persistent abnormal) • Ratio of insulin AUC : glucose AUC) in OGTT and/or IVGTT • OGTT & glucagon in subset • 10 y post KK Ratio of Insulin AUC:glucose AUC in 90 min IVGTT	prepared NR	AUC in OGTT very low in MN on admission and ↑after 3-6 wks • Insulin & insulin/glucose AUC in IVGTT less affected than OGTT in MN and ↑ after 3-6 w NR • KK ↑ more for Insulin:glucose AUC than MS • 16/49 at 3-6 wks recovery Insulin abnormal • Some low insulin responses still evident after 2-10 m NR but similar to controls • At long-term follow-up, no difference between recovered MN and control in insulin/glucose AUC	Insulin <20 uU/ml not based on controls – noted 2/10 controls probably not normal; • at follow-up 6/10 MN still had low WfA • normal IVGTT but low insulin in OGTT suggests enterocyte rather than pancreas problem
Becker et al., 1972[31]	Clinical cohort	South Africa V. Low	8 - 38 m	• 38 KK • 16 MS • 10 age-matched non-MN controls	Inclusion: MS or KK Controls with wt > 3rd Boston percentile Exclusion: obvious infection, anemia, or gross	• KK defined clinically • MS: <=60% WfA without edema	• Admission and after 1-6 m NR • Glucose & insulin in OGTT and/or IVGTT	• Locally prepared NR	• Analysed as patterns of insulin responses to OGTT/IVGTT; 4 patterns: a) most common flat low insulin curve after OGTT & flat/normal after IVGTT (n=35/54 MN); b) sustained insulin curve after OGTT & IVGTT; c) delayed insulin response after OGTT & normal IVGTT; d) delayed insulin response after IVGTT only – in 7 with MS-KK	• Note overlap of pops with [29] • Normal response defined from a typical normal control • Pattern classifications based on OGTT & IVGTT, but only 14

Author & reference	Study design	Country/ Quality assessment	Age when malnourished	No of participants	Inclusion/ exclusion criteria	Definitions of MN	Pancreatic function times and tests	Intervention or Nutritional Rehabilitation (NR)	Main relevant findings	Comments
					diarrhoea				(denominator not reported) • After NR, all patterns were normal	children had both tests. • No statistics & unclear denominators
Becker et al., 1975[40]	RCT - 2 arm	South Africa Low	6 - 27 m	10 MN, no controls	Inclusion: Hospitalized children with KK • Exclusion: overt infection • severe gastroenteritis	• KK defined clinically	• Admission, d2, d5 and discharge after 3-5 w NR • Insulin:glucose AUC ratio (IGR) and insulin AUC during OGTT (60 min)	• Alternatively assigned to high oral potassium (n=5) or conventional potassium supplementation (n=5)	• Early insulin release (AUC in 60 mins) during OGTT low in MN • Insulin AUC & IGR↑ by 3-5 weeks NR but no controls so unclear if it reached normal levels • Insulin AUC 60 mins ↑ in high vs low K supp group	• Small sample size • Not randomized
Becker et al., 1975[41]	Clinical cohort	South Africa V. Low	8 - 38 m	7 MS, 28 KK or MS-KK	Inclusion: MS or KK Exclusion: obvious infection, severe anemia, gross diarrhoea	• KK defined clinically • MS: ≤60% WfA without edema	• At admission, subsets repeated at 24 or 72 hr after either albumin, amino acid infusion or milk feed and at clinical recovery (3-6 w) • Insulin insulin:glucose AUC (IGR) & glucose disappearance	Standard local hospital diet	• Glucose disappearance rate low at admission but increased with NR • Peak insulin associated with glucose clearance rate only at admission • Peak Insulin and albumin correlated at admission but no consistent effects of acute infusions, except possible ↑ in IGR after aa infusion	• Note sub-pop of [29] Multiple testing • No controls • Main purpose of analysis is to assess correlations of insulin and glucose responses to markers of protein or aa status

Author & reference	Study design	Country/ Quality assessment	Age when malnourished	No of participants	Inclusion/ exclusion criteria	Definitions of MN	Pancreatic function times and tests	Intervention or Nutritional Rehabilitation (NR)	Main relevant findings	Comments
							rate during IVGTT (120 mins)			
Bowie et al., 1964[32]	Cross-sectional	USA V. Low	Infants and children (ages not given)	• 24 KK • 10 MS • 5 normal weight controls	Inclusion and exclusion criteria unclear	• KK defined clinically • MS: low weight & no edema	• After 3d admission and milk feeding • Glucose disappearance rate during IVGTT • 4 children also given insulin infusion	Milk feeding	• Slower glucose disappearance in KK than in MS or well-nourished • Slow disappearance rate in KK not improved by insulin infusion	• Incomplete study methods • No statistical analysis • factors other than insulin production may be responsible for poor glucose utilization in KK
Fransis-Emmanuel et al., 2014[44]	Case-control	Jamaica Medium	6-18 m	• 38 KK • 42 MS • 70 community control • 40 birth-wt matched control	Inclusion: • Hospitalized 6-18 months children with KK & MS during 1963-1992 • Controls: Never experienced MN Exclusion: • Acutely ill, pregnant, lactating, on glucocorticoid,	• KK & MS by welcome criteria	• FBG & fasting insulin • Glucose and insulin during OGTT	Not applicable	• No group differences in FBG • ↑ peak levels of glucose during OGTT in post-MS vs post-KK • ↓ insulin sensitivity in post-MS vs post-KK • ↓ insulinogenic and oral disposition index in post-MS vs all	• Findings are unlikely confounded by survival effect

Author & reference	Study design	Country/ Quality assessment	Age when malnourished	No of participants	Inclusion/ exclusion criteria	Definitions of MN	Pancreatic function times and tests	Intervention or Nutritional Rehabilitation (NR)	Main relevant findings	Comments
					or had hemoglobinopathy					
Garg et al., 1989[35]	Cross-sectional	India Low	2 - 10 y	• 15 MN, 5 at each of grades II, III, IV • 5 normal controls	Inclusion: • Children with varying grades MN • Adequately nourished controls Exclusion: No other illnesses	• MN defined by % of reference weight • Normal >=80% • Grade II 60-69% • Grade III: 50-59% • Grade IV: <50%	• FBG & fasting insulin • Glucose and insulin during OGTT	Not applicable	• No group differences in FBG & fasting insulin • ↑ peak levels of glucose during OGTT in grades III and IV MN vs controls • ↑ Peak insulin during OGTT in grades III and IV MN vs controls	• Unclear from where and how the children were recruited • Unclear duration of MN or when pancreas assessments done • Authors said insulin responses were blunted in MN in relation to glucose levels but provided no analysis to this
Gonzalez-Barranco et al., 2003[45]	Case-control	Mexico Medium	Mean age 4.5 [sd 3.1] m	• 52 MN • 50 healthy controls	Inclusion: Nondiabetic men with history of MN during 1st y of life Exclusion criteria not specified	• MN defined by % of reference weight • Degree I 76-90% • Degree II 61-75%	• FBG & insulin • AUC of glucose, & insulin • Insulin sensitivity	• Not applicable	• ↑ fasting & during OGTT glucose & insulin in post-MN vs controls • ↑ AUCO glucose, & insulin in post-MN vs controls • ↓insulin sensitivity in post-MN vs controls	• Nondiabetic cases included • Cases were from lower socioeconomic strata

Author & reference	Study design	Country/ Quality assessment	Age when malnourished	No of participants	Inclusion/ exclusion criteria	Definitions of MN	Pancreatic function times and tests	Intervention or Nutritional Rehabilitation (NR)	Main relevant findings	Comments
						• Degree III: 30-60%				
Hadden et al., 1967[33]	Clinical cohort	Uganda V. Low	Mean age 15 [sd 6] m	• 24 KK • 9 MS	Inclusion: 'clinical and biochemical criteria' for KK & MS but not described Exclusion criteria not specified	• KK defined clinically • MS: ↓ weight, no edema	• Admission (d1) & several times up to d14 of NR • FBG & Insulin • IVGTT at d1 & d14 • Glucose disappearance rate	• Locally sourced diet plus multivitamin supplements	• Limited differences in FBG between groups or over time • At d1 & d14 fasting insulin higher in KK than MS; • Insulin tended to normalize during NR • At admission, slow glucose disappearance in KK but improved after NR; glucose disappearance rate negatively correlated with fasting blood fatty acid level • Normal glucose disappearance in MS and no correlation with fatty acids	• Lacking statistical methods • No well-nourished controls; children own controls over time • Values at d14 judged to be comparable to normal • Association of glucose disappearance with fatty acids suggests insulin resistance related to high blood fatty acids in KK from metabolic block in utilization
James et al., 1970[34]	Cross-sectional	Jamaica V. Low	6-18 m	• 26 MN, • 28 treated	Inclusion • Clinical MN diagnosis	• MN: mean 72%	• 3-18 d or 6-20 d after hospital admission	• Locally sourced protein & energy	• No group differences in FBG • Glucose disappearance low in untreated MN; increased	• Unclear definition of MN

Author & reference	Study design	Country/ Quality assessment	Age when malnourished	No of participants	Inclusion/ exclusion criteria	Definitions of MN	Pancreatic function times and tests	Intervention or Nutritional Rehabilitation (NR)	Main relevant findings	Comments
				MN • 5 non-MN hospital controls	• Control: hospitalized for bronchitis with no clinical evidence of malnutrition. Exclusion criteria: infection, anaemia, severe diarrhea or jaundice	expected WfH • Treated MN: 89% expected WfH • Control 92% expected WfH	• FBG • Insulin and glucose during IVGTT • Glucose disappearance rate • OGTT in subset of MN & treated children	supplement	with NR but not to control levels • Insulin during IVGTT low in untreated MN and increased slightly but not to control levels after NR	• Impaired glucose tolerance persisted after treatment, possibly due to persistent low insulin production
Milner et al., 1971[47]	Clinical cohort	Jamaica V. Low	6-27 m	• 11 MS • 5 KK • 10 MS-KK	Inclusion: • MS: weight <66% expected, no edema • KK: weight>60& expected, edema • Marasmic KK: weight < 60% expected, edema	• MS, KK, & marasmic KK based on % expected weight and edema	• 1-2 d post-hospital admission & 6-12 w NR • FBG in all • Repeated IVGTT in 10 children • Repeated Glucagon injection in 9 children	• Local milk diet refeeding	• FBG similar at admission and post-NR • Fasting insulin higher after NR than at admission • Glucose tolerance improved post-NR • Insulin higher in IVGTT post-NR • Blood glucose after glucagon injection higher post-NR; no difference in insulin	• No healthy controls; children post-NR were their own controls • Multiple t-tests for several analytes at different time points within IVGTT
Pereyra et al., 2021[46]	Retrospective cohort	Chile Low	12 months	• Cohort-1: 1232 participants born betwee	Inclusion: • Cohort-1: participants born between 1974 & 1978;	• Stunted: LAZ <-2 SD; • Severe	• At age 22-28 y • 12-h FPG; • Fasting insulin; • Homeostasis	• N/A	• ↑ adulthood SPISE in underweight subjects; • Adulthood glycemia positively associated	• Participants selected randomly; • Possibilities of

Author & reference	Study design	Country/ Quality assessment	Age when malnourished	No of participants	Inclusion/ exclusion criteria	Definitions of MN	Pancreatic function times and tests	Intervention or Nutritional Rehabilitation (NR)	Main relevant findings	Comments
				n 1974 & 1978; • Cohort-2: 1000 participants born between 1988 & 1992	• Cohort-2: participants born between 1988 & 1992 **Exclusion** • Missing data for birth weight, FPG, & fasting insulin	stunted: LAZ<-3 SD; • Underweight: WAZ <-2 SD; • Severe underweight: WAZ<-3 SD; • Wasted: WLZ<-2SD; • Risk of wasting: WLZ<-1SD; • Birth weight • Conditional growth: regressing weight/length on birth weight and earlier measure	model assessment of insulin resistance (HOMA-IR); • Single point insulin sensitivity estimator (SPISE)		wasting and at risk of wasting condition; • ↓glycemia adulthood associated with ↑ WLZ at 12 m	selection bias due to missing data; 1,070 inc in final analyses • Probability of error on routine records at birth and 12 months

Author & reference	Study design	Country/ Quality assessment	Age when malnourished	No of participants	Inclusion/ exclusion criteria	Definitions of MN	Pancreatic function times and tests	Intervention or Nutritional Rehabilitation (NR)	Main relevant findings	Comments
						of weight and length				
Prinsloo et al., 1971[37]	Clinical cohort	South Africa V. Low	Mean age 55.6 [sd 20.5] m	16 KK; 15 pellagra controls	Inclusion: • Hospitalised for KK • Control with pellagrous skin lesions without oedema Exclusion: • Patients moribund on admission	• KK defined clinically	• 2-5 d after admission and after 4-5 w NR • FBG • Glucose and insulin during IVGTT; & glucose disappearance rate	• Usual hospital diet plus milk, potassium, multivitamins	• At admission, no group difference in FBG but lower insulin and slower glucose disappearance in MN • after NR increased insulin and improved glucose disappearance, now similar to controls	• Authors stated pellagra controls had normal glucose tolerance • NR normalized insulin and glucose
Robinson et al., 1982[38]	Non randomised 2-arm trial	Jamaica V. Low	6-20 m; median 12 m	20 MN 11 healthy adults to provide normal glucagon levels	Inclusion: Severe MN Exclusion criteria not specified	• Severe MN: expected WfH 52.6%-83.6%	• Admission and weekly intervals until recovery • FBG • Fasting glucagon & insulin	• Maintenance diet followed by 1 of 2 different locally made recovery diets (high carb vs high fat)	• FBG similar during MN and recovery • Low fasting glucagon, insulin during MN which increased during first few weeks of recovery but then declined slightly, correlated with growth rates & insulin: glucagon ratio increased at period of max growth rate	• Missing information about study participants and statistical methods • Adult controls for glucagon level; children also served as their own controls • No diff of diets on rate weight gain but high

Author & reference	Study design	Country/ Quality assessment	Age when malnourished	No of participants	Inclusion/ exclusion criteria	Definitions of MN	Pancreatic function times and tests	Intervention or Nutritional Rehabilitation (NR)	Main relevant findings	Comments
										carbohydrate diet ↓ glucagon responses
Slone 1961[36]	Cross-sectional	South Africa V. Low	0.5-3 y	•20 KK •20 control	Inclusion: • KK Exclusion: dehydration	•KK by clinical diagnosis	•2 d post-hospital admission •FBG in all •IVGTT in 9 MN	NA	•Low FBG in MN •Mild glucose intolerance in IVGTT but controls not studied	•No statistical analyses and no controls in IVGTT
Spoelstra et al., 2012[39]	Cross-sectional	Malawi Medium	Mean age 25.3 [sd 15] m	•6 KK/MS-KK •8 MS • 3 non-MN hospital controls	Inclusion: •Children clinical diagnosed KK or MS. With or without HIV •Control: Minor orthopedic problem or recovered from respiratory illness Exclusion: •Multiple indicators of severe illness	•KK defined clinically •MS: WAZ<-3 or MUAC < 11 cm	•During stabilization phase of NR •Glucose infusion (4hr) and OGTT (at 2 hr of glucose infusion) with doubly isotopically labelled glucose •Modeled glucose clearance in OGTT	WHO recommended NR [(1)]	•Oral rate of glucose appearance reduced in KK; •Lower glucose clearance in both MN groups with low insulin response. Low ratio of glucose clearance AUC: insulin AUC –strongly suggesting B-cell impairment not insulin resistance •Correlation between plasma albumin and glucose clearance rate	• Glucose clearance rate excludes endogenously produced glucose • investigation using isotopically labelled •Both HIV-infected and uninfected children recruited •Inflammation possibly associated with lower albumin, or oxidative stress could have

Author & reference	Study design	Country/ Quality assessment	Age when malnourished	No of participants	Inclusion/ exclusion criteria	Definitions of MN	Pancreatic function times and tests	Intervention or Nutritional Rehabilitation (NR)	Main relevant findings	Comments
										contributed to low glucose clearance
Cook et al., 1967[42]	Cross-sectional	Uganda V. Low	• Ages not given, likely 8-16 y since MN aged 1 - 4.4 y when MN	• 14 recovered KK, 20 community control	Inclusion: • History of hospitalization for KK • Community control with no history of KK Exclusion criteria not specified.	• KK by clinical criteria	• 6-12 y post hospitalization for KK • Glucose disposal rate during IVGTT	NA	• Slower glucose disposal rate in recovered KK vs controls	• Some study details missing
Kajubi et al., 1972[43]	Cross-sectional	Uganda Low	11-19 y after hospitalised with MN aged 1.5 - 3 y	• 15 post-KK • 8 controls	Inclusion: • Previously registered as KK • Exclusion criteria not specified Controls – convenience, no reported history of KK	• KK by clinical criteria	• Age 11-19 y • OGTT for 40 min with glucagon and tolbutamide given after 30 min to elicit maximum insulin release	NA	• ↓ fasting insulin in post-KK vs controls • ↑ glucose during OGTT not significantly different but didn't calculate AUC or glucose disappearance rate • Comparable maximum insulin in recovered KK & control	• Suggest the comparable maximum insulin indicates no permanent damage to the pancreas • Statistical analysis methods missing. • No differences in weight, height and hemoglobin between post-

Author & reference	Study design	Country/ Quality assessment	Age when malnourished	No of participants	Inclusion/ exclusion criteria	Definitions of MN	Pancreatic function times and tests	Intervention or Nutritional Rehabilitation (NR)	Main relevant findings	Comments
										KK & control group

AUC, area under curve; EPI, exocrine pancreatic insufficiency; FBG, fasting blood or plasma glucose; FE, fecal elastase-1; HbA1c, glycosylated hemoglobin; HIV, human immunodeficiency virus; IVGTT, intravenous glucose tolerance test; KK, kwashiorkor; Length-for-age (LAZ), MN, malnutrition or malnourished; MUAC, mid-upper arm circumference; NR, nutrition rehabilitation; OGTT; oral glucose tolerance test; PERT, pancreatic enzyme replacement therapy; RCT, randomized controlled trial; SAM, severe acute malnutrition; SEPI, severe exocrine pancreatic insufficiency; SST, stimulation test with secretin or cholecystokinin; WAZ; weight-for-age Z score; WfA, weight-for-age using percentiles; WfH, weight-for-height/length using percentiles; WHZ/WLZ, weight-for-height/length Z score; WHO, World Health Organization

Table 2. Association between late childhood or adult malnutrition and pancreatic function

Author and reference	Study design	Country/ Quality assessment	Age when MN	Number of study participants	Inclusion/ exclusion criteria	Definitions of MN	Pancreatic Function times and tests	Intervention/ Treatments	Main findings	Comments
Exocrine pancreas function										
Martinez-Olmos et al., 2013[50]	Clinical cohort	Spain V. Low	26 y	•10 AN	Inclusion: •Hospitalised for AN •BMI <17.1 kg/m^2 Exclusion: Other chronic disease	•Hospitalised for AN	•Admission and at discharge when BMI>20 kg/m^2 •Fecal elastase •Also measured triglyceride and D-xylose absorption to study gut function	Therapy for AN	•No difference in elastase before and after weight gain	•Participants after recovery were their own controls •Triglyceride and D-xylose tests were normal
Tandon et al., 1969[48]	Cross-sectional	India V. Low	22 - 55 y	•16 MN •10 normal weight hospital controls	Inclusion: •MN in hospital •Control: ambulatory outpatients without symptoms or signs of disease; Exclusion •If pancreatic or biliary disease	•Muscle wasting or peripheral edema defined clinically •Low serum albumin	•Duodenal juice amylase, lipase, trypsin after SST.	NA	•↓ trypsin & lipase, concentration both basal and stimulated in MN vs control •Amylase lower in MN after stimulation but not in basal samples •Steatorrhea in MN patients	•Conducted when serum albumin considered to indicate protein deficiency •Authors suggested larger decreases in stimulated than basal enzymes indicated low pancreatic reserve
Tandon et al., 1970[49]	Clinical cohort	India	22-55 y	•8 MN •10	Inclusion •Patients clinically	•Pallor, dry scaly skin, muscular	•Admission & after 12-14 weeks	Local protein-	•↓trypsin at admission, both	•Non-standard definition of

Author and reference	Study design	Country/ Quality assessment	Age when MN	Number of study participants	Inclusion/ exclusion criteria	Definitions of MN	Pancreatic Function times and tests	Intervention/ Treatments	Main findings	Comments
		V. Low		healthy controls	diagnosed Exclusion • clinical history of alcoholism or chronic pancreas or biliary tract disorders	wasting, and generalized edema.	treatment • Duodenal juice lipase, trypsin, amylase, basal and post SST	energy rich diet plus iron and vitamins	basal & stimulated; little increase with NR • Lipase low before NR but normalized after NR • Amylase low post-stimulation at admission; normalised after NR	MN; dietary history suggested prolonged low intakes • Multiple t-tests with small numbers of participants
Endocrine pancreas function										
Blickle et al., 1984[51]	Cross-sectional	France V. Low	19-25 y	• 26 AN • 14 normal weight controls	• Women in hospital with AN • Controls in hospital for minor disorders	• Clinical AN, 44-82% ideal weight	• Within a few days of hospital admission • Glucose, insulin and glucagon fasting and during IVGTT & arginine perfusion • Insulin/glucose ratio	Not applicable	• Fasting glucose & insulin correlated with % ideal weight • Low glucose in IVGTT in AN vs control but normal glucose disappearance rate • ↓insulin and insulin/glucose ratio during IVGTT and arginine infusion in AN • No difference in fasting glucagon or glucagon response in IVGTT in AN vs control	• Wide variability of plasma glucagon may have obscured group differences • Also measured growth hormone during the tests
Brown et al., 2003[57]	Cross-sectional	UK Low	29.4 [sd 8.2] y	• 18 recovered AN	Inclusion • women recovered from AN with	• Clinical AN	• Unclear time post AN diagnosis or recovery	Not applicable	• Comparable FBG & glucose response to meal;	• Missing details of AN severity and

Author and reference	Study design	Country/ Quality assessment	Age when MN	Number of study participants	Inclusion/ exclusion criteria	Definitions of MN	Pancreatic Function times and tests	Intervention/ Treatments	Main findings	Comments
				• 18 healthy controls	BMI>18.5 kg/m^2, resumption of menses & normal eating habits • Controls: no history of eating disorder; similar BMI to recovered AN Exclusion Bulimic patients		• Glucose & insulin fasting and after a standard meal • Glucose/insulin ratio		• ↓ fasting insulin, and slow rise in insulin in response to meal in recovered AN group • ↑fasting glucose/insulin ratio in recovered AN group, suggesting ↑ insulin sensitivity in face of ↓insulin production	time since recovery from AN • Also analysed leptin and β-hydroxybutyrate
Casper et al., 1988[58]	Cross-sectional from prospective cohort	USA Medium	8-10 y before current age of 21–40 y	• 19 AN recovered • 7 AN unrecovered • 14 age-matched controls	Inclusion: • Women recovered from AN with normal body weight, resumption of menses • Women unrecovered from AN with weight <85% expected, sporadic or absent menses • Controls: women with normal body weight Exclusion: • taking medication	• Clinical AN	• 8-10 y after AN diagnosis • Fasting plasma glucose & insulin • OGTT • IGT: FPG <140 mg/dl and glucose 140-200 mg/dl during OGTT • DM: FPG >140 mg/dl or glucose >200 mg/dl during OGTT •	Given standard diet for 5 d before testing	• Comparable FPG & fasting insulin in all groups • ↑ maximum glucose during OGTT in unrecovered AN but not recovered AN • Slow rise insulin during OGTT in unrecovered AN but not in recovered AN vs control • DM plus IGT diagnosis greater in unrecovered and recovered AN than control	• Few long-term glucose metabolism problems in recovered AN • Authors also investigated glucose associations with psychological variables and levels of cortisol, growth hormone and fatty acids

Author and reference	Study design	Country/ Quality assessment	Age when MN	Number of study participants	Inclusion/ exclusion criteria	Definitions of MN	Pancreatic Function times and tests	Intervention/ Treatments	Main findings	Comments
Fujii et al., 1989[55]	Clinical cohort	Japan Medium	13 – 35 y	•16 females with AN •8 age-matched normal weight females	Inclusion: •Women with AN •Control: healthy well-nourished, without family history of diabetes	•Clinically diagnosed AN	• Within a week of admission and after 5 m • Plasma glucose and glucagon in response to insulin infusion • Plasma glucose, glucagon and insulin in response to arginine infusion (pre-treatment only)	5 m treatment for AN	•Lower FPG & delayed glucose recovery after insulin in AN vs control; returned to normal after NR •Low fasting glucagon and glucagon response to insulin-induced hypoglycemia in AN vs control; normalized after NR •After arginine infusion, no difference in glucose or glucagon response but insulin response lower in AN vs controls	•Focus on glucagon production but insulin production also low in AN
Filteau et al., 2021[65]	Prospective cohort	Tanzania Medium	>18 y	•630	Inclusion • participated in previous research projects on malnutrition Exclusion • Missing information on glucose and insulin	•SMN: BMI <17 kg/m^2; •MN: BMI =≥17-<18.5 kg/m^2; •Normal weight: BMI ≥18.5kg/m^2	• HbA1c, glucose, and plasma insulin fasting and during OGTT	Not applicable	•Prior MN associated with lower insulin concentration in men only • Current MN had lower insulin concentration irrespective of sex	•Duration of being MN unclear
Kanis et al., 1974[64]	Clinical cohort	UK V. Low	15-43 y	• 24 AN, but OGTT data	Inclusion: •hospitalized with AN	•Clinical AN	• At admission & follow-up after 5-15 months	Psychiatric treatmen	•Blood glucose remained high longer during OGTT	• No healthy controls •Glucose and

Author and reference	Study design	Country/ Quality assessment	Age when MN	Number of study participants	Inclusion/ exclusion criteria	Definitions of MN	Pancreatic Function times and tests	Intervention/ Treatments	Main findings	Comments
				shown only for 13 patients followed up	• female Exclusion: • Male AN patients		• Glucose and insulin fasting and during OGTT	t for AN	before treatment than after • Plasma insulin remained high longer before than after treatment	insulin results shown only for subset of AN patients
Kobayashi et al., 1992[56]	Clinical cohort	Japan V. Low	21 y	• 14 AN • 6 bulimic • 6 age-matched healthy controls	Inclusion: • hospitalized with AN or bulimia • Control without personal and family history of diabetes Exclusion: • Liver disease	• Clinical AN or bulimia	• Within 2 w of hospitalization and after weight gain (8 AN patients only) • Blood glucose, serum insulin & C-peptide fasting & after IV glucagon	Local dietary therapy for AN	• Comparable glucose fasting & after glucagon in AN, bulimia & control • Lower insulin and C-peptide after i.v. glucagon in AN vs controls • No change in glucose, insulin or C-peptide in AN after weight gain.	• No description of study population
Kumai et al., 1988[52]	Clinical cohort	Japan Low	22 y	• 25 AN patients • 15 age-matched healthy controls	Inclusion: • Female patients diagnosed with AN • Healthy controls within 10% of ideal body weight without family history of DM Exclusion: • males • taking medication	• Clinically diagnosed AN	• Within 7 d of admission & before discharge, ~ 6 m later, when weight similar to controls • Glucose, insulin and glucagon fasting and during OGTT	NR and other therapy for AN	• Lower FPG but raised glucose during OGTT at admission; both became more normal after NR • Low fasting insulin & delayed and lower response (levels and total AUC) during OGTT; still abnormal after NR • Glucagon low fasting & increased, not	• Large decreases in insulin not improved by NR although glucose did improve after NR suggesting residual low insulin production; • possibly ↑ peripheral insulin

Author and reference	Study design	Country/ Quality assessment	Age when MN	Number of study participants	Inclusion/ exclusion criteria	Definitions of MN	Pancreatic Function times and tests	Intervention/ Treatments	Main findings	Comments
									decreased, during OGTT at admission; normalised post NR	sensitivity post NR
Ji et al., 2016[59]	Population-based cohort	Sweden High	Median age 17 y for females, 9 y for males	• 17,135 AN •12,910 sibling pairs without AN as controls	Inclusion: •Prior hospitalisation for AN based on national register Exclusion: •12 participants with prior DM	•Hospitalized with clinical AN 1964-2010; diagnosis based on ICD codes	• DM incidence on national register; post age 39 y to exclude type 1 DM		• During 259,088 p-y follow-up, 34 individuals developed DM • 30% ↓risk of DM in AN vs general population • Comparable risk of DM in AN vs siblings	•Investigating whether caloric restriction decreases chronic disease risk •Low DM incidence, possibly related to low prevalence of obesity in former AN patients
Letiexhe et al., 1997[60]	Cross-sectional	Belgium Low	16 – 39 y	•9 AN •9 age-matched healthy controls	Inclusion: •Female patients with AN with normal renal and liver function •Female healthy controls Exclusion: • Bulimia nervosa •Physical exercise 2 days before test	•Clinical AN, BMI 10.2-15.7 kg/m^2	• At hospital admission, before NR • Glucose, insulin and C-peptide fasting and during IVGTT, AUCs calculated • Insulin sensitivity index • Glucose effectiveness index		•Comparable fasting levels and AUC for glucose & C-peptide in both groups •↓ fasting insulin and insulin AUC in AN vs control •↑ insulin metabolic clearance rate •↓ glucose tolerance in AN vs control	•Multiple indices of insulin secretion and clearance •Suggested the low insulin in AN is not due to increased insulin clearance, but to low insulin secretion •Wide range of

Author and reference	Study design	Country/ Quality assessment	Age when MN	Number of study participants	Inclusion/ exclusion criteria	Definitions of MN	Pancreatic Function times and tests	Intervention/ Treatments	Main findings	Comments
					• Medications that interfere glucose metabolism		• Insulin metabolic clearance rate • Glucose metabolic clearance rate			duration of AN
Sizonenko et al., 1975[54]	Cross-sectional	Switzerland V. Low	AN 14 y	• 6 AN • 10 normal controls • 32 patients with endocrine abnormalities not relevant here	Girls hospitalized for AN	• Clinical AN, <65% ideal weight and amenorrhea	• Unclear time of tests with respect to hospital admission • Glucose, insulin and glucagon fasting and during arginine infusion	Not applicable	• Lower FBG and glucose during arginine infusion in AN vs control • Lower insulin fasting and during arginine infusion in AN vs control • Comparable fasting glucagon in AN vs control; glucagon remained high longer during infusion in AN than controls but not significantly so	• Statistical analyses unclear • Study underpowered for AN vs control • Focus of study was hormonal growth problems
Wallenstein et al., 1991[53]	Cross-sectional	Sweden Low	AN 13-16 y	• 7 AN • 32 obese children • 16 healthy controls	Inclusion • AN from inpatient clinics • Obese from outpatient clinics • Healthy controls studied previously in same laboratory	• Clinical AN	• AN patients when stable weight during hospitalization • 24 h urinary C-peptide excretion	Not applicable	• Comparable total urinary C-peptide in AN vs control but increased in AN when calculated per kg weight	• Unclear at what stage of hospitalization AN patients studied • Obese children were main focus of the study

Author and reference	Study design	Country/ Quality assessment	Age when MN	Number of study participants	Inclusion/ exclusion criteria	Definitions of MN	Pancreatic Function times and tests	Intervention/ Treatments	Main findings	Comments
					• No clear exclusion criteria					
Zuniga-Guajardo et al., 1986[61]	Clinical cohort	Canada V. Low	25.2 [sd, 1.9] y	• 9 AN, including bulimia • 7 healthy controls	Inclusion: • Female patients diagnosed with AN or bulimia • Female healthy controls Exclusion: • Taking medications • associated illnesses	• Clinical AN & bulimia	• At outpatient visit; 4 patients studied again post-treatment • Fasting glucose, insulin, C-peptide • Glucose & insulin infusion for euglycemic clamp • Metabolic clearance rate of glucose & insulin • M/I ratio: glucose metabolised/ unit insulin	Therapy for AN	• Lower FPG, fasting insulin & C-peptide in AN patient vs control • Higher glucose metabolic clearance rate in AN vs control • Higher insulin sensitivity in AN vs control, based on euglycemic clamp test • After treatment, FPG, insulin, and C-peptide concentration normalized in AN	• Unclear how participants selected initially and after treatment;
Sathiaraj et al., 2010[62]	case-control	India medium	32.1 [sd 14] y	• 89 tropical pancreatitis of < 1y duration • 101 age- and sex-matched community healthy controls	Inclusion • Tropical pancreatitis, including calcification or abnormalities on ultrasound, CT scan or endoscopy • Duration <1-y; Exclusion	• MN: BMI <18.5 kg/m^2; • Normal weight: BMI =18.5-24.9 kg/m^2; • Overweight and obese: BMI >25 kg/m^2	• At admission • DM: FBG >126 mg/dl and 2-h postprandial glucose >200 mg/dl	Not applicable	• No difference in % MN pre-pancreatitis compared to controls. • Generally, weight loss occurred in pancreatitis as a result of low diet intake after disease onset, i.e. MN a consequence, not a cause of tropical	

Author and reference	Study design	Country/ Quality assessment	Age when MN	Number of study participants	Inclusion/ exclusion criteria	Definitions of MN	Pancreatic Function times and tests	Intervention/ Treatments	Main findings	Comments
					• Acute exacerbation of pancreatitis, alcoholic liver disease, renal failure, pancreatic cancer, tuberculosis, HIV/AIDS, pregnancy				pancreatitis • 13.5% of tropical pancreatitis had DM	
Smith et al., 1975[63]	Clinical cohort	India V. Low	Adults, age not specified	• 17 MN	• No clear inclusion or exclusion criteria; • MN patients from outpatient clinics, public places, and refugee camps	MN definition not given but most had edema.	• Admission and after 2-4 m of NR • FBG • Insulin and glucose during IVGTT and arginine infusion • Glucose disposal rate (% fall of blood glucose/min): during IVGTT.	Locally sourced high protein, high energy supplement	• Lower FBG before NR than after • ↓glucose disposal rate on admission vs after NR • At admission compared with post-NR, insulin during IVGTT had a slow rise but stayed high for longer • Both glucose and insulin responses to arginine blunted in MN compared to after NR	• No well-nourished comparison group; patients after NR were their own controls • Missing age and other participant details • Missing statistical methods

AN, anorexia nervosa; AUC, area under the curve; BMI, body mass index; DM, diabetes mellitus; FBG, fasting blood glucose; FPG, fasting plasma glucose; ICD, International Classification of Diseases; IVGTT; intravenous glucose tolerance test; MN, malnutrition/malnourished; NR, nutrition rehabilitation; OGTT; oral glucose tolerance test; SST, secretin stimulation test

Table 3. Association between famine experience during childhood and adult endocrine pancreatic function

Author and reference	Study design	Country/ Quality assessment	Age when exposed to famine	Age at pancreas assessment	Number of study participants	Inclusion/ exclusion criteria	Pancreatic Function tests	Main findings	Comments
Finer et al., 2016[66]	Cross-sectional study	Bangladesh Medium	• Postnatal (born 1-2 y before start of famine) • Fetal (exposed during gestation) • Unexposed (conceived 6 m to 2 y after famine) • Older children exposed when > 16 y	25-64 y	• 81 postnatal exposure • 40 fetal exposure • 70 unexposed • 112 exposed after age 16 y	Inclusion: • Famine exposure defined by date of birth with respect to famine in July 1974 - June 1975	• OGTT (0 & 120 min glucose) & standard criteria of: • Impaired fasting glucose (IFG) 0 min glucose 5.6 – 6.9 mmol/l • Impaired glucose tolerance (IGT): 120 min glucose 7.8 – 11.0 mmol/l • DM: 120 min glucose ≥11.1 mmol/l	• More underweight in fetal exposed • More overweight in postnatal exposed • No overall differences in glucose outcomes but interaction with current BMI and 120 min blood glucose: underweight fetal exposed higher than other groups	• No differences in glucose outcomes between postnatal exposed and unexposed • Missing many statistical details and use of multiple post-hoc subgroup analyses • Likely survivor bias in those famine-exposed
Hult et al., 2010[67]	Cross-sectional study	Nigeria High	• Early childhood (born 1965-7) • Fetal & infant (born 1968-70) • Unexposed born post famine transition period (1971-3)	40-43 y	388 childhood exposure 292 fetal & infant exposure 486 unexposed	• Famine exposure defined by date of birth with respect to famine in 1967-70 • Participants born during transition period, Feb - Dec 1970, excluded.	• Random plasma glucose (RPG) • DM: RPG >=11.1 mmol/l; • IGT: RPG 7.8-11.0 mmol/l.	• Comparable risk for DM and IGT in childhood exposed and unexposed, but higher mean RPG & risk of IGT in fetal and infant famine exposure group compared to non-exposed • Similar odds ratios seen for those with BMI < or > 25 kg/m^2	• No association of RPG with famine exposure in childhood but exposure in fetal or infant life increased risk • Known survivor bias, i.e. famine-exposed may have died in infancy or childhood.

Author and reference	Study design	Country/ Quality assessment	Age when exposed to famine	Age at pancreas assessment	Number of study participants	Inclusion/ exclusion criteria	Pancreatic Function tests	Main findings	Comments
Li et al., 2010[68]	Cross-sectional study. Subset of 2002 China National Nutrition & Health Survey	China High	• Childhood exposed born 10/1952-09/1958, divided in 2y age bands for exposure in late childhood, mid-childhood, early childhood • Fetal and infant born 10/1959-09/1961 • Unexposed born post famine, 10/1962-09/1964	38-49 y	• 1673 late childhood • 1588 mid-childhood • 1654 early childhood • 1005 fetal and infant • 1954 unexposed	• Famine exposure defined by date of birth with respect to famine in 1959-61 • Rural residence • Participants born during transition periods, 10/1958-09/1959 and 10/1961-09/1962 excluded.	• FPG • OGTT in people with FPG>5.5 mmol/L • DM: FPG >7 mmol/L and/or 2-h glucose >=11.1 mmol/l and/or previously diagnosed with DM; • Hyperglycemia: FPG >6.1 mmol/L and/or 2-h glucose> 7.8 mmol/l	• All exposed groups ↑ FPG compared to non-exposed • Late childhood exposed group ↑ hyperglycemia, and DM vs unexposed, similar in severe and less severe famine. In contrast, fetal exposed group affects were limited to severe famine exposure – significant interaction tests, • Prevalence of hyperglycemia increased if exposed cohort consumed an affluent/western diet/higher BMI at time of glucose assessment	• Large sample size, and consideration of effect modification by current diet • Area of current residence used as proxy as area of birth • Likely survivor bias because famine-exposed may have died in childhood
Lu et al., 2020[80]	Cohort study. Subset of China Cardiometabolic Disease and	China medium	• Childhood exposed born 01/1949 - 12/1958	>40 y at start of follow-up for DM incidence	• 41,148 childhood • 13,195 fetal & early childhood • 23,582 unexposed	• Famine exposure defined by date of birth with respect to famine in 1959-61 Exclusion:	• FPG • OGTT • DM: FPG >7 mmol/L and/or 2-h glucose >=11.1 mmol/l and/or previously	• Childhood exposed group ↑ DM rate vs unexposed, similar in fetal exposed group • Age and Sex-adjusted relative risk 1.20 times ↑ in childhood famine exposed group	• Large sample size • Due to large number of lost to follow-up, poses serious threats to validity • Likely survivor bias because famine-

Author and reference	Study design	Country/ Quality assessment	Age when exposed to famine	Age at pancreas assessment	Number of study participants	Inclusion/ exclusion criteria	Pancreatic Function tests	Main findings	Comments
	Cancer Cohort (4C) study		• Fetal and early childhood exposure born 01/1959 - 12/1962 • Unexposed born post famine, 01/1963 - 12/1974			•Missing baseline blood glucose measurements •Diagnosed, and screen-detected diabetes at baseline •Missing information on BMI, smoking status, diet habits, physical activity, and follow-up glucose measurement •Participants born before 12/1948 excluded.	diagnosed with DM;	vs non-exposed group, but non-significant when further adjusted, and in stratified analyses by non-ideal cardiovascular health metrics, or by sex	exposed may have died in childhood
Meng et al., 2018[69]	Cohort study of diabetes incidence	China High	• Unexposed born Oct 1962 – Sep 1964 • Fetal exposed born Oct 1959 – Sep. 1962 •Early childhood-exposed born Oct	42-48 y at start of follow-up for DM incidence	•31,363 early childhood •18,879 fetal •38,588 unexposed	Inclusion: •Born Oct 1956 – Sep 1964 (famine was 1959-61) Exclusion: •Those born transition period Oct 1958 – Sep 1959 to minimize misclassification •Diagnosed DM since interested in	• Incident DM on clinical register over median of 7.3 y	• 1372 cases of incident DM •After adjustment for age & other confounders, ↑ DM incidence in fetal exposed compared to non-exposed & early childhood exposed combined, no diffs by sex. •No evidence of effects in childhood exposed	• Study of diabetes incidence over ~7 y in mid-life in selected participants of China Kadoorie Biobank •~3 times as many prevalent DM cases excluded as incident cases found so difficult to determine

Author and reference	Study design	Country/ Quality assessment	Age when exposed to famine	Age at pancreas assessment	Number of study participants	Inclusion/ exclusion criteria	Pancreatic Function tests	Main findings	Comments
			1956 – Sep 1958			DM incidence • Those with heart disease, stroke, or cancer		group • Adult obesity & abdominal obesity had additive effects with early MN on diabetes incidence, esp in women, significant interaction	overall effect of famine exposure
Portrait et al., 2011[70]	Cohort study – Analysis of subset for cumulative % of DM cases	Netherlands Medium	• Fetal & infant (0-1 y) • Childhood (1-5 y) • Pre-adolescent (6-10 y) • Adolescent (11-14 y)	60-76 y	• 278 famine-exposed comprising: 31 - 0-1 -y 102 - 1-5 y 83 - 6-10 y 62 - 11-15 y • 521 unexposed	• Famine exposure: resident in Western Netherlands Nov 1944-May 1945 • Unexposed: resident in North, or East Netherlands same period • Excluded if resident Southern Netherlands due to unclear famine exposure in region	DM as reported in the database	• ↑ odds of DM in adolescent-exposed females but not males, results adjusted for age current waist circumference (& other factors)	• Exposure and outcome Data derived from Longitudinal Aging Study Amsterdam, nationally representative cohort, but final sample included in this study is not • Note possible error in Table 5 adj OR and crude ORs same for females
Stanner et al., 1997[71]	Cross-sectional survey	Russia Medium	• Fetal exposed born 11/1941 – 6/1942 • Infant exposed born 1/1941	52-53 y	• 169 fetal exposed • 192 infant exposed • 188 unexposed	• Famine exposure defined by date of birth with respect to famine in Sep 1941- Jan 44 • Unexposed group born during same period but not	• OGTT: Glucose & insulin @0 and 120 min • Fasting proinsulin, C-peptide	• No reported differences between FBG, glucose tolerance, insulin, proinsulin and C-peptide in all groups	• Exposed participants selected from Register of Society of children of the Siege, but final exposed group =361 out of 1229

Author and reference	Study design	Country/ Quality assessment	Age when exposed to famine	Age at pancreas assessment	Number of study participants	Inclusion/ exclusion criteria	Pancreatic Function tests	Main findings	Comments
			– 6/1941 • Unexposed group born 1/1941 – 6/1942			under siege Exclusion • Died or migrated • DM			eligible from register. • ~68% remained in Leningrad during ~2 y Siege period. • Unclear analysis and comparisons mostly appear to be between fetal and infant exposed rather than non-exposed
Sun et al., 2018[72]	Cross-sectional study : subset of China National Health & Retirement Longitudinal Study	China High	• Late childhood exposed born 1949-52 • Mid-childhood exposed born 1953-5 • Early childhood exposed born 1956-8 • Fetal and infant exposed born 1959-62 • Unexposed born 1963-6	45-62 y	• 7262 comprising: • 1499 late childhood • 1476 mid-childhood • 1297 early childhood • 1389 fetal and infant • 1601 unexposed	• Famine exposure defined by date of birth with respect to famine in 1959-62 • Inclusion = Available FPG & never migrated from province where born. • Participants excluded if lacking key variables or were outliers.	• FPG • HbA1c • Self-report of having been diagnosed with DM • DM: FPG >=7 mmol/L and/or HbA1c ≥6.5%; • IFG: FPG 5.6 - 6.9 mmol/L and/or HbA1c 5.7 to 6.4%; • Hyperglycemia: if DM or IFG	• After adjustment for sex and famine severity, hyperglycemia (IFG or DM) ↑ for all ages of famine exposure in females but not males compared to not exposed. Further adjustments don't change this pattern • After adjustment, lower risk of DM (but not hyperglycemia) in males with early and late childhood exposure compared to unexposed. • Effect in women mostly due to IFG;	• Probable overlap of study population with [77] • Participants and data from baseline data of Nationally representative China Health & Retirement Longitudinal Study • Famine severity calculated by excess death rate for each province • Authors suggest sex difference may be due to different survival of famine between boys and girls

Author and reference	Study design	Country/ Quality assessment	Age when exposed to famine	Age at pancreas assessment	Number of study participants	Inclusion/ exclusion criteria	Pancreatic Function tests	Main findings	Comments
								effect in men due to DM	
Thurner et al., 2013[73]	Nationwide excess risk DM by year of birth	Austria High	All ages: people born between 1917 and 2007; famine exposures were 1918-19, 1938, 1946-47	Various ages	325,998 cases of DM (T2DM & T1DM) born 1917-2007 8.3 million Austrian population of same age range from National census	• National database of all pharmacologically treated DM, mostly type 2 • No exclusions because national database	• DM determined clinically and managed with drugs • Reported as % of total population being treated for DM using national census data as denominator	• ↑ risk of DM for both sexes born during or right after all 3 famines, indicating risk of fetal exposure. Largest effect in provinces most affected by famine • No excess risk if born just before famines which would have been childhood exposure	• Large database • Analysis adjusted for internal migration flows over time
Van-Abeelen et al., 2012[74]	Cohort study: subset of Prospect-EPIC cohort	Netherlands High	0-21 y • Age at Dutch famine exposure grouped into 0-9y; 10-17 y; 18-21y • median ages of non-exposed, mod- & sev-exposed to famine were 8.3y, 9.5y & 10.1y	49 -70 y	By self-report/recall: • 3572 unexposed to famine • 2975 moderately exposed • 1290 severely exposed	Inclusion: • Women born before or during Dutch famine 1944-5 who were part of the EPIC cohort study which collected outcome data Exclusion: • Born after the famine or outside blockaded area 1944-5 • Missing exposure data	• DM by self-report or urinary glucose strip during FU and/or diabetes from national hospital register, verified by data from GP/pharmacist	• End of FU 1st Jan 2006 407 incident DM • Adjusted and only age-adjusted ↑ DM risk in moderate and severely exposed vs unexposed with significant trend with increased severity of famine • Increased risk and severity trend most prominent in those aged 0-9 y during famine; but effect modification by age-group was NS (low sub-group size to	• Only women studied

Author and reference	Study design	Country/ Quality assessment	Age when exposed to famine	Age at pancreas assessment	Number of study participants	Inclusion/ exclusion criteria	Pancreatic Function tests	Main findings	Comments
						• If didn't permit access of data from national medical/statistics databases • Already diagnosed DM at enrolment		detect this)	
Wang et al., 2015[75]	Cross-sectional survey - Survey of Prevalence in East China on Metabolic Disease & Risk factors SPECT-China 2014	China High	• Unexposed born after 1963 • Fetal exposed born 1959 - 1962 • Childhood-exposed born 1949 - 1958, • Adolescent-exposed born 1921 - 1948.	Mean ages: • Unexposed <51 y, • Fetal exposed 52 - 55 y, • Childhood exposed 56 - 65 y • Adolescent exposed 66 - 93 y.	• 6,897 comprising: • 3053 unexposed • 745 fetal exposed • 1911 childhood exposed • 1188 adolescent exposed	Inclusion: • 18yrs old, resident, Chinese citizens, resident in current area>6m Exclusion: • Missing laboratory or questionnaire data • <18 y • Born in 1959 or 1962 (reported in discussion)	• FPG & fasting Insulin • HbA1c • DM defined as FPG≥7.0mmol/L or HbA1c≥6.5% &/or previous diagnosis by health professional • Calculations of: • HOMA-IR • HOMA-β% • Insulin disposition index (IDI)	• Adjusted DM risk ↑in childhood exposed compared to non-exposed. Effect appears to be due to effect in women with ↑risk in both childhood and adolescent exposed groups and no effect in men. • Exposed child/adolescent women, ↑HOMA-IR, less effect HOMA- β % • Exposed child/adolescent males ↓ HOMA- β %, no effect HOMA-IR	• Sample representative of E China, stratified for urban/rural & high/low econ status • Indicators of insulin production and glucose metabolism show sex difference
Wang et al., 2016[78]	Cross-sectional and incident DM/hyperglycemi	China High	• Late childhood born 10/1952-09/1954 • Mid-	56.4 (SD 3.3) y	• 7,801 in cross-sectional • 1,953 late childhood • 1,712 mid-childhood	Included • Participants in ongoing dynamic cohort exposed to China Famine 1959-61	• FPG • HbA1c • DM: FPG>= 7 mmol/L or physician diagnosis	• ↑ FPG, HbA1c and hyperglycemia after childhood famine exposure • ↑risk of DM in late and mid-childhood	• Participants from a cohort of retirees • Severity of famine exposure assessed by region of birth & famine excess

Author and reference	Study design	Country/ Quality assessment	Age when exposed to famine	Age at pancreas assessment	Number of study participants	Inclusion/ exclusion criteria	Pancreatic Function tests	Main findings	Comments
	a in a subset		childhood born 10/1954-09/1956 • Early childhood born 10//1956-09/1958 • Fetal and infant born 10/1959-09/1961 • unexposed born after the famine 10/1962-09/1964		• 1,932 early childhood • 1,266 fetal or infant • 938 unexposed • 3,100 in cohort analysis 5yr follow-up	Excluded: • Missing FBG or birth date • Participants born during transition periods, 10/1958-09/1959 and 10/1961-09/1962 excluded.	• Hyperglycemia: FPG 6.1 - 6.9 mmol/L;	famine-exposed groups; association significant only in women • More severe famine exposure increased risk • No difference in results when stratified by current BMI	mortality rates by regions • Authors suggest lack of increased DM in men may be due to survivor bias since men more likely to die in famine
Wang et al., 2017[76]	Cross-sectional subset of Survey of Prevalence in East China on Metabolic Disease & Risk factors SPECT-China 2014-15	China High	• Unexposed born 1963-1974 • Fetal exposed born 1959 - 1962 • Childhood-exposed born 1949 - 1958, • Adolescent and adult-exposed	41-72 y	• 1632 unexposed • 489 fetal-infant exposed • 1140 childhood • 706 adolescent & adult- exposed	Inclusion: • Participants from eastern China cohort, representative sampling • Time of exposure to famine 1959-62 defined by date and place of birth Exclusion: • Missing FPG or HbA1c	• FPG • HbA1c • DM: FBG >=7 mmol/l or HbA1c >=6.5%	• ↑DM risk in child or adolescent-adult exposed vs unexposed • HbA1c more affected by famine exposure than FPG • Risk increased in areas most severely affected by famine	• Not clear if overlap with those in [70] • Outcome data appears to be same round as [70] • Good control of confounders • Main comparisons between severe and moderate famine exposure but also some comparisons with unexposed born

Author and reference	Study design	Country/ Quality assessment	Age when exposed to famine	Age at pancreas assessment	Number of study participants	Inclusion/ exclusion criteria	Pancreatic Function tests	Main findings	Comments
			born 1926-1948.						post-famine
Wang et al., 2018[77]	Cross-sectional analysis of baseline data of subset of China National Health & Retirement Longitudinal Study	China Medium	•Unexposed born Oct 1962-Sep 1964 •Fetal exposed born Oct 1959 – Sep 1961 •Infant exposed born Jan 1958 – Dec 1958 •Preschool-exposed born Jan 1956 - Dec 1957	≥45 y	•1536 unexposed •832 fetal exposed •519 infant exposed •1251 preschool-exposed	Inclusion: •Participants from a corporate database of retirees •Time of exposure to famine 1959-61 defined by date and place of birth Exclusion: Missing FPG or HbA1c	•FPG •HbA1c •DM: FBG >=7 mmol/l or HbA1c >=6.5%	• Comparable mean FPG & HbA1c among groups • ↑DM risk in fetal and infant exposed vs unexposed • ↑DM risk in overweight/obese fetal exposed vs unexposed; not significant in normal weight people	•Note probable overlap with study population in [67] •Large representative cohort and good control of confounders •Analysis focused on fetal exposed group so used postnatal exposed as a control for some analyses, thus masking postnatal exposure effects vs unexposed
Woo et al., 2010[81]	Cross-sectional study, recruiting 2001-2004)	Hong Kong (Chinese Population) Low	• Childhood not well defined. Mean age at self-reported exposure was 12 (SD=6) y	≥65 y	•1510 unexposed •2222 childhood exposed	Inclusion: Participants who were ambulant and living home. Had complete data. Exclusion: Terminal illness and dependent on oxygen	•Self-reported DM, being treated by a doctor	• No DM risk difference between famine exposed vs unexposed group	•Famine exposure, but self-reported insufficient food for at one year during childhood. Likely to reporting bias; • DM not well defined •DM not main focus of the study

Author and reference	Study design	Country/ Quality assessment	Age when exposed to famine	Age at pancreas assessment	Number of study participants	Inclusion/ exclusion criteria	Pancreatic Function tests	Main findings	Comments
Zhang et al., 2018[79]	Cross-sectional analysis of subset of 2012 Chronic Disease Survey 2012 in Jilin Province	China Medium	• Early childhood exposed born 1956-8 • Fetal and infant exposed born 1959-61 • Transitional period born 1962 • Unexposed born 1963-5	47-55 y	• 1582 early childhood • 1442 fetal and infant • 680 transitional period • 1986 unexposed	Inclusion: • Representative sample from large northeast Chinese database • Individuals born in 1956 – 1965 with timing of exposure to famine defined by date of birth • Exclusion criteria not mentioned.	• FBG • Blood glucose 2h after breakfast • DM: FBG >=7 mmol/L or 2h glucose>=11.1 mmol/L or previous diabetes diagnosis • Hyperglycemia: FBG >=6.1 - 6.9 mmol/L or 2h glucose 7.8 - 11.0 mmol/L.	• ↑risk of hyperglycemia in early childhood exposed women only • ↑ risk of DM in crude analysis in women only exposed during fetal life or childhood; still significant after adjusting for current BMI but only for fetal exposure after adjusting for other confounders	• Large representative sample and control for several confounders • Risk of glucose intolerance after famine exposure significant in women only
Zheng et al., 2012[82]	Cross-sectional	China Medium	• Fetally-exposed born 1963-1964 • Post-natal exposed born 1957-1958 • Control born 1963-1964	44-51 y	• 1022 fetally-exposed • 1344 post-natal • 2674 control	**Inclusion** • Born 1963-1964 used data from subjects for annual physical examinations from January to December 2008 in Public Health Center of the First Affiliated Hospital of Chongqing Medical University in Chongqing, China; Exclusion	• Dysglycemia: fasting plasma glucoseX6.1 mmol/l or drug treatment for diabetes	• ↑ dysglycemia prevalence in fetally and postnatally exposed groups than in control group	• ↑Metabolic syndrome in both famine groups

Author and reference	Study design	Country/ Quality assessment	Age when exposed to famine	Age at pancreas assessment	Number of study participants	Inclusion/ exclusion criteria	Pancreatic Function tests	Main findings	Comments
						• Subjects born in 1959 and 1962			
Zhou et al,. 2017[83]	Cross-sectional	China (Hefei city; E. China) Medium	• Unexposed born Oct 1962-Sep 1964 • Fetal exposed born Oct 1959 – Sep 1961 • Early childhood exposed born Sep 1956 – Oct 1958 • Mid childhood exposed born Sep 1954 – Oct 1956 • Late childhood-exposed born Sep 1952 – Oct 1954	45-60 y	• 381 unexposed • 84 fetal exposed • 160 early childhood exposed • 173 mid childhood - exposed • 141 late childhood-exposed	Inclusion: • Individuals born in 1956 – 1965 with timing of exposure to famine defined by date of birth Exclusion criteria: • Participants born during transition periods, 10/1958-09/1959 and 10/1961-09/1962 excluded.	• FBG • Blood glucose 2h after breakfast • DM: FBG >=7 mmol/L or previous self-reported diabetes diagnosed and under anti-diabetic medication	• ↑risk of DM in crude and adjusted analysis in early- and mid-childhood exposed groups vs unexposed group; • ↑ risk of DM in early and mid-childhood and degree of high-fat & high-salt dietary pattern in adulthood	• Missing data resulted in 837 being excluded compared to 939 included; • Analyses also conducted by current dietary pattern; • Significant additive interaction for all exposed groups vs unexposed with dietary-pattern of traditional. Healthy vs ↑fat and ↑salt diets.

BMI, body mass index; DM, diabetes mellitus; FBG, fasting blood glucose; FPG, fasting plasma glucose; HbA1c, Glycosylated hemoglobin; HOMA, homeostatic model assessments; HOMA-β, HOMA β cell function; HOMA-IR, HOMA insulin resistance; IDI, insulin disposition index; IGT, impaired glucose tolerance; OGTT; oral glucose tolerance test; RPG, random plasma glucose

Figure 1. A systematic review flow diagram of the number of articles identified and examined at each stage of the review.

Fig 1 footnotes
*Reference lists from identified full text articles