**Meat, poultry and fish and risk of colorectal cancer: pooled analysis of data from the UK Dietary Cohort Consortium.**

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**Abstract**

A number of epidemiological studies using food frequency questionnaires report that high intakes of red and processed meat increase the risk of colorectal cancer. In the UK Dietary Cohort Consortium, we examined the associations of meat, poultry and fish intakes with colorectal cancer risk using standardised individual dietary data pooled from seven UK prospective studies. Four to seven-day diet diaries were analysed, disaggregating the weights of meat, poultry and fish from composite foods in order to investigate dose-response relationships in detail. 579 cases of colorectal cancer were identified and matched with 1,996 controls on age, sex and recruitment date. Conditional logistic regression models were used to estimate the odds ratios for colorectal cancer associated with meat, poultry and fish intakes, adjusting for age, height, weight, smoking, and intakes of alcohol, energy and dietary fibre. Disaggregated intakes were moderately low, e.g. mean red meat intakes were 38.2g/day among male and 16.0g/day among female controls. For red and processed meat combined, the odds ratio for highest (median 97.1g/day) compared with lowest (median 0.6g/day) intake was 0.88 (95% CI 0.65-1.20), P for trend=0.68. High (median 44.3g/day) compared with low (median 0g/day) intake of fatty fish was associated with reduced risk of colorectal cancer: OR 0.73 (95% CI 0.54-0.98) but there was no evidence of a linear trend (P=0.33). This study using pooled data from prospective diet diaries, among cohorts with low to moderate meat intakes, shows little evidence of association between consumption of red and processed meat and colorectal cancer risk.

Keywords: prospective; diet diary; meat; fish; colorectal cancer.

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## Introduction

Studies using food frequency questionnaires or diet histories to assess dietary intakes have typically reported an increased risk of colorectal cancer for those with higher intakes of red or processed meat[1]. Based on a systematic review of published worldwide data, an expert panel concluded that the evidence for an increased risk of colorectal cancer associated with high intakes of red and processed meat was convincing[2]. Some published data also suggest that high intakes of fish, particularly fatty fish, may be associated with reduced risk of colorectal cancer[3].

The use of diet diaries provides an opportunity to measure the intakes of foods that are of interest in relation to cancer risk more accurately than food frequency questionnaires, by quantifying portion sizes as well as capturing detail on cooking ingredients and composition of mixed food items[4,5]. Correlations with some biomarkers of dietary intake including urinary nitrogen and potassium have been shown to be higher for diet diary data than food frequency data[6]. In this analysis we examine data from the UK Dietary Cohort Consortium to assess the risk for colorectal cancer associated with intakes of meat, poultry and fish. This pooled analysis used standardised dietary data from diet diaries in case control studies nested within prospective cohorts. Particular attention was paid to quantifying disaggregated intakes of meat, poultry and fish from all sources including mixed dishes[7], with the aim of clarifying dose response relationships.

## Materials and Methods

### *Participants*

We analysed data from the UK Dietary Cohort Consortium, pooling and standardising four- to seven-day diet diary data for 2575 individuals participating in seven established prospective cohort studies in the UK. The cohorts included were: EPIC-Norfolk, EPIC-Oxford, Guernsey Study, MRC National

Survey of Health and Development (NSHD), Oxford Vegetarian Study, Whitehall II, UK Women's Cohort Study (UKWCS) (Table 1). Participants in each cohort gave informed consent and each cohort study obtained ethics committee approval from the relevant agencies: the methods of recruitment, study design and relevant ethics committee approval have been described for these cohorts in detail elsewhere[8-14]. Each cohort collected dietary information using four-day (Guernsey, Oxford Vegetarian Study, UKWCS), five-day (NSHD) or seven-day diet diaries (EPIC-Norfolk, EPIC-Oxford, Whitehall II), either at recruitment or during a subsequent survey. Participants were asked to record all the foods and drinks they consumed, usually within times of day presented in the food diary (e.g. before breakfast; breakfast; mid-morning), and with photographs showing servings of representative food items to aid estimation of portion sizes[8,15]. Information on age, sex, height, weight, smoking, education, socio-economic status, use of hormone replacement therapy among women, physical activity, family history of colorectal cancer and use of aspirin was collected either in interviews or in questionnaires administered prior to completion of the diet diary.

*Follow-up and ascertainment of cases of colorectal cancer*

Follow-up for diagnosis of colorectal cancer is provided through record linkage with the Office of National Statistics and local cancer registries, and in Guernsey through local record linkage. The 9$^{th}$ and 10$^{th}$ Revisions of the International Statistical Classification of Diseases, Injuries and Causes of Death (ICD) were used, and cancer of the colorectum was defined as codes 153.0-154.1 or C18-20, as appropriate. For each cohort in this study, closure dates of the study period were defined as the latest dates of complete follow-up for both cancer incidence and vital status. For this study, the last dates of follow-up for each cohort were: EPIC-Norfolk 31.12.06, EPIC-Oxford 31.12.04, Guernsey Study 31.12.03, NSHD 31.12.06, Oxford Vegetarian Study 31.12.04, Whitehall II Study 31.12.04, UKWCS 31.12.06 (Table 1).

Case patients were individuals who were free of cancer (except non-melanoma skin cancer) at the time of diary completion and who developed colorectal cancer at least 12 months after the date of diary commencement and before the end of the study period, defined for each study centre by the latest date of complete follow-up for cancer incidence and vital status. Diet diary data for the current analysis was available for 321 cases in EPIC-Norfolk, 133 cases in EPIC-Oxford, 29 cases in the Guernsey Study, 8 cases in NHSD, 34 cases in the Oxford Vegetarian Study, 51 cases in Whitehall II and 37 cases in the UKWCS.

*Selection of matched controls*

Each case patient was matched to control participants, selected at random from all cohort members free of cancer (except non-melanoma skin cancer) at the date of diary commencement, and free of colorectal cancer at the end of follow-up, within the appropriate stratum of matching criteria. Controls had at least as much follow-up duration as their matched cases. Matching criteria included: study centre, age at enrolment (± 3 years), sex, and calendar month of diary completion (±3 months). The number of controls varied by study and was as follows: EPIC-Norfolk 4 controls, EPIC-Oxford 2 or 3 controls, Guernsey 2 or 3 controls, NSHD 4 controls, Oxford Vegetarian Study 2 or 3 controls, Whitehall II 4 controls, UKWCS 4 or 5 controls.

*Measurement of food and nutrient intake*

Information from the diet diaries was coded to give nutrient intakes and food groups information, mainly using the DINER program, described previously[16]. For diaries completed by the UKWCS participants, 94 (47%) were coded using the DINER program and 107 (53%) were coded using the DANTE program[17]. A comparison of nutrients from 100 diaries coded using both these two methods showed excellent agreement; geometric mean intakes of energy and carbohydrate from DANTE were both just 2% lower (95% CI, 0% to 5%) than from DINER. The NSHD diaries had previously been coded using the DIDO program[18] and it was decided to retain these data for use because the DIDO coding program used portion sizes contemporary to the dates of diary completion (1989). Each matched set was coded with either DINER, DANTE, or DIDO and the conditional logistic regression analysis ensured that comparisons of rates for estimating odds ratios were only done within coding program type.

The following food groups were defined and used in these analyses: red meat, processed meat, poultry, white fish and fatty fish. Red meat included beef, pork, lamb, and the meat from burgers and other non-processed meat items made with these meats; it did not include offal or offal products and it excluded processed red meat. Processed meat included ham, bacon, the meat component of sausages and other items made with processed meat. Poultry (white meat) included chicken, turkey and the flesh component of products made with poultry. White fish included all non-fatty fish, not including shellfish. Fatty fish included salmon, herring, fresh tuna and other oily fish. Dietary fibre was defined as non-starch polysaccharides (NSP).

Work within the NHSD cohort has demonstrated that the consumption of meat, poultry and fish is overestimated if composite foods are not disaggregated to their component parts[7]. To obtain an accurate estimate of red meat, processed meat, poultry or fish consumed, additional coding was applied to existing McCance and Widdowson food codes to record the proportion of meat, poultry or fish found in mixed products such as meat pies, pasta dishes, sausages, stews and curries, including products containing only small fractions of meat, poultry or fish. Information from Prynne and coworkers[7], recipe information in McCance and Widdowson’s The Composition of Foods[19] and its supplements and recipe information from food product manufacturers were used to estimate the proportions of meat, poultry, or fish in mixed dishes. For example, 100g of lasagne was recorded as providing 18g of red meat and 110g of baked chicken kiev was recorded as providing 40g poultry.

*Statistical methods*

Spearman's rank correlation coefficients were calculated for the correlation between dietary variables, among men and women separately. Conditional logistic regression models were applied to calculate odds ratios and 95% confidence intervals (95% CI) for each of colorectal cancer (using data for all participants), colon cancer (using data for cases having the ICD codes 153.0-153.9 or C18, together with their matched controls) and rectal cancer (ICD codes 154.0-154.1 or C19-20), according to categories of intake of meat, fish and poultry. The distributions of intake were not normal, with a number of non-consumers. To divide the data reasonably evenly and use comprehensible cutpoints we categorised intakes using cutpoints used in the European Prospective Investigation into Cancer and Nutrition (EPIC) study of meat and colorectal cancer risk[20]. To test for linear trends in odds ratio over the distribution of intake the continuous intake variable was used.

To allow for the effects of potential confounders (in addition to the matching criteria, controlled for by design), the analyses were adjusted for anthropometric and lifestyle factors. Since the age matching between cases and controls was ± 3 years, age was additionally adjusted for in years. The analyses were additionally adjusted for height (<170, 170-174, 175-179, ≥180 cm for men; <157, 157-160, 161-164, ≥165 cm for women), weight (<72, 72-78, 79-85, ≥86 kg for men; <58, 58-64, 65-71, ≥72 kg for women), smoking (never, past, present), alcohol intake (<1, 1-7, 8-19, ≥20 g/day), energy intake (sex-specific fifths) and NSP (sex-specific fifths). For each of height, weight and smoking a small proportion (<2%) of values was unknown; these values were included in the analyses using a separate "missing" category for each of these variables. Five further potential confounding factors (education level, socio-economic status, physical activity, family history of colorectal cancer and aspirin use) were of interest, but were available only for a subset of the main dataset. Therefore the analyses were repeated among participants with full information on all these variables, and then repeated with additional adjustment for these variables. To investigate potential interaction of dietary fibre (NSP) intakes with the association of meat, poultry or fish with risk of colorectal cancer, analyses were repeated within categories of NSP intake: <18g/day and ≥18g/day.

Two-sided P values less than 0.05 were considered statistically significant. All statistical analyses were done using Stata version 10 (StataCorp, Texas, US).

## Results

579 individuals (266 men and 313 women) diagnosed with colorectal cancer from recruitment until the end of follow-up and 1996 matched participants (980 men and 1016 women) without colorectal cancer were included in the analyses. Table 1 shows characteristics and case numbers in the study cohorts. Cases and controls did not differ significantly in height, weight, smoking, education level, physical activity, social class or intakes of energy, alcohol or dietary fibre (data not shown).

Figure 1 shows the intakes of red meat, processed meat, poultry, white fish and fatty fish for each cohort, within cases and controls. Mean intakes of meat, poultry and fish were low to moderate, and varied between the cohorts. However, in most cohorts there was little difference between the cases and controls.

Table 2 shows odds ratios for colorectal, colon and rectal cancer according to intakes of meat, poultry and fish. There was very little evidence that intakes of red meat, processed meat, poultry, white fish or fatty fish were associated with risk for colorectal, colon or rectal cancer cancer. The odds ratios for colorectal cancer, compared with the lowest intake group of <25g/day, were 0.81 (95% CI 0.61-1.09), 0.79 (0.59-1.07) and 0.88 (0.65-1.20) for combined intakes of red and processed meat of 25-<50, 50-<75 and 75 or more g/day, respectively. For colorectal cancer, the linear trend for poultry consumption was borderline statistically significant (P=0.05), but the categorical analysis showed that no odds ratio was significantly different from unity. Consumption of 30g or more of fatty fish was associated with a reduced risk of colorectal cancer: OR=0.73 (95% CI 0.54-0.98); however, in the test for trend using the continuous food intake variable, there was no evidence of a linear association

(P=0.33). In the analyses for rectal cancer, risk was decreased for those consuming 30g or more processed meat daily (OR 0.50, 95% CI 0.29 – 0.85), however, the test for trend was not significant (P=0.07).

There was no evidence of heterogeneity in risk estimates between the studies contributing data to the analysis: P for heterogeneity in trends between studies for colorectal cancer risk ranged from 0.18 to 0.95.

These analyses were repeated among subsets of participants for whom additional information was available on physical activity (not available for 7% of participants, including all of Guernsey, NSHD), family history of colorectal cancer (not available for 33% of participants, including all of EPIC-Oxford, Guernsey, OVS, NSHD, Whitehall), use of aspirin at recruitment (not available for 27% of participants, including all of Guernsey, NSHD, Whitehall), socio-economic status (not available for 5% of participants) and attained education level (not available for 8% of participants, including all of OVS). There was no material difference in the risk estimates in these analyses, with or without adjustment for these additional covariables.

To investigate the hypothesis that associations between red and processed meat and risk for colorectal cancer are present only among those with low dietary fibre (NSP) intakes, we repeated the analyses within subgroups of non-starch polysaccharides intake. There was no evidence of any associations between red meat, processed meat, or red and processed meat combined, among participants with an NSP intake of less than 18g per day, nor among participants with an NSP intake of 18g per day or more (P values for trend test 0.4 to 0.9).

## Discussion

In this study of 579 colorectal cancer cases using prospective diet diary data, we found no statistically significant dose response associations between intakes of meat, poultry or fish and risk for colorectal cancer, colon cancer or rectal cancer. There was some evidence of a reduction in risk of colorectal cancer among those with the highest intakes of fatty fish, and of rectal cancer among those with the highest intakes of processed meat, but no evidence of a linear trend for either of these associations.

This is the first large prospective study on this topic to use diet diaries to assess dietary data. Diet diaries are intended to comprehensively capture the range of food items and preparation methods used by study participants and they allow the estimation of actual portion sizes as consumed[4,5]. Improving the accuracy of dietary assessment helps to reduce the impact of measurement error on estimates of relative risk associated with intakes of foods and nutrients. Nitrogen and potassium intakes estimated using diet diaries are more closely correlated with urinary nitrogen and potassium than are intakes of those nutrients estimated using a food frequency questionnaire[5,6,21]. This means we would expect major, frequently consumed protein sources including meat to be estimated better by the diary method than using a food frequency questionnaire, whereas for fatty fish, which is an infrequently consumed food item, there may not be an important difference between the dietary assessment methods[16].

In this study, particular attention was given to accurately estimating intakes of meat, poultry and fish within composite foods (foods comprising more than one ingredient). Based on work within the NSHD cohort[7], as well as using information from recipes published in the McCance and Widdowson "The Composition of Foods" series[19] and its supplements and food product manufacturers, the percentage by weight of meat, poultry or fish was assigned for each individual food item containing these ingredients. In the work by Prynne and coworkers, after disaggregating the component parts of composite foods, the group estimates of consumption were lower by approximately 50-70% for red meat, 30-48% for processed meat, and 20-43% for poultry[7]. Thus, the intakes reported here are likely to be lower than those reported in studies which have used the total weight of a composite food item containing meat to be the estimate of meat intake. It is also possible that associations for meat, poultry or fish reported in previous studies have been confounded by other components of mixed dishes, for example, sources of saturated fat such as pastry or dairy ingredients.

Dietary intakes were measured prospectively; subsequently, incident cases were identified and controls were selected to match closely on important criteria including age, sex, study centre and calendar month of dietary assessment. Thus, the study was designed to avoid bias in reporting associated with the diagnosis of colorectal cancer. The influence of measurement error on risk estimates in prospective studies needs to be considered. Repeat disaggregated data on meat, poultry and fish intakes are not available, which precludes us from adjusting our estimates for measurement error. However, given that our results show null associations between the food items studies and risk of colorectal cancer, we would not expect adjustment for measurement error in this study to alter the interpretation of our findings.

We were able to examine the influence of several potentially confounding factors on the observed relationships between meat, poultry or fish intakes and risk of colorectal cancer. Energy intake, alcohol intake and NSP intake were available for all participants; height, weight and smoking were available for 99% of participants. Further information on physical activity, education level, socioeconomic status, family history of colorectal cancer and aspirin use were only available for between 67% and 93% of participants. However, when the analyses were repeated within subsets of participants with full data on these factors, there was no evidence of associations between meat, poultry or fish intake and risk of colorectal cancer, before or after further adjustment for these factors.

Prospective studies which included participants with much higher intakes of red and processed meat[1,23] have shown increased risks for colorectal cancer associated with these intakes, but it is not clear whether there is an increase in risk for colorectal cancer for participants with low to moderate intakes of red and processed meat. A meta-analysis of prospective data showed borderline significant evidence for a reduced risk of colorectal cancer associated with high intakes of fish[3]. In the current study the results show some limited evidence of reduced risk of colorectal cancer for participants with the highest intakes of fatty fish, but there was no evidence of a linear trend in this association and more data are needed on this.

In summary, this study of prospectively measured diet diary data and risk for colorectal cancer shows little evidence that red meat, processed meat, poultry, fish, white fish or fatty fish are related to the risk of colorectal cancers.

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**Table 1.** Characteristics of the 7 cohorts participating in the UK Dietary Cohort Consortium.

| Cohort | Participants | Dates of diet diary completion | Last follow up date | Cases | Controls | Mean age at baseline (SD; yrs) |
|---|---|---|---|---|---|---|
| EPIC Norfolk | General population in Norfolk | 1993-1998 | 31.12.2006 | 321 | 1284 | 64.0 (7.9) |
| EPIC Oxford | General population and vegetarians in the UK | 1993-1998 | 31.12.2004 | 133 | 318 | 61.5 (10.5) |
| Guernsey Study | Women living on Guernsey | 1987-1991 | 31.12.2003 | 29 | 57 | 59.3 (10.0) |
| National Survey of Health and Development (NSHD) | March 1946 birth cohort in England, Scotland and Wales | 1989 | 31.12.2006 | 8 | 32 | 43 (0.0) |
| Oxford Vegetarian Study | Vegetarians and non-vegetarians in the UK | 1985-1987 | 31.12.2004 | 34 | 79 | 55.7 (14.0) |
| UK Women's Cohort Study | Middle aged women in the UK | 1999-2003 | 31.12.2006 | 37 | 164 | 63.2 (8.1) |
| Whitehall II | Civil servants in the UK | 1991-1993 | 30.09.2005 | 56 | 224 | 53.3 (4.9) |

**Table 2.** Association between consumption of meat, poultry and fish and colorectal, colon and rectal cancers in the UK Dietary Cohort Consortium.

| Food intake (g/day) | Median intake within category (g/day) | No cases/ no. controls | OR (95% CI) for colorectal cancer* | No. cases/ no. controls | Colon cancer | No. cases/ no. controls | Rectal cancer |
|---|---|---|---|---|---|---|---|
| Red meat | | | | | | | |
| <5 | 0 | 156/427 | 1.00 (reference) | 104/269 | 1.00 (reference) | 52/158 | 1.00 (reference) |
| 5-<25 | 16.6 | 124/462 | 0.84 (0.62-1.14) | 77/302 | 0.73 (0.50-1.08) | 47/160 | 1.11 (0.66-1.89) |
| 25-<50 | 36.7 | 157/599 | 0.82 (0.61-1.11) | 98/414 | 0.70 (0.49-1.01) | 59/185 | 1.20 (0.71-2.02) |
| ≥50 | 68.4 | 142/508 | 0.91 (0.66-1.24) | 101/331 | 0.92 (0.62-1.35) | 41/177 | 0.87 (0.50-1.52) |
| $P_{trend}$** | | | *0.89* | | *0.72* | | *0.78* |
| Processed meat | | | | | | | |
| <5 | 0 | 173/477 | 1.00 (reference) | 110/314 | 1.00 (reference) | 63/163 | 1.00 (reference) |
| 5-<15 | 10.2 | 101/419 | 0.78 (0.58-1.06) | 67/285 | 0.81 (0.56-1.18) | 34/134 | 0.70 (0.41-1.21) |
| 15-<30 | 21.6 | 176/560 | 1.02 (0.78-1.35) | 111/374 | 1.02 (0.72-1.45) | 65/186 | 1.00 (0.62-1.61) |
| ≥30 | 43 | 129/540 | 0.76 (0.56-1.03) | 92/343 | 0.90 (0.62-1.31) | 37/197 | 0.50 (0.29-0.85) |
| $P_{trend}$** | | | *0.36* | | *0.94* | | *0.07* |
| Red and processed meat | | | | | | | |
| <25 | 0.6 | 172/464 | 1.00 (reference) | 113/295 | 1.00 (reference) | 59/169 | 1.00 (reference) |
| 25-<50 | 38.7 | 126/478 | 0.81 (0.61-1.09) | 78/333 | 0.68 (0.47-0.99) | 48/145 | 1.08 (0.66-1.79) |
| 50-<75 | 61.5 | 130/513 | 0.79 (0.59-1.07) | 86/340 | 0.76 (0.53-1.10) | 44/173 | 0.86 (0.51-1.45) |
| ≥75 | 97.1 | 151/541 | 0.88 (0.65-1.20) | 103/348 | 0.88 (0.60-1.29) | 48/193 | 0.83 (0.49-1.42) |
| $P_{trend}$** | | | *0.68* | | *0.74* | | *0.22* |
| Poultry | | | | | | | |
| <1 | 0 | 211/588 | 1.00 (reference) | 131/397 | 1.00 (reference) | 80/191 | 1.00 (reference) |

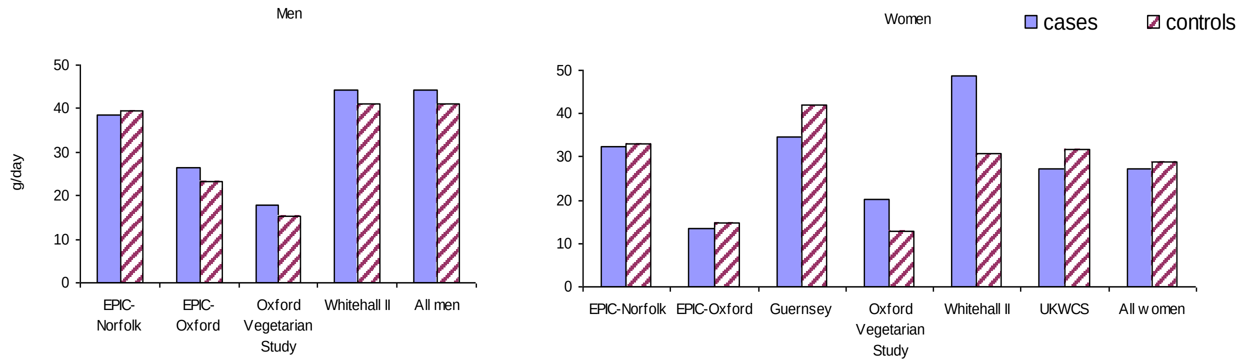
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 1-<15 | 9.2 | 86/332 | 0.81 (0.60-1.09) | 56/217 | 0.86 (0.59-1.25) | 30/115 | 0.65 (0.39-1.10) |
| 15-<30 | 21.4 | 136/504 | 0.84 (0.64-1.10) | 96/317 | 1.10 (0.79-1.53) | 40/187 | 0.49 (0.30-0.79) |
| ≥30 | 44.7 | 146/572 | 0.80 (0.62-1.04) | 97/385 | 0.87 (0.63-1.19) | 49/187 | 0.69 (0.44-1.09) |
| $P_{trend}$** | | | *0.05* | | *0.11* | | *0.32* |
| White fish | | | | | | | |
| <1 | 0 | 230/747 | 1.00 (reference) | 153/490 | 1.00 (reference) | 77/257 | 1.00 (reference) |
| 1-<15 | 11.1 | 91/325 | 1.07 (0.80-1.44) | 51/209 | 0.90 (0.62-1.31) | 40/116 | 1.36 (0.85-2.20) |
| 15-<30 | 20.4 | 172/578 | 1.12 (0.88-1.42) | 119/376 | 1.15 (0.86-1.54) | 53/202 | 1.07 (0.70-1.65) |
| ≥30 | 40.5 | 86/346 | 0.86 (0.64-1.16) | 57/241 | 0.80 (0.56-1.14) | 29/105 | 1.04 (0.61-1.78) |
| $P_{trend}$** | | | *0.56* | | *0.32* | | *0.63* |
| Fatty fish | | | | | | | |
| <1 | 0 | 309/961 | 1.00 (reference) | 199/629 | 1.00 (reference) | 110/332 | 1.00 (reference) |
| 1-<15 | 8.6 | 95/403 | 0.81 (0.62-1.06) | 58/260 | 0.77 (0.55-1.08) | 37/143 | 0.86 (0.55-1.35) |
| 15-<30 | 21.4 | 105/317 | 1.08 (0.83-1.41) | 74/204 | 1.24 (0.90-1.73) | 31/113 | 0.78 (0.48-1.28) |
| ≥30 | 44.3 | 70/315 | 0.73 (0.54-0.98) | 49/223 | 0.73 (0.51-1.04) | 21/92 | 0.68 (0.39-1.18) |
| $P_{trend}$** | | | *0.33* | | *0.21* | | *0.95* |

* Adjusted for age, height, weight, smoking, intakes of energy, alcohol and non-starch polysaccharides, in addition to the matching criteria.

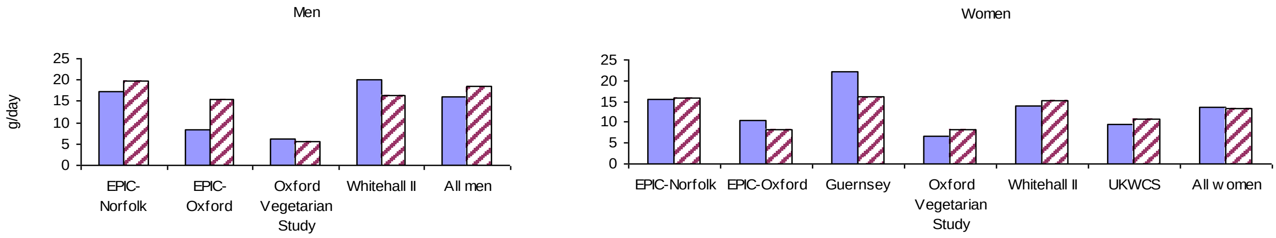
**The test for trend was obtained using the continuous food intake variable.

**Figure 1.** Intakes of meat, poultry and fish within cases and controls, by cohort*.

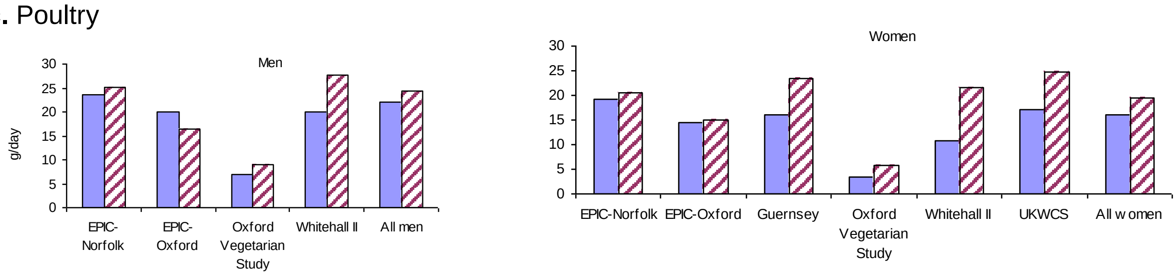
**1a.** Red meat



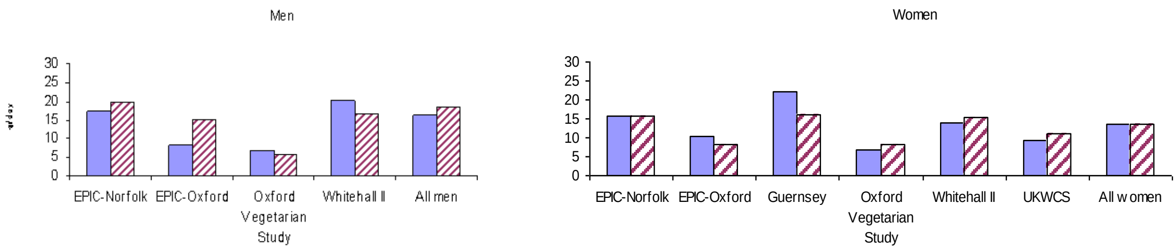

**1b.** Processed meat



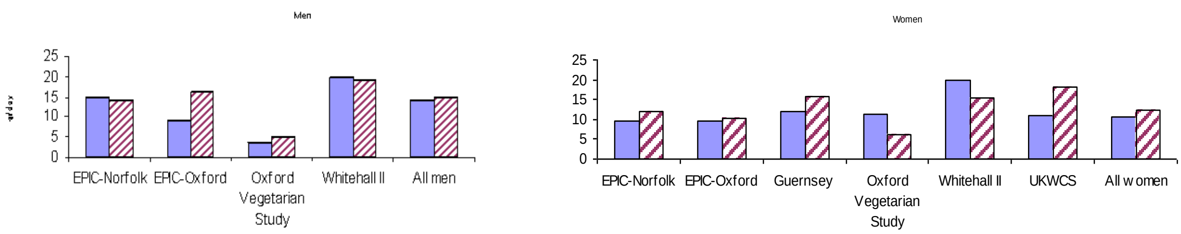

**1c.** Poultry




**1d.** White fish




**1e.** Fatty fish




*Case control numbers were too low to examine NSHD separately.