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Annual Ambient UVB at Wavelengths that Induce Vitamin D Synthesis is Associated with Reduced Oesophageal and Gastric Cancer Risk: a Nested Case-Control Study

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Short title: UVB and Oesophageal and Gastric Cancer Risk

ABSTRACT

Vitamin D has been shown to be beneficial at reducing the risk of cancer, however studies examining oesophageal and gastric cancer have been scarce and findings inconsistent. The UK Biobank cohort was used for this nested case-control study (N=3,732). Primary, incident oesophageal and gastric cancer cases diagnosed after recruitment were identified via linkage to National Cancer Registries. Tropospheric emissions monitoring internet service database was used to calculate ambient annual

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UVB dose (D-UVB). Conditional logistic regression was used to investigate the relationship between annual ambient D-UVB and risk of oesophageal and gastric cancer and odds ratios (OR) are reported. In total, 373 oesophageal and 249 gastric cancer cases and 3,110 age- and gender-matched controls were included in the study. We found a strong inverse association between annual ambient UVB and odds of developing oesophageal or gastric cancer: compared to the lowest tertile, OR for the highest tertile was 0.64 (95%CI:0.51-0.79) in adjusted analysis. The association was strengthened when restricted to oesophageal cancer (OR=0.60;95%CI:0.45-0.80), and oesophageal adenocarcinoma cases (OR=0.48;95%CI:0.34-0.68). Similar results were found in unadjusted and stratified analysis. In conclusion, ambient UVB radiation is inversely associated with the development of oesophageal and gastric cancer, even in a high latitude country.

Keywords: oesophageal cancer; gastric cancer; UV radiation; UVB; vitamin D

INTRODUCTION

An estimated 456,000 new cases and 400,000 deaths in 2012, make oesophageal cancer the eighth most common cancer worldwide, but the sixth most common cause of cancer death due to a very poor survival (1). Similarly, gastric cancer is the fifth most common malignancy, but the third leading cause of cancer death worldwide (951,000 new cases and 723,000 deaths) (1). Two main histological subtypes of oesophageal cancers are adenocarcinoma and squamous cell carcinoma (SCC). Notably, the two subtypes differ in terms of their risk factors and incidence patterns (2-4). The majority of adenocarcinoma cases develop from Barrett's mucosa in the lower third of the oesophagus, while SCC typically occurs in the upper two-thirds of the oesophagus (3).

Synthesis of vitamin D in the skin following exposure to UVB from sunlight is the main source of vitamin D for humans, particularly among those who do not take vitamin D supplements (5). Vitamin D has been associated with reduced risk of multiple internal cancers (6-8). For oesophageal and gastric cancer, the evidence is sparse and vastly mixed: a recent systematic review (9) found an *increased* risk of oesophageal cancer overall with higher 25-hydroxyvitamin D [25(OH)D] concentration; a non-significantly *increased* risk for adenocarcinoma with higher dietary vitamin D intake, but a non-significantly *decreased* risk for SCC (10-12). Finally, a single study reported a significantly *decreased* risk of adenocarcinoma with higher lifetime UVB exposure (13). In a similar study, a non-significantly *decreased* risk of gastric cancer was observed with higher 25(OH)D, but a non-significantly *increased* risk with higher vitamin D intake (14). Therefore, mixed evidence from a limited number of mostly small studies prevents any conclusions from being drawn and highlights the need for more research (14, 15). Additionally, dietary sources of vitamin D from food have been shown to be poor determinants of vitamin D in some studies (8, 16) and therefore the results from studies measuring only dietary sources from foods should be interpret with caution. 25(OH)D is known as the best measure of vitamin D status *at a given point in time*, however, it is strongly affected by the season of blood draw and other, sometimes particular circumstances (e.g. return from sun-holiday); moreover, it does not capture exposure over a prolonged time period. This may be important when examining the relationship between 25(OH)D and conditions which take time to develop. Furthermore, 25(OH)D concentration *at the time of blood draw* may be of limited relevance: for example, vitamin D status *at cancer diagnosis* is of limited value when assessing the role in cancer *occurrence*. Therefore, using UVB instead of 25(OH)D offers some important advantages for epidemiological studies, provided it can be captured accurately – but this has largely not been the case to date, as most studies use total UV dose, ignore important factors such as cloud cover and ozone, or assume equal exposure for the large geographical region; in addition, majority of published studies that used UV are ecological in design.

In this study, we seek to examine the association between the annual ambient UVB at the place of residence and oesophageal and gastric cancer occurrence in a large, nested prospective case-control study. The UVB measure we used improves on variables used previously in multiple dimensions, and offers the most accurate estimate of ambient, vitamin-D-synthetizing UVB dose to date.

METHODS

Study participants. Data from the UK Biobank cohort of 500,000 community-dwelling individuals (aged 40-70 years) recruited across England, Scotland and Wales between 2006 and 2010 were used (17). Ethical approval was obtained and all participants gave informed consent (18). This project was conducted under application number 12653. A subset for this cohort with information on residential location was selected for this study (n=466,206).

Participants filled in a number of questionnaires, providing information on socio-demographic characteristics and lifestyle, including: age, gender, residential location, education [a number was assigned in a hierarchical fashion; 1: none of the above, 2: Certificate of Secondary Education or ordinary level general certificate of education, 3: advanced level general certificate of education, 4: National Vocational Qualification or Higher National Diploma/Certificate, 5: other professional qualifications, 6: college or university degree], smoking, alcohol use, vitamin D supplement use [derived from reported use of supplements], diet (frequency of consumption of different foods, including oily fish), physical activity levels in the last four weeks [None; low: walking for pleasure (not as a means of transport) and light DIY (eg: pruning, watering the lawn); medium: heavy DIY (eg: weeding, lawn mowing, carpentry, digging) and other exercises (eg: swimming, cycling, keep fit, bowling); high: strenuous sports], ease of tanning, use of sun protection and time spent outdoors (average number of hours/day in summer and winter; the average of these was calculated and categorised: 0-2 hrs/day represented "low" category, 2-5 hrs/day "intermediate" and >5hrs/day "high" level of time spent outdoors).

Information about participants' health was collected. Self-reported presence of different oesophageal or gastric problems was identified (including: gastro-oesophageal reflux, Barrett's oesophagus or gastric ulcers) and information on other conditions, such as osteoporosis, cardiovascular conditions, diabetes etc. was also collected. Participant's height and weight were taken and used to calculate BMI. More detail about the cohort can be found elsewhere (17, 19, 20).

Case-control cohort. Information on cancer diagnosis after recruitment to UK Biobank was gathered via linkage to the national cancer registries, which register and collect data on all cancers diagnosed. This provided detailed information on cancer characteristics including tumour histological information (oesophageal SCC or adenocarcinoma) and ICD-10-CM diagnosis codes – these were used to identify oesophageal and gastric cancer cases and obtain exact location of oesophageal cancer: C15.3/15.4 denoted upper and middle thirds of the oesophagus (typical location for SCC) and C15.5 denoted lower third (typical location for adenocarcinoma) (21).

Flow chart of participant selection is outlined in Figure 1. In total, there were 416,936 participants with no cancer diagnosis at the time of recruitment. There were 622 incident oesophageal and gastric cancer cases diagnosed after recruitment and these were kept in our study. Eligible controls were selected from the pool of individuals (n=396,306) who had never had a diagnosis of cancer (including skin cancer), either self-reported (N=7,213) and not on the national registry or registered in the national cancer registry (N=42,057). All individuals in the cohort who matched in gender and ± one year of age, for a given case were identified, and five were randomly chosen from that set for a given case, as age- and gender-matched controls. Controls could not be matched to cases based on their recruitment date as recruitment was linked to location; as a consequence, unwanted matching by UVB would occur.

UVB data source and annual ambient D-UVB. UV dose data from the Tropospheric Emissions Monitoring Internet Service (TEMIS) database (www.temis.nl/uvradiation/UVdose.html; version 2.0) were used (22). This service, provided by the Royal Netherlands Meteorological Institute in conjunction with the European Space Agency, determines the amount of UV radiation incident at the surface of earth in Wm^{-2}, as a function of the total ozone column (derived from satellite observations) and the solar zenith angle at a given local solar time (22). As the potential to induce vitamin D synthesis varies dramatically with wavelength, only UVB radiation restricted specifically to wavelengths which can induce cutaneous vitamin D production was considered (290-315 nm) and a weighting function was applied (peak synthesis occurs at 295-298 nm) (23). Moreover, a correction for cloud cover, surface elevation and surface UV reflectivity (UV albedo) is applied to the estimate. We denote this as D-UVB (further detail can be found elsewhere (15, 22)). The data are provided on a 0.25° × 0.25° (longitude × latitude) grid with each grid covering an area of approximately 28 km (north-south) X 17 km (east-west); 782 such grids cover Scotland, England and Wales.

Each participant was assigned a TEMIS grid cell based on their residential location. We calculated the annual ambient D-UVB dose for each participant by summing up daily doses, for the year (365 days) preceding the date of recruitment to UK biobank. Median and interquartile range (IQR) were reported. The annual ambient D-UVB at a given location does not change dramatically from year to year, hence the annual D-UVB dose in a 1-year period is predictive of the annual D-UVB dose for another 1-year period (Supporting Information Figure S1). As D-UVB is seasonal, it is important to include D-UVB doses for an entire year to prevent seasonal bias in the estimate leading to misclassification of D-UVB dose received by individuals. An example of D-UVB dose's over one location (London) is shown in Figure S1.

Statistical analysis. Conditional logistic regression was used for primary analysis of an association between annual D-UVB dose and odds of developing oesophageal or gastric cancer. Each case was assigned a specific 5 controls for this, so when stratified by cancer type/cancer location the controls were stratified according to their specific case's cancer diagnosis. Odds ratios and confidence intervals were calculated based on annual D-UVB tertiles (lowest as reference). P-for trend was also determined using annual D-UVB as a continuous variable. Covariates used in the final model were: smoking status, alcohol intake, BMI, qualifications, gastro-oesophageal reflux and gastric ulcers. Backwards stepwise regression was used to determine the final model and model was selected by balancing the lower numbers of AIC/BIC scores, along with a high r^2 number and a low number of missing samples. Other covariates were also considered, but excluded in final model (ease of tanning, use of sun protection, average sun exposure, skin colour, oily fish consumption, average time spent outdoors, egg consumption, vitamin D supplementation, osteoporosis, cardiovascular condition and diabetes). The 10% rule was also used to determine confounders, however, there was little difference observed between the two methods and the final method chosen was backwards stepwise regression. Conditional logistic regression based on quintiles of annual D-UVB and unconditional logistic regression using tertiles of annual D-UVB was also carried out and is shown in supplementary tables.

Stratified analysis by gender, BMI, age, cancer type, oesophageal cancer subtype (gastric cancer subtype was unavailable to us), cancer location, alcohol consumption, smoking status, time spent outdoors over summer and winter months, sun protection used, oily fish consumption, skin colour, physical activity and supplement use was also carried out. In accordance with Abnet et al. (10), unconditional logistic regression was used in stratified analysis. All analyses were performed in R (R Development Core Team, 2011) and using the R-package 'Survival' (Thomas Lumley, 2015). $P<0.05$ was considered statistically significant.

RESULTS

In total, 3732 participants (622 cases and 3110 controls) were included. Median age of the cohort was 63 years (inter quartiles range, IQR: 59-66 y) and nearly three quarters (74%) were male. Cases and controls were similar in terms of baseline characteristics, although there was a higher proportion of those with Barrett's oesophagus (2.1% vs 0.4%), gastric/oesophageal reflux (7% vs 5%) and those who are previous or current smokers (66% vs 52%) among cases (Table 1). Median time from attendance to cancer diagnosis was 3.09 years.

The majority of participants (78%) reported fair or very fair skin tone. A minority (3%) used vitamin D supplements, but 58% reported consuming oily fish more than once a week. There was little difference between cases and controls with oily fish consumption, supplement use and time spent outdoors, on average or during the summer. A general trend towards lower annual D-UVB doses as the latitude increases was observed (Figure 2a). Median annual ambient D-UVB among controls was 749 kJ/m^{-2} (IQR: 708-817 kJ/m^{-2}), and it was lower among cases (741 kJ/m^{-2}, IQR: 690-803 kJ/m^{-2})

(Figure 2b).

A significant inverse association was found between annual D-UVB and any primary upper gastrointestinal cancer, in unadjusted (OR=0.60, 95%CI: 0.49-0.75) and adjusted analysis (OR=0.64, 95%CI: 0.51-0.79) when comparing highest to lowest tertile (Table 2). Stratification by cancer location revealed a 40% decreased odds of developing oesophageal cancer (OR=0.60, 95%CI: 0.45-0.80), and 32% reduction in gastric cancer (OR=0.68, 95%CI: 0.48-0.96). The association was further strengthened when restricted to cancer of the lower third of the oesophagus (OR=0.47, 95%CI: 0.32-0.70), and adenocarcinoma, the histological type typical for this location (OR=0.48, 95%CI: 0.34-0.68). Near-identical results were found with unconditional logistic regression (Table S1). In addition, higher D-UVB dose were found to be associated with decreased risk of oesophageal and gastric cancer in stratified analysis (Table 3).

Greater risk reduction was observed when comparing tertile 3 to tertile 1 than tertile 2 to tertile 1. For example a risk of adenocarcinoma was reduced by 33% in Tertile 2, but by 36% in Tertile 3. This demonstrates that higher UVB has a greater effect on risk. Similar results were also found when annual D-UVB was split by quintiles, with decreasing odds of upper-gastrointestinal cancer incidence with increasing quintile: for quintiles 2-5 versus quintile 1, OR were: 0.66, 0.59, 0.59 and 0.52. Similar trend was also observed for when restricted by cancer type and subtype (Table S2).

DISCUSSION

In this large, prospective, nested case-control study, a strong protective effect of higher annual vitamin-D-inducing UVB dose at a place of residence on upper gastrointestinal cancer risk was observed: a 42% reduction in oesophageal cancer, and a 32% reduction in gastric cancer risk were found when comparing the highest tertile of UVB with the lowest. This relationship was particularly clear for oesophageal adenocarcinoma, where risk reduction of 52% was noted for those in the highest tertile of annual D-UVB. This inverse relationship persisted after adjustment for a range of potential confounders (including smoking, alcohol, BMI, and different oesophageal or gastric problems), in stratified analysis.

As UVB is one of the main sources of vitamin D in humans, the results in this study not only add important clarity to the relationship between UVB and upper gastrointestinal cancer risk, but they also have important implications for the relationship between vitamin D and cancer outcomes. Evidence of a protective effect vitamin D may have on cancer occurrence is accumulating in the literature, although findings from randomised clinical trials (RCTs), observational and experimental studies are often inconsistent (24). Some RCTs have noted significant associations between vitamin D and a reduction in cancer occurrence (7, 25), while others have not. With the latter being mainly due to poor study design and low supplementation dose given (26, 27).

In experimental studies, vitamin D has been shown to regulate multiple cellular processes that can affect cancer development and progression (28, 29), while risk reduction with better vitamin D status has been shown for multiple cancers in numerous epidemiological studies (7, 30), as has improved survival in cancer patients (31).

Our study adds important information to the sparse and conflicting evidence on the relationship between vitamin D and upper gastrointestinal cancer. In this study we investigated the impact of ambient D-UVB dose, a key determinant of vitamin D status, on upper gastrointestinal risk. A fundamental benefit of using D-UVB over 25(OH)D measurement is that exposure over a prolonged period of time is captured. Limiting the exposure only to the wavelengths that induce vitamin D synthesis further supports the hypothesis that the mechanism by which UV may affect cancer development is via vitamin D synthesis and its effect on vitamin D status.

Our results are in agreement with the findings of *Tran et al.* who have found that higher lifetime UV radiation was associated with reduced odds of oesophageal adenocarcinoma (13); however, we also observed some suggestive evidence of protective effect on SCC. Although the number of SCC cases was much smaller in both studies, we used a more specific exposure variable with greater spatial resolution, which potentially increased the power to detect associations in our study.

The study by Tran *et al.* was carried out in Australia, where UV radiation is dramatically higher than in the UK (32). Strikingly, the protective effect of ambient UVB was still observed in the current study, and it was stronger for higher annual D-UVB levels, suggesting a dose-response relationship. This was observed to a greater extend when split into annual D-UVB quintiles with a 34% reduction in oesophageal cancer incidence for quintile 2, a 41% reduction for quintile 3, a 41% reduction for quintile 4 and finally a 48% reduction in cancer incidence in quintile 5. This suggests that risk reduction could be even greater than what is reported here in some instances, including in individuals who spend more time outdoors or in regions with greater UVB radiation. For comparison, mean yearly UVB in Greece is almost 2.5-fold higher compared to Ireland or the UK (33).

Although none have used as detailed and vitamin-D specific UVB measure, other studies that investigated UVB dose have also found a reduction in cancer incidence (34, 35) and in addition to those, a large number of ecological studies are also in agreement with our study, reporting a strong inverse relationship between UV radiation and oesophageal and gastric cancer risk (36-41). Interestingly, a recent monograph by the World Health Organisation outlines evidence of an inverse relationship between UV radiation and breast, colorectal, prostate, ovarian cancers and Non-Hodgkin's lymphoma (42). This is the largest study to date examining the odds of developing oesophageal and gastric cancer in relation to vitamin D-inducing UVB dose. Nesting our case-control study within a large cohort with extensive data on many aspects of lifestyle and health allowed us to assigning controls to cases at 5:1 ratio, conduct matching by important characteristics, and adjust analysis for a range of potential confounders. Moreover, we had the information on vitamin D supplement use and oily fish consumption (the major dietary source of vitamin D) (43).

Furthermore, for this prospective study cancer data used was gathered via linkage to cancer registries, and due to available information and large sample we were able to examine different cancer types and subtypes independently, which is relevant due to the different underlying aetiologies and presents a serious limitation of most previous studies. Annual ambient D-UVB dose was calculated for each participant individually based on their residential address, offering much greater special resolution to previous studies. This D-UVB measure has also been corrected for many important factors which can considerably alter the D-UVB dose reaching earth, such as cloud cover, ozone column and altitude. The strength of a similar D-UVB measurement has been discussed in detail previously (15) and the D-UVB used in this paper is of even greater special and temporal resolution (22). Furthermore, this ambient UVB dose took into account annual D-UVB in order to get a “long term average” UVB dose for each individual, rather than a seasonally biased estimate, which would have been the case if a point estimate of vitamin D, such as 25(OH)D was utilised. We excluded all individuals who had received a diagnosis of cancer, including skin cancer. Due to an established relationship between higher UV exposure and skin cancer (44, 45), individuals who spend comparatively more time outdoors or sunbathing might have been selected-out from our study. As a consequence, the upper gastrointestinal risk reduction may be even greater than what is reported here.

Data used in this study was pre-collected data, therefore we did not have information about some factors of specific relevance to the research question: for example, Helicobacter Pylori is an important risk factor for gastric cancer and adjustment for this could have impacted the results. We did not have information on “utilisation” of ambient D-UVB for vitamin D production, however, exact information on this is virtually impossible to get for free-living subjects as it is determined by the length and timing of time spend outside, clothes and skin products warn, angle to the sun, choice of sunny or shady spot etc. Additionally, we did not have information on the duration individuals resided at the residence given, this is a limitation of this study as we calculated D-UVB dose based on their location of residence. We also unfortunately did not have 25(OH)D concentration, although strong relationship between D-UVB and 25(OH)D has been shown previously (15, 44). While 25(OH)D is the best marker of vitamin D status *at the time of blood draw*, this provides little information about the average exposure over a prolonged period of time cancer takes to develop (45).

In conclusion, our study found that ambient vitamin-D-synthetizing UVB radiation is inversely associated with the development of oesophageal and gastric cancer, even in a high latitude country with climatologically limited UVB radiation. Controlled exposure to sunlight, or vitamin D supplements might be an economical and safe way to reduce upper gastrointestinal cancer incidence, but further research is needed.

SUPPORTING INFORMATION

Additional Supporting Information can be found in the online version of this article:

Figure S1. Relationship between total annual ambient D-UVB from 2004-2016 in some UK cities.

Figure S2. Average daily D-UVB doses from 2014-2016 in London.

Table S1. Unconditional logistic regression looking at the association between annual D-UVB dose (tertiles) and the odds of developing oesophageal or gastric cancer, and stratified by cancer type.

Table S2. Conditional logistic regression looking at the association between quintiles of annual ambient D-UVB dose at a place of residence and oesophageal and gastric cancer occurrence, overall and by cancer location.

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References

1. Ferlay, J., I. Soerjomataram, R. Dikshit, S. Eser, C. Mathers, M. Rebelo, D.M. Parkin, D. Forman, and F. Bray, *Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012.* Int J Cancer, 2015. **136**(5): p. E359-86.
2. Arnold, M., I. Soerjomataram, J. Ferlay, and D. Forman, *Global incidence of oesophageal cancer by histological subtype in 2012.* Gut, 2015. **64**(3): p. 381-7.
3. Enzinger, P.C. and R.J. Mayer, *Esophageal cancer.* N Engl J Med, 2003. **349**(23): p. 2241-52.
4. Cook, M.B., W.H. Chow, and S.S. Devesa, *Oesophageal cancer incidence in the United States by race, sex, and histologic type, 1977-2005.* Br J Cancer, 2009. **101**(5): p. 855-9.
5. W.H.O., *Protection Against Exposure to Ultraviolet Radiation* 1995.
6. Holick, M.F., *Vitamin D: importance in the prevention of cancers, type 1 diabetes, heart disease, and osteoporosis.* The American Journal of Clinical Nutrition, 2004. **79**(3): p. 362-371.

7. Lappe, J.M., D. Travers-Gustafson, K.M. Davies, R.R. Recker, and R.P. Heaney, *Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial.* Am J Clin Nutr, 2007. **85**(6): p. 1586-91.
8. Giovannucci, E., Y. Liu, E.B. Rimm, B.W. Hollis, C.S. Fuchs, M.J. Stampfer, and W.C. Willett, *Prospective study of predictors of vitamin D status and cancer incidence and mortality in men.* J Natl Cancer Inst, 2006. **98**(7): p. 451-9.
9. Zgaga, L., F. O'Sullivan, M.M. Cantwell, L.J. Murray, P.N. Thota, and H.G. Coleman, *Markers of Vitamin D Exposure and Esophageal Cancer Risk: A Systematic Review and Meta-analysis.* Cancer Epidemiol Biomarkers Prev, 2016. **25**(6): p. 877-86.
10. Abnet, C.C., Y. Chen, W.H. Chow, Y.T. Gao, K.J. Helzlsouer, L. Le Marchand, M.L. McCullough, J.M. Shikany, J. Virtamo, S.J. Weinstein, Y.B. Xiang, K. Yu, W. Zheng, D. Albanes, A.A. Arslan, D.S. Campbell, P.T. Campbell, R.B. Hayes, R.L. Horst, L.N. Kolonel, A.M. Nomura, M.P. Purdue, K. Snyder, and X.O. Shu, *Circulating 25-hydroxyvitamin D and risk of esophageal and gastric cancer: Cohort Consortium Vitamin D Pooling Project of Rarer Cancers.* Am J Epidemiol, 2010. **172**(1): p. 94-106.
11. Chen, W., S.M. Dawsey, Y.L. Qiao, S.D. Mark, Z.W. Dong, P.R. Taylor, P. Zhao, and C.C. Abnet, *Prospective study of serum 25(OH)-vitamin D concentration and risk of oesophageal and gastric cancers.* Br J Cancer, 2007. **97**(1): p. 123-8.
12. Lipworth, L., M. Rossi, J.K. McLaughlin, E. Negri, R. Talamini, F. Levi, S. Franceschi, and C. La Vecchia, *Dietary vitamin D and cancers of the oral cavity and esophagus.* Ann Oncol, 2009. **20**(9): p. 1576-81.
13. Tran, B., R. Lucas, M. Kimlin, D. Whiteman, and R. Neale, *Association between ambient ultraviolet radiation and risk of esophageal cancer.* Am J Gastroenterol, 2012. **107**(12): p. 1803-13.
14. Khayatzadeh, S., A. Feizi, P. Saneei, and A. Esmaillzadeh, *Vitamin D intake, serum Vitamin D levels, and risk of gastric cancer: A systematic review and meta-analysis.* J Res Med Sci, 2015. **20**(8): p. 790-6.
15. O'Sullivan, F., Laird, E., Kelly, D., van Geffen, J., van Weele, M., McNulty, H., Hoey, L., Healy, M., McCarroll, K., Cunningham, C., Casey, M., Ward, M., Strain, J. J.m Molloy, A. M., Zgaga, L., *Ambient UVB Dose and Sun Enjoyment Are Important Predictors of Vitamin D Status in an Older Population.* J Nutr, 2017. **147**(5): p. 858-868.
16. Touvier, M., M. Deschasaux, M. Montourcy, A. Sutton, N. Charnaux, E. Kesse-Guyot, K.E. Assmann, L. Fezeu, P. Latino-Martel, N. Druesne-Pecollo, C. Guinot, J. Latreille, D. Malvy, P. Galan, S. Hercberg, S. Le Clerc, J.C. Souberbielle, and K. Ezzedine, *Determinants of vitamin D status in Caucasian adults: influence of sun exposure, dietary intake, sociodemographic, lifestyle, anthropometric, and genetic factors.* J Invest Dermatol, 2015. **135**(2): p. 378-88.
17. Sudlow, C., J. Gallacher, N. Allen, V. Beral, P. Burton, J. Danesh, P. Downey, P. Elliott, J. Green, M. Landray, B. Liu, P. Matthews, G. Ong, J. Pell, A. Silman, A. Young, T. Sprosen, T. Peakman, and R. Collins, *UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age.* PLoS Med, 2015. **12**(3): p. e1001779.
18. Biobank, U. *Consent forms for UK Biobank*. 30/1/17]; Available from: http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=200.
19. Elliott, P. and T.C. Peakman, *The UK Biobank sample handling and storage protocol for the collection, processing and archiving of human blood and urine.* Int J Epidemiol, 2008. **37**(2): p. 234-44.
20. *UK Biobank*. Available from: http://www.ukbiobank.ac.uk.
21. Yang, P.C. and S. Davis, *Incidence of cancer of the esophagus in the US by histologic type.* Cancer, 1988. **61**(3): p. 612-7.
22. Zempila, M.-M., J.H. van Geffen, M. Taylor, I. Fountoulakis, C. Meleti, and D. Balis, *TEMIS UV product validation using NILU-UV ground-based measurements in Thessaloniki, Greece.*
23. Bouillon, R., J. Eisman, M. Garabedian, M.F. Holick, J. Kleinschmidt, T. Suda, I. Terenetskaya, and A.R. Webb, *Action Spectrum for the Production of Previtamin D3 in Human Skin*. 2006, UDC: Vienna. p. 612.014.481-06.
24. Theodoratou, E., I. Tzoulaki, L. Zgaga, and J.P.A. Ioannidis, *Vitamin D and multiple health*

outcomes: umbrella review of systematic reviews and meta-analyses of observational studies and randomised trials. BMJ, 2014. **348**(apr01 2): p. g2035-g2035.
25. Bolland, M.J., A. Grey, G.D. Gamble, and I.R. Reid, *Calcium and vitamin D supplements and health outcomes: a reanalysis of the Women's Health Initiative (WHI) limited-access data set.* Am J Clin Nutr, 2011. **94**(4): p. 1144-9.
26. Grant, W.B., B.J. Boucher, H.P. Bhattoa, and H. Lahore, *Why vitamin D clinical trials should be based on 25-hydroxyvitamin D concentrations.* The Journal of Steroid Biochemistry and Molecular Biology, 2017.
27. Grant, W.B. and B.J. Boucher, *Randomized controlled trials of vitamin D and cancer incidence: A modeling study.* PLoS One, 2017. **12**(5): p. e0176448.
28. Feldman, D., A.V. Krishnan, S. Swami, E. Giovannucci, and B.J. Feldman, *The role of vitamin D in reducing cancer risk and progression.* Nat Rev Cancer, 2014. **14**(5): p. 342-57.
29. Deeb, K.K., D.L. Trump, and C.S. Johnson, *Vitamin D signalling pathways in cancer: potential for anticancer therapeutics.* Nat Rev Cancer, 2007. **7**(9): p. 684-700.
30. Garland, C.F., F.C. Garland, E.D. Gorham, M. Lipkin, H. Newmark, S.B. Mohr, and M.F. Holick, *The role of vitamin D in cancer prevention.* Am J Public Health, 2006. **96**(2): p. 252-61.
31. Vaughan-Shaw, P.G., F. O'Sullivan, S.M. Farrington, E. Theodoratou, H. Campbell, M.G. Dunlop, and L. Zgaga, *The impact of vitamin D pathway genetic variation and circulating 25-hydroxyvitamin D on cancer outcome: systematic review and meta-analysis.* Br J Cancer, 2017.
32. Gies, P., C. Roy, J. Javorniczky, S. Henderson, L. Lemus-Deschamps, and C. Driscoll, *Global Solar UV Index: Australian measurements, forecasts and comparison with the UK.* Photochem Photobiol, 2004. **79**(1): p. 32-9.
33. O'Neill, C.M., A. Kazantzidis, M.J. Ryan, N. Barber, C.T. Sempos, R.A. Durazo-Arvizu, R. Jorde, G. Grimnes, G. Eiriksdottir, V. Gudnason, M.F. Cotch, M. Kiely, A.R. Webb, and K.D. Cashman, *Seasonal Changes in Vitamin D-Effective UVB Availability in Europe and Associations with Population Serum 25-Hydroxyvitamin D.* Nutrients, 2016. **8**(9).
34. Grant, W.B., *Solar ultraviolet irradiance and cancer incidence and mortality*. 2008. p. 16-30.
35. Grant, W.B., *Roles of Solar UVB and Vitamin D in Reducing Cancer Risk and Increasing Survival.* Anticancer Res, 2016. **36**(3): p. 1357-70.
36. Grant, W.B., *An ecological study of cancer incidence and mortality rates in France with respect to latitude, an index for vitamin D production.* Dermatoendocrinol, 2010. **2**(2): p. 62-7.
37. Boscoe, F.P. and M.J. Schymura, *Solar ultraviolet-B exposure and cancer incidence and mortality in the United States, 1993-2002.* BMC cancer, 2006. **6**.
38. Grant, W.B., *Does solar ultraviolet irradiation affect cancer mortality rates in China?* Asian Pac J Cancer Prev, 2007. **8**(2): p. 236-42.
39. Chen, W., M. Clements, B. Rahman, S. Zhang, Y. Qiao, and B.K. Armstrong, *Relationship between cancer mortality/incidence and ambient ultraviolet B irradiance in China.* Cancer Causes Control, 2010. **21**(10): p. 1701-9.
40. Grant, W.B., *An estimate of premature cancer mortality in the U.S. due to inadequate doses of solar ultraviolet-B radiation.* Cancer, 2002. **94**(6): p. 1867-75.
41. Grant, W.B. and C.F. Garland, *The association of solar ultraviolet B (UVB) with reducing risk of cancer: multifactorial ecologic analysis of geographic variation in age-adjusted cancer mortality rates.* Anticancer Res, 2006. **26**(4a): p. 2687-99.
42. W.H.O., *Radiation: A review of Human Carcinogens.* IRAC monographs, 2012. **100D**.
43. Zgaga, L., E. Theodoratou, S.M. Farrington, F. Agakov, A. Tenesa, M. Walker, S. Knox, A. Michael Wallace, R. Cetnarskyj, G. McNeill, J. Kyle, M.E. Porteous, M.G. Dunlop, and H. Campbell, *Diet, environmental factors, and lifestyle underlie the high prevalence of vitamin D deficiency in healthy adults in Scotland, and supplementation reduces the proportion that are severely deficient.* Journal of Nutrition, 2011. **141**(8): p. 1535-1542.
44. Kelly, D., E. Theodoratou, S. Farrington, R. Fraser, H. Campbell, M.G. Dunlop, and L. Zgaga, *The Contributions of Adjusted Ambient UVB at the Place of Residence and Other Determinants to Serum 25-Hydroxyvitamin D Concentrations.* Br J Dermatol, 2015.

45. Wang, Y., E.J. Jacobs, M.L. McCullough, C. Rodriguez, M.J. Thun, E.E. Calle, and W.D. Flanders, *Comparing methods for accounting for seasonal variability in a biomarker when only a single sample is available: insights from simulations based on serum 25-hydroxyvitamin d.* Am J Epidemiol, 2009. **170**(1): p. 88-94.

Table 1: Baseline characteristics of participants †.

Characteristics	*Cases Oes‡ N=373 (60%)††*	*Controls Oes N=1865 (60%)‡‡*	*Cases Gas‡ N=249 (40%)††*	*Controls Gastric N=1245 (40%)‡‡*	*All cases N=622 (100%)††*	*All controls N=3110 (100%)‡‡*
Sex						
Female	86 (23)	430 (22)	75 (30)	375 (29)	161 (26)	805 (26)
Male	287 (77)	1435 (74)	174 (70)	870 (67)	461 (74)	2305 (74)
Age (median, IQR)	63 (59-66)	63 (59-66)	63 (59-67)	63 (59-67)	63 (59-66)	63 (59-66)
BMI (NA=18) §						
Underweight/Normal (<24.9)	78 (21)	494 (32)	65 (26)	346 (28)	143 (23)	840 (27)
Overweight (25-29.9)	123 (33)	584 (38)	120 (48)	584 (47)	290 (47)	1481 (48)
Obese (>30)	170 (46)	464 (30)	64 (26)	306 (25)	187 (30)	770 (25)
Skin colour (NA=53)						
Very fair/Fair	292 (79)	1421 (77)	188 (76)	953 (78)	480 (78)	2374 (78)
Light olive/Dark olive	75 (20)	375 (20)	54 (22)	231 (19)	129 (21)	606 (20)
Brown/Black	2 (1)	39 (2)	5 (2)	38 (3)	7 (1)	77 (2)
Smoking Status (NA=18)						
Current smoker	72 (19)	177 (10)	45 (18)	114 (9)	117 (19)	291 (9)
Past smoker	191 (51)	802 (43)	99 (40)	515 (42)	290 (47)	1317 (43)
Never smoked	109 (29)	879 (47)	103 (42)	606 (49)	212 (34)	1485 (48)
Alcohol Consumption (NA=4)						
Current drinker	334 (90)	1746 (94)	223 (92)	1150 (92)	557 (90)	2896 (93)
Past drinker	27 (7)	62 (3)	17 (7)	50 (4)	44 (7)	112 (4)
Never drank	11 (3)	54 (3)	3 (1)	45 (4)	19 (3)	99 (3)
Oily Fish ||						
Low (0-<1 times/wk.)	160 (43)	765 (41)	95 (38)	529 (42)	255 (41)	1294 (42)
Medium (1-4 times/wk.)	207 (55)	1073 (58)	153 (61)	703 (56)	360 (58)	1776 (57)
High (≥5 times/wk.)	6 (2)	27 (1)	1 (1)	13 (1)	7 (1)	40 (1)
Vitamin D Supplement						
Yes	11 (3)	64 (3)	8 (3)	47 (4)	19 (3)	111 (3)
No	362 (97)	1801 (97)	241 (97)	1198 (96)	603 (97)	2999 (97)
Barrett's oesophagus						
Yes	9 (2)	8 (0)	4 (2)	6 (0)	13 (2)	14 (<1)
No	364 (98)	1857 (100)	245 (98)	1239 (100)	609 (98)	3096 (100)
Gastric ulcers						
Yes	6 (2)	15 (1)	7 (3)	17 (1)	13 (2)	32 (1)
No	367 (98)	1850 (99)	242 (97)	1228 (99)	609 (98)	3087 (99)
Oesophageal/Gastric Reflux						
Yes	30 (8)	115 (4)	12 (5)	85 (4)	42 (7)	149 (5)
No	343 (92)	1750 (67)	237 (95)	1160 (58)	580 (93)	2961 (95)
D-UVB (median, IQR) (kJ/m^2)	740 (690-803)	749 (710-818)	741 (689-804)	748 (706-815)	740 (690-803)	749 (708-815)
D-UVB						
Tertile 1 (<717 kJ/m^2)	155 (42)	561 (30)	109 (39)	418 (34)	264 (42)	979 (32)
Tertile 2 (718-796 kJ/m^2)	113 (30)	645 (35)	69 (28)	415 (33)	182 (29)	1060 (34)
Tertile 3 (>797 kJ/m^2)	105 (28)	659 (35)	71 (29)	412 (33)	176 (17)	1071 (34)
Physical Activity (NA=17) ¶						
None	28 (8)	95 (5)	17 (7)	51 (4)	41 (6)	259 (8)
Low	111 (30)	440 (24)	68 (27)	269 (22)	179 (29)	709 (23)

Medium	210 (56)	1166 (63)	144 (58)	816 (66)	354 (59)	1982 (64)
High	22 (6)	158 (8)	19 (8)	101 (8)	41 (6)	146 (5)

Characteristics	*Cases Oes*[7] *N=373*	*Controls Oes* *N=1865*	*Cases Gas*[3] *N=249*	*Controls Gastric* *N=1245*	*All cases* *N=622*	*All controls* *N=3110*
Time spent outdoors Summer (NA=37)						
Low (0-2 hrs/day)	109 (30)	500 (27)	69 (28)	354 (28)	178 (29)	845 (28)
Medium (2.1-5 hrs/day)	151 (40)	843 (46)	100 (41)	558 (45)	251 (41)	1401 (45)
High (>5.1hrs/day)	109 (30)	505 (27)	77 (31)	331 (27)	186 (30)	836 (27)
Time spent outdoors Winter (NA=35)						
Low (0-2 hrs/day)	260 (70)	1294 (70)	160 (66)	875 (71)	420 (68)	2169 (70)
Medium (2.1-5 hrs/day)	81 (22)	424 (23)	64 (26)	266 (22)	145 (24)	690 (22)
High (>5.1hrs/day)	29 (8)	135 (7)	20 (8)	87 (7)	49 (8)	222 (7)
Sun Protection use (NA=6)						
Always	55 (14)	210 (17)	44 (18)	303 (16)	99 (16)	513 (17)
Mostly	104 (28)	360 (29)	78 (31)	608 (33)	182 (29)	968 (31)
Sometimes	144 (39)	473 (38)	90 (36)	688 (37)	234 (38)	1161 (37)
Rarely/Never	63 (17)	190 (15)	34 (14)	256 (14)	97 (16)	446 (14)
Do not go out in the sun	7 (2)	9 (1)	2 (1)	6 (0)	9 (1)	15 (<1)
Education (NA=43) ‡						
None	95 (26)	430 (23)	86 (35)	286 (23)	181 (29)	897 (24)
CSE or O-levels	57 (15)	249 (14)	38 (15)	172 (14)	95 (15)	516 (14)
A-levels	16 (4)	107 (6)	12 (5)	67 (5)	28 (5)	202 (5)
NVQ or Higher National Diploma/Certificate	55 (15)	230 (12)	34 (14)	158 (13)	89 (14)	477 (13)
Other professional qualifications	56 (15)	288 (16)	23 (9)	187 (15)	79 (13)	554 (15)
College or university degree	91 (25)	540 (29)	53 (22)	359 (29)	144 (23)	1043 (28)

Footnote:

† Controls include age- and gender-matched participants with no history of cancer in 5:1 ratio. NA values shown are for both cases and controls.

‡ Gas: gastric cancer cases; oes: oesophageal cancer; CSEs: Certificate of Secondary Education; O levels: Ordinary level general certificate of education; A levels: advanced level general certificate of education; NVQ: National Vocational Qualification

§ WHO classification was used for categorisation into underweight, normal, overweight and obese.

||Oily fish consumption of less than once a week was considered “low”, 1-4 times a week “intermediate” and 5-6 times per week/more or more “high”

¶ None; low: walking for pleasure (not as a means of transport) and light DIY (eg: pruning, watering the lawn); medium: heavy DIY (eg: weeding, lawn mowing, carpentry, digging) and other exercises (eg: swimming, cycling, keep fit, bowling); high: strenuous sports.

†† Percentage of all cases

‡‡ percentage of all controls

Table 2. Conditional logistic regression looking at the association between annual ambient D-UVB dose at a place of residence and oesophageal and gastric cancer occurrence, overall and by cancer location. Cases were matched to controls by age and sex in a 1:5 ratio. Each case was assigned a specific 5 controls so when stratified by cancer type/ cancer location the controls were stratified according to their specific case's cancer diagnosis. Abbreviations: Unadj: unadjusted; Adj: Adjusted; Oes: Oesophageal; AC: adenocarcinoma; SCC: squamous cell carcinoma. Adjusted model was adjusted for: smoking status, alcohol intake, BMI, highest qualifications, oesophageal-gastric reflux, gastric ulcers.

Age- and gender-matched controls	Cancer risk	Number of cases	Number of controls	**Tertile 1 (<717 kJ/m²)**			**Tertile 2 (718-796 kJ/m²)**					**Tertile 3 (>797 kJ/m²)**					**p-Trend**
				N cases	**N controls**	**OR**	**N cases**	**N controls**	**OR**	**95% CL**	**p-val**	**N cases**	**N controls**	**OR**	**95% CL**	**p-val**	
All	Unadj	622	3110	264	978	Ref	182	1059	0.64	0.52 - 0.78	**$2x10^{-5}$**	176	1073	0.60	0.49 - 0.75	**$3.6x10^{-5}$**	**$2.8x10^{-8}$**
All	*Adj*	622	3110	264	978	Ref	182	1059	0.66	0.54 - 0.82	**$2x10^{-4}$**	176	1073	0.64	0.54 - 0.82	**$5x10^{-5}$**	**$7.8x10^{-7}$**
Cancer location	*Unadj Oesophageal*	373	1865	155	561	Ref	113	645	0.63	0.48 - 0.82	**$7.5x10^{-4}$**	105	659	0.57	0.43 - 0.75	**$6.2x10^{-5}$**	**$8.2x10^{-6}$**
Cancer location	*Adj Oesophageal*	373	1865	155	561	Ref	113	645	0.66	0.50 - 0.87	**$3.6x10^{-3}$**	105	659	0.60	0.45 - 0.80	**$5.6x10^{-4}$**	**$1.6x10^{-4}$**
Cancer location	*Unadj Up/mid third oes*	50	250	18	70	Ref	17	82	0.80	0.38 - 1.68	0.56	15	98	0.59	0.28 - 1.26	0.17	**0.02**
Cancer location	*Adj Up/mid third oes*	50	250	18	70	Ref	17	82	0.91	0.41 - 2.03	0.82	15	98	0.68	0.28 - 1.62	0.38	**0.04**
Cancer location	*Unadj Lower third oes*	198	990	91	309	Ref	91	342	0.58	0.40 - 0.83	**$3x10^{-3}$**	48	339	0.47	0.32 - 0.70	**$1.4x10^{-4}$**	**$2.21x10^{-5}$**
Cancer location	*Adj Lower third oes*	198	990	91	309	Ref	59	342	0.58	0.38 - 0.81	**2.410^{-3}**	48	339	0.48	0.32 - 0.73	**$4.3x10^{-4}$**	**$1.7x10^{-4}$**
Cancer location	*Unadj Gastric*	249	1245	109	417	Ref	69	414	0.64	0.46 - 0.89	**$8.1x10^{-3}$**	71	414	0.66	0.47 0.91	**0.01**	**$7.6x10^{-4}$**
Cancer location	*Adj Gastric*	249	1245	109	417	Ref	69	414	0.66	0.47 - 0.93	**0.02**	71	414	0.68	0.48 - 0.96	**0.03**	**$1x10^{-3}$**

Histology	*Unadj Oes AC*	243	1215	107	362	Ref	76	434	0.59	0.42 - 0.81	**1.4x10^{-3}**	60	419	0.48	0.34 - 0.68	**3.6x10^{-5}**	**1.3x10^{-5}**
	Adj Oes AC	243	1215	107	362	Ref	76	434	0.61	0.43 - 0.86	**4x10^{-3}**	60	419	0.52	0.36 - 0.75	**4x10^{-4}**	**3x10^{-4}**
	Unadj Oes SCC	76	380	29	107	Ref	23	123	0.68	0.38 - 1.24	0.21	24	150	0.58	0.32 - 1.06	*0.08*	*0.09*
	Adj Oes SCC	76	380	29	107	Ref	23	123	0.67	0.35 - 1.29	0.23	24	150	0.54	0.27 - 1.07	*0.08*	0.10

Table 3. Unconditional Logistic regression looking at the association between tertiles of annual ambient D-UVB at a place of residence on the risk of developing primary upper gastrointestinal cancer (oesophageal and gastric), stratified by various important variables using age- and gender-matched controls. Tertiles of ambient annual D-UVB at place of residence were used to explore the relationship. Adjusted model has been adjusted for: smoking status, BMI, alcohol consumption, oesophageal-gastric reflux, highest qualifications, and gastric ulcers, minus what was being stratified.

Cancer risk	Number of cases	Number of controls	Tertile 1 (<717 kJ/m2)			Tertile 2 (718-796 kJ/m2)					Tertile 3 (>797 kJ/m2)				
			N cases	N controls	OR	N cases	N controls	OR	95% CL	p-val	N cases	N controls	OR	95% CL	p-val
BMI															
Under/Healthy weight	37	301	62	230	Ref	33	275	0.39	0.24-0.64	**0.0002**	48	335	0.54	0.35-0.82	**0.005**
Overweight	114	602	120	481	Ref	88	522	0.70	0.51-0.95	**0.02**	82	478	0.70	0.50-0.95	**0.02**
Obese/extremely obese	91	306	82	265	Ref	60	255	0.78	0.52-1.18	0.24	45	2550	0.64	0.41-0.99	**0.05**
Age															
<63	116	593	127	488	Ref	87	483	0.76	0.55-1.04	**0.09**	82	535	0.66	0.48-0.91	**0.01**
≤63	127	622	137	490	Ref	95	576	0.56	0.42-0.76	**0.0002**	94	538	0.64	0.47-0.86	**0.004**
Sex					Ref										
Female	34	170	69	265	Ref	50	245	0.76	0.49-1.17	0.21	42	295	0.50	0.32-0.77	**0.002**
Male	209	1045	195	713	Ref	132	814	0.60	0.46-0.77	**8×10^{-5}**	134	778	0.70	0.55-0.91	**0.007**
Alcohol															
Never[7]	6	23	6	28	Ref	8	26	1.09	0.27-0.43	0.90	5	45	0.57	0.13-0.23	0.43
Previous	11	43	19	35	Ref	10	35	0.50	0.18-1.30	0.16	15	42	0.73	0.29-1.78	0.49
Current	225	1146	238	915	Ref	163	998	0.64	0.51-0.81	**0.0002**	156	983	0.65	0.52-0.82	**0.0003**
Smoking															
Never	65	553	96	469	Ref	62	499	0.65	0.45-0.92	**0.02**	54	518	0.54	0.37-0.79	**0.001**
Previous	128	536	115	401	Ref	90	469	0.66	0.48-0.90	**0.009**	85	445	0.69	0.50-0.95	**0.02**
Current	50	121	52	102	Ref	28	86	0.63	0.35-1.03	0.11	37	104	0.81	0.48-1.37	0.43

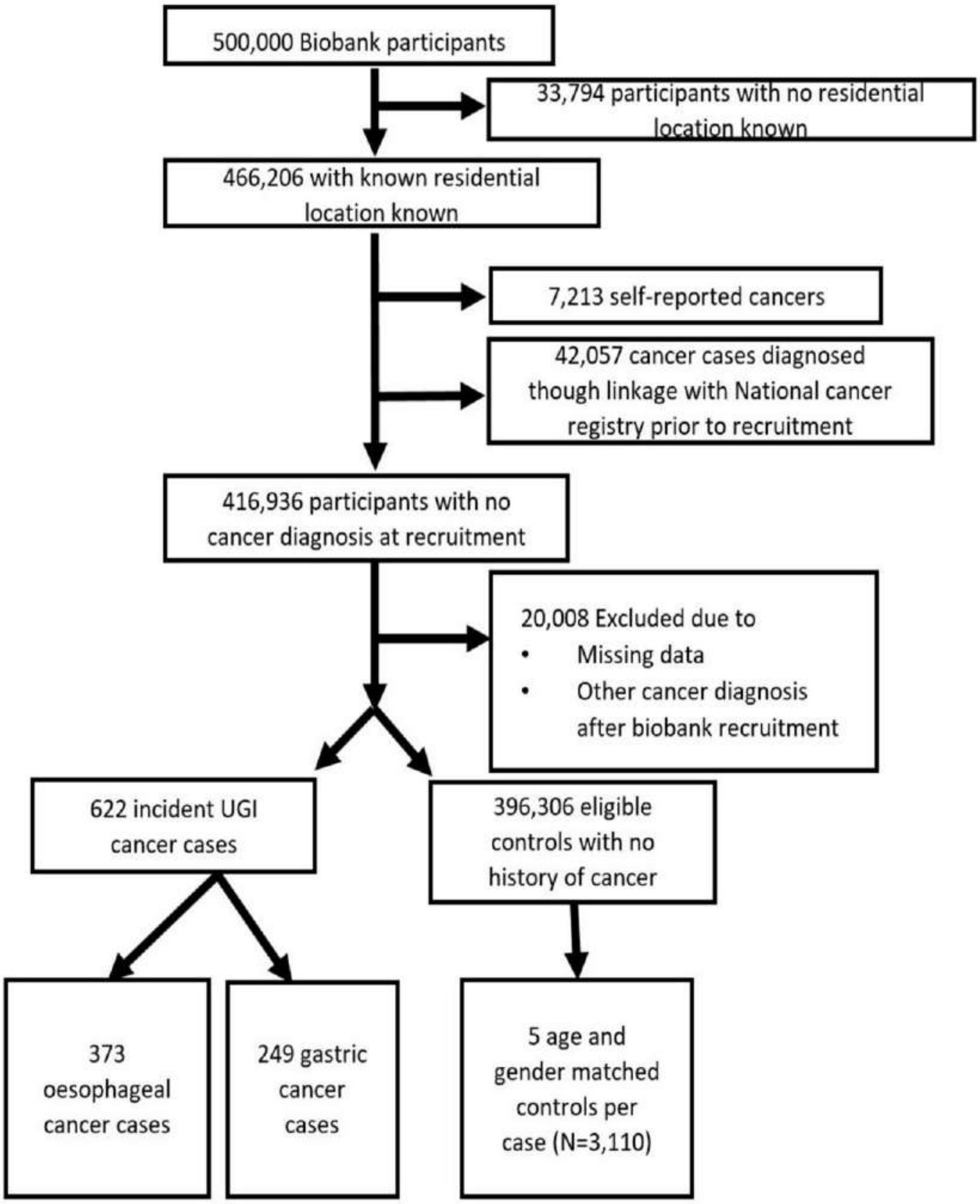
Cancer risk	Number of cases	Number of controls	Tertile 1			Tertile 2					Tertile 3				
			N cases	N controls	OR	N cases	N controls	OR	95% CL	p-val	N cases	N controls	OR	95% CL	p-val
Oily Fish consumption [4]															
High/Medium	138	708	161	558	Ref	103	633	0.53	0.40-0.70	**$1x10^{-5}$**	103	624	0.62	0.46-0.82	**0.0007**
Low	105	507	103	420	Ref	79	426	0.86	0.60-1.20	0.38	73	449	0.71	0.50-1.01	*0.06*
Time spent outdoors [4]															
High	47	247	52	183	Ref	48	224	0.75	0.47-1.19	0.22	32	184	0.65	0.39-1.09	0.10
Medium	128	643	130	542	Ref	87	575	0.65	0.48-0.88	**0.006**	89	548	0.71	0.52-0.97	**0.03**
Low	68	325	82	253	Ref	47	260	0.56	0.37-9.86	**0.008**	55	341	0.56	0.37-0.83	**0.005**
Time spent outdoors in summer [4]															
High	74	343	82	249	Ref	63	313	0.59	0.40-0.87	**0.008**	41	273	0.47	0.30-0.73	**0.0007**
Medium	101	540	100	467	Ref	71	482	0.71	0.50-1.00	**0.05**	80	454	0.85	0.61-1.19	0.36
Low	66	325	79	246	Ref	46	256	0.56	0.36-0.86	**0.009**	53	342	0.54	0.35-0.80	**0.003**
Time spent outdoors in winter [4]															
High	19	94	15	70	Ref	18	82	0.88	0.38-2.03	0.76	16	69	1.07	0.52-2.61	0.88
Medium	53	283	59	239	Ref	47	238	0.83	0.53-1.28	0.40	39	213	0.71	0.44-1.14	0.16
Low	168	829	185	662	Ref	115	727	0.58	0.45-0.77	**0.0001**	120	781	0.62	0.48-0.81	**0.0004**
Skin colour [5]															
Very fair/fair	196	946	198	764	Ref	803	149	0.74	0.58-0.94	**0.02**	133	807	0.69	0.53-0.88	**0.004**
Olive/dark olive	44	225	61	190	Ref	216	30	0.42	0.25-0.69	**0.0008**	38	200	0.56	0.35-0.91	**0.02**
Sun protection															
Always/Mostly	104	576	128	496	Ref	76	504	0.60	0.43-0.82	**0.002**	77	481	0.66	0.48-0.91	**0.01**
Sometimes/Never/rarely	136	636	134	478	Ref	100	548	0.65	0.48-0.89	**0.006**	97	581	0.65	0.47-0.88	**0.005**
Supplement use [6]															
No	237	1178	256	953	Ref	181	1017	0.67	0.54-0.84	**0.0004**	166	1028	0.64	0.51-0.80	**0.0001**

Physical Activity															
High	17	114	19	82	Ref	11	89	0.47	0.18-1.14	0.10	11	88	0.50	0.19-1.20	0.13
Medium	135	762	142	590	Ref	100	690	0.60	0.45-0.80	**0.0006**	112	701	0.68	0.51-0.90	**0.007**
Low	73	275	80	260	Ref	58	219	0.88	0.58-1.33	0.54	41	231	0.63	0.40-0.98	**0.04**
None	45	146	22	44	Ref	13	56	0.43	0.16-1.08	*0.08*	10	46	0.53	0.19-1.41	0.21

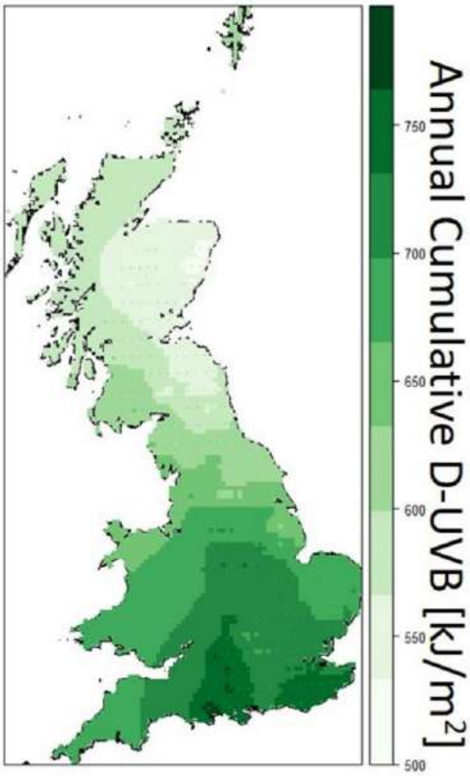
Figure Legends:

Figure 1. Flow chart of case and control selection from UK Biobank cohort. This figure demonstrates how we extracted the relevant incident cases and controls for the study. Controls had no previous history of cancer and no cancer diagnosis (including non-melanoma skin cancer) at follow-up. Cases were matched to controls in a 1:5 ratio. Controls were matched in two ways-by gender and ±1 year age and then further matched on smoking status, alcohol consumption and BMI.

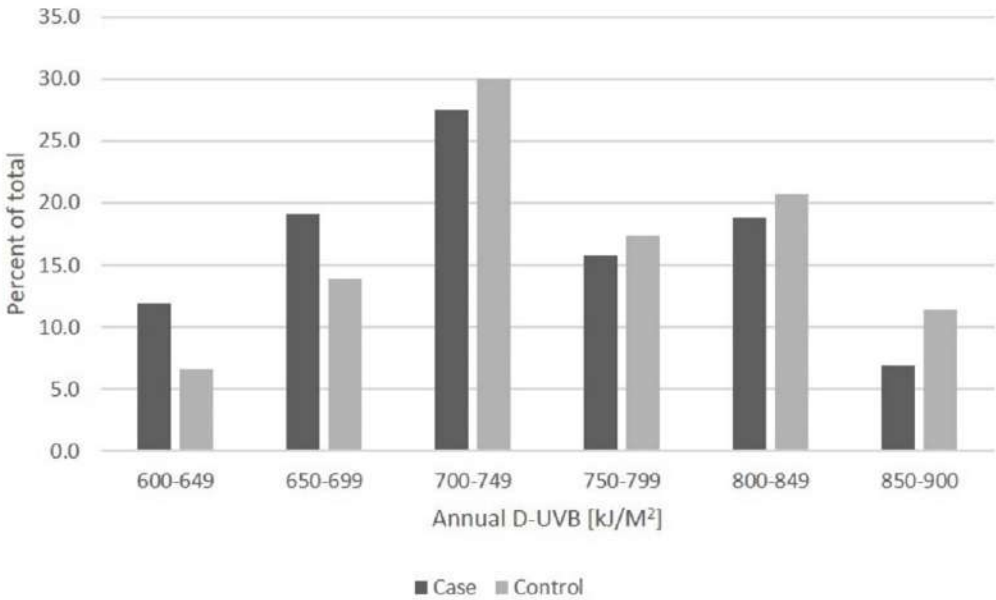
Figure 2. This figure shows **A**) the average cumulative annual D-UVB dose (kJ/m^2) over the UK from 2004-2017 from the Tropospheric Emissions Monitoring Internet Service (TEMIS) database. This was calculated by first finding the mean D-UVB dose per day from 2004-2017 in each grid. Each of the 365 daily D-UVB doses for each grid was then summed to give a cumulative dose for each of the 782 grids covering the UK. This was then mapped to the UK map to demonstrate a latitude gradient **B**) a histogram of the distribution of annual D-UVB doses in both cases (n=622) and controls (n=3110).


500,000 Biobank participants
33,794 participants with no residential location known
466,206 with known residential location known
7,213 self-reported cancers
42,057 cancer cases diagnosed though linkage with National cancer registry prior to recruitment
416,936 participants with no cancer diagnosis at recruitment
20,008 Excluded due to
• Missing data
• Other cancer diagnosis after biobank recruitment
622 incident UGI cancer cases
396,306 eligible controls with no history of cancer
373 oesophageal cancer cases
249 gastric cancer cases
5 age and gender matched controls per case (N=3,110)

A


Annual Cumulative D-UVB [kJ/m²]
750
700
650
600
550
500

B


35.0
30.0
25.0
20.0
15.0
10.0
5.0
0.0
Percent of total
600-649
650-699
700-749
750-799
800-849
850-900
Annual D-UVB [kJ/M²]
Case
Control