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1 **Investigating nutrition and lifestyle factors as determinants of abdominal obesity: An**  
2 **environment-wide study**

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46 **ABSTRACT**

47 **Background:** The increasing global trends in obesity and its associated burden of disease  
48 indicate a need to identify modifiable determinants of obesity.

49 **Methods:** A total of 182 nutrition and lifestyles factors were investigated in relation to  
50 abdominal obesity among 7,403 male and 8,328 female participants of the Third U.S.  
51 National Health and Examination Survey (NHANES III). We used the first phase (1988-  
52 1991) of the NHANES III to identify factors with a false discovery rate (FDR) of <5%. Of  
53 these, we tentatively replicated our findings in the second phase (1992-1994) of the survey.  
54 Principal component analysis was performed to identify unobserved factors underlying the  
55 association between validated factors and abdominal obesity, defined as waist circumference  
56 >88 cm for women and >102 cm for men.

57 **Results:** We found 5 tentatively replicated factors showing significant associations with  
58 abdominal obesity in men: serum  $\alpha$ -carotene,  $\beta$ -carotene, serum  $\beta$ -cryptoxanthin, serum  
59 vitamin D, and vigorous physical activity. In women, 7 factors were identified: serum  $\alpha$ -  
60 carotene,  $\beta$ -carotene, serum  $\beta$ -cryptoxanthin, serum vitamin C, serum vitamin D, vigorous  
61 physical activity, and aspartame intake. In contrast to the other factors which showed inverse  
62 associations with abdominal obesity, aspartame intake displayed a positive relationship with  
63 this outcome (OR: 1.18, 95% CI: 1.10-1.26 for each log increase in aspartame intake in  
64 women). Principal component analysis suggested three principal components underlying such  
65 associations, each comprising: 1) serum antioxidants; 2) serum vitamin D and vigorous  
66 physical activity; and 3) aspartame intake. All three principal components also displayed  
67 significant associations with abdominal obesity.

68 **Conclusion:** Our observational investigation that systematically investigates multiple  
69 modifiable factors simultaneously has enabled the creation of data-driven hypotheses

70 regarding the possible role of determinants of abdominal obesity and has identified potential  
71 avenues for mechanistic investigations to clarify suitable targets of intervention.

## 72 **Introduction**

73 The obesity pandemic remains a challenging health problem worldwide [1], with  
74 approximately 2.1 billion individuals estimated to be overweight or obese in 2013. Although  
75 some countries have shown indications of rate stabilisation during the past decade, the  
76 prevalence of obesity continues to increase in both developed and developing regions [1–3].  
77 High body mass index (BMI), a widely accepted indicator of obesity, is a well-known risk  
78 factor for diseases with serious implications including cardiovascular disease and several  
79 cancers [4,5], and accounted for over 33 million disability-adjusted life years (DALYs) lost  
80 in 2000 [6]. Moreover, obesity-related diseases confer a large economic burden, with an  
81 estimated rise in total medical costs of \$48–66 billion/year in the U.S. and £1.9–2 billion/year  
82 in the UK by 2030 [7]. Nevertheless, outcomes of public health strategies aimed at reducing  
83 obesity rates are unsatisfactory. Although interventions based on reduction in energy intake  
84 lead to weight loss, the lengthy period required for an obese individual to reach their normal  
85 weight implies limited efficiency [8], which indicates that policies should be directed towards  
86 obesity prevention rather than its reversal.

87

88 Identification of suitable targets of obesity prevention requires an understanding of at least  
89 two key concepts: 1) clinically relevant definition of obesity and 2) factors involved in  
90 mechanisms underlying obesity. Although obesity is conventionally defined by high BMI, the  
91 Third Report of Adult Treatment Panel (ATP III) of the National Cholesterol Education  
92 Program refers to waist circumference as the recommended measurement since abdominal  
93 obesity is closely related to metabolic disorders such as abnormal lipid profile, glucose

94 tolerance, and blood pressure [9]. Nevertheless, heterogeneity in other metabolic features has  
95 been reported within the same obesity categories [10], which underlines the importance of  
96 taking into account variation in metabolic indicators in assessing determinants of obesity.

97  
98 Although around 40% of obesity cases are considered heritable [11,12], environmental  
99 factors such as energy intake and physical activity remain the major driving forces underlying  
100 obesity [13]. Additionally, environmental factors may indirectly contribute to obesity through  
101 interaction with susceptibility genes [14]. Many studies have documented correlations  
102 between these factors and obesity, but most of them focused on individual associations  
103 without their co-existence, which is in contrast with a real life situation. Recently, Patel and  
104 colleagues introduced an environment-wide association study approach derived from  
105 methods used in genome-wide association studies (GWAS) to investigate the association of  
106 multiple nutrition and environmental factors with clinical phenotypes including blood  
107 pressure, diabetes, and mortality [15–17]. Here, we utilised this approach to comprehensively  
108 assess nutrition and lifestyle factors in relation to abdominal obesity in the Third U.S.  
109 Nutrition Health and Examination Survey (NHANES III). Additionally, we took into account  
110 other metabolic disorders and unobserved underlying factors while assessing abdominal  
111 obesity.

## 112 **Methods**

### 113 **Study population**

114 The National Health and Nutrition Examination Survey (NHANES) is a cross-sectional  
115 health survey conducted by the National Center for Health Statistics (NCHS) in  
116 representative samples of the non-institutionalized U.S. population [18]. Participants were  
117 selected through a multistage stratified, clustered probability sampling. The survey included

118 an interview conducted at home and an extensive physical examination with a blood sample  
119 taken in a mobile examination center (MEC). Institutional Review Board (IRB) approval was  
120 obtained for the NHANES and documented consent was obtained from participants. The  
121 present study was based on data from the Third NHANES (NHANES III) which was  
122 performed in two phases: 1988-1991 and 1991-1994, each of which provides independent  
123 unbiased national estimates of health and nutrition characteristics. From this population, we  
124 selected a total of 15,721 participants (7,403 men and 8,328 women) aged 20 and older with  
125 measurements of waist circumference. The first phase of NHANES III (N = 7,743) was used  
126 as a discovery set and findings from this dataset were replicated in the second phase of  
127 NHANES III (N = 7,988).

### 128 **Obesity assessment**

129 Abdominal obesity referred to waist circumference (WC) of >88 cm in women and >92 cm in  
130 men as defined by the experts in the Adult Treatment Panel (ATP) under the National  
131 Cholesterol Education Program (NCEP) [9]. All body measurements were performed using  
132 standardized methods and equipment [18]. WC was measured at the high point of the iliac  
133 crest at minimal respiration using a steel measuring tape to the nearest 1 mm [18]. Waist-to-  
134 hip ratio was calculated from WC and hip circumference. Body mass index (BMI) was  
135 calculated from measured weight and height. Weight was measured with an electronic weight  
136 scale in pounds and automatically converted to kilograms. Participants only wore underwear,  
137 disposable paper gowns and foam rubber slippers. Standing height was measured with a fixed  
138 stadiometer to the nearest 1 mm.

### 139 **Assessment of exposures and covariates**

140 A total of 182 nutrition and lifestyle factors in NHANES III were assessed (Table S1,  
141 Supplementary Data). Data collected ranged from information obtained through the

142 interview, such as smoking history, as well as physical and laboratory examination, e.g.  
143 serum vitamin C concentrations. Examples of markers and categories are presented in Table  
144 1. Excluding reproductive-related factors such as external hormone use, 176 factors were  
145 equally assessed in both men and women. These factors were assessed either as continuous or  
146 categorical variables. The majority of continuous variables had a right-skewed distribution.  
147 We transformed these variables into standardised z-scores by subtracting the mean and  
148 dividing by the standard deviation (SD) of the population. For categorical variables, we  
149 consistently defined one value as the referent category or the “negative” result, e.g. “never  
150 smoker” as the reference for “current smoker”. Vigorous physical activity (yes, no) was  
151 defined as participating three or more times per week in leisure-time physical activities with  
152 metabolic equivalent (MET)  $\geq 6$  for those aged 60 and older, and MET  $\geq 7$  for those younger  
153 than 60 [19]. Secondary exposure to smoking among never smokers (never smoked  $\geq 100$   
154 cigarettes) was defined as exposure to smoke at home ( $\geq 1$  person smoke at home) or at work  
155 ( $\geq 1$  hours smoke exposure at work). All exposure variables were assessed with standard  
156 procedures as detailed in the NHANES III documentation [18,20].

157

158 The following variables have been suggested to strongly affect environmental factors and  
159 obesity and were therefore considered as confounders in our study: age, sex, race/ethnicity,  
160 education and socioeconomic status (SES). Race/ethnicity was categorised into Non-Hispanic  
161 white, Non-Hispanic black, Mexican-American, and other. We classified educational  
162 attainment as less than high school, high school equivalent, and higher than high school. SES  
163 was estimated with poverty-to-income ratio (PIR), a ratio of total family income to the  
164 official poverty threshold at the family level. A PIR  $< 1$  indicated that income was less than  
165 the level of poverty. We categorised PIR into  $< 1$ ,  $1 - < 2$ ,  $2 - < 3$ , and  $\geq 3$ , indicating lowest to  
166 highest SES as previously described [21].

167

168 The ATP-III definition of metabolic syndrome apart from waist circumference was used to  
169 define presence of other metabolic disorders [9]. Hypertension was defined by blood pressure  
170 of  $\geq 130/\geq 85$  mmHg or any use of antihypertensive drugs. Diabetes was defined as fasting  
171 glucose  $\geq 110$  mg/dL or any use of insulin or glucose-lowering drugs. Any HDL-cholesterol  
172 levels  $< 40$  mg/dL for men or  $< 50$  mg/dL for women were considered as low.  
173 Triglyceridaemia was defined as any levels of triglycerides  $\geq 150$  mg/dL. Blood pressure was  
174 measured with mercury manometer and the average of the second and third blood pressure  
175 measurements was taken. Fasting plasma glucose levels were measured by using a modified  
176 hexokinase enzymatic method (Roche Diagnostic Systems, Inc., Montclair, NJ). Blood lipids  
177 were enzymatically measured using the Hitachi 704 Analyzer (Boehringer Mannheim  
178 Diagnostics, Indianapolis, IN) [18].

### 179 **Statistical analysis**

180 Sampling weights specific to each phase were included in all analyses. Fig 1 summarises the  
181 analytical steps in this study which were similar to previously published nutrient- and  
182 environment-wide studies [15,16,22,23]. WC was used as an outcome instead of BMI, and  
183 was assessed as a dichotomous instead of a continuous outcome given that this definition of  
184 abdominal obesity has been widely accepted to be clinically relevant to risk of diabetes and  
185 cardiovascular disease [24]. We selected factors corresponding to categories of  
186 environmental exposures used in a previous EWAS study as summarised in Table 1 [16].  
187 First, each of the 182 nutrition and lifestyle factors was assessed in relation to abdominal  
188 obesity in the discovery set, phase I of the NHANES III. Survey-weighted logistic regression  
189 was used to examine the association of continuous and dichotomous nutrition and lifestyle  
190 factors in men and women separately. All models were linearly adjusted for age,  
191 race/ethnicity, education and PIR by adding each term into the regression model.



192

193 Next, we estimated the false discovery rate (FDR) among findings in the discovery set. FDR  
194 is the expected proportion of false discoveries, among all significant findings at a given  
195 significance level [25]. Using a significance level  $\alpha$  of 0.05, we estimated FDR using the  
196 Benjamini-Hochberg step down method [26] to select factors with statistically significant  
197 association with obesity status and  $FDR < 5\%$  in the discovery set. A sensitivity analysis was  
198 performed by selecting all factors with  $FDR < 1\%$ . Because physical activity and smoking  
199 status classifications were derived from other variables, we performed a sensitivity analysis  
200 including the four categories of physical activity (vigorous, moderate, light physical activity,  
201 and sedentary) [19] instead of using it dichotomously. Similarly, for smoking status we  
202 repeated our analyses by only including the main smoking categorisation (current, former and  
203 never smokers) [27] and continuous levels of serum cotinine, the primary metabolite of  
204 nicotine [28], as indicators of smoking exposures.

205

206 Replicated analysis of assessed nutrition and lifestyle factors was subsequently performed by  
207 re-running similar logistic regression models in the second dataset, namely phase II of  
208 NHANES III (Fig 1). Only nutrition or lifestyle factors with both  $FDR < 5\%$  in the first  
209 dataset and  $p$  value  $< 0.05$  in the replication set were considered valid. Furthermore, analysis  
210 for replicated factors in the overall study population was repeated in additional multivariable  
211 models adjusting for other metabolic disorders (i.e., hypertension, diabetes, low HDL, and  
212 hypertriglyceridaemia) and models incorporating all replicated factors. To account for  
213 potential effects of body type differences, a sensitivity analysis was performed by a further  
214 adjustment for BMI or waist-to-hip ratio as a continuous variable.

215

216 Finally, our secondary aim was to understand any underlying factors associated with  
217 abdominal obesity based on inter-correlation among tentatively replicated nutrition and  
218 lifestyle factors in the overall study population. For this purpose, we performed a principal  
219 component analysis with an orthogonal varimax rotation procedure. An eigenvalue of  $>1$  was  
220 used to define the number of principal components to be extracted from our data [29].  
221 Proportion of variance in abdominal obesity explained by each principal component was  
222 estimated, and 95% confidence intervals of this estimation were obtained using 1000  
223 bootstrap resampling [30]. We further estimated the value of principal components identified  
224 and assessed them in relation to abdominal obesity using similar multivariable approach.  
225 McFadden  $R^2$  values were computed to estimate variance explained by the model, and the  
226 variance explained only by replicated nutrition and lifestyle factors or principal components.  
227  
228 The NHANES III datasets were prepared with Statistical Analysis Software (SAS) release 9.3  
229 (SAS Institute, Cary, NC). All analyses were performed with R version 3.1.2 (R Foundation  
230 for Statistical Computing). The *survey* package was used to account for sampling weights and  
231 the *psych* package was used to perform principal component analysis.

## 232 **Results**

233 Characteristics of study participants are shown in Table 2, whereas means, standard  
234 deviations and frequencies of investigated nutrition and lifestyle factors are available in Table  
235 S1 (Supplementary Information). Using the ATP III definition for abdominal obesity, 55.6%  
236 of women and 28.8% of men were abdominally obese. Prevalence of other metabolic  
237 disorders was higher in both obese men and women compared to the non-obese counterparts.  
238

239 We performed a systematic screening of the relationships of the 182 nutrition and lifestyle  
240 factors with abdominal obesity in men and women separately. A total of 30 factors with  
241 FDR<5% in men and 36 factors in women in the discovery set were examined for  
242 significance ( $P<0.05$ ) in the replication set. In men, this resulted in 5 tentatively replicated  
243 factors showing significant inverse associations for serum  $\alpha$ -carotene,  $\beta$ -carotene, serum  $\beta$ -  
244 cryptoxanthin, serum vitamin D, and vigorous physical activity with abdominal obesity  
245 (Table 3). A total of 7 factors were replicated in women: serum vitamin C, serum  $\alpha$ -carotene,  
246  $\beta$ -carotene, serum  $\beta$ -cryptoxanthin, serum vitamin D, and vigorous physical activity were  
247 inversely correlated with abdominal obesity, whereas aspartame intake was positively  
248 associated with abdominal obesity. Replicated findings did not alter when we performed a  
249 sensitivity analysis including only factors with FDR<1% in the discovery survey or when we  
250 used the alternative categorisation of physical activity and smoking status (results not  
251 shown). Fig 2 depicts the distribution of P-values for each investigated factor and effect sizes  
252 (“Manhattan plot”). As seen in Fig 2, stronger associations between common factors and  
253 abdominal obesity were observed in women compared to men. Detailed results on  
254 associations between all factors and abdominal obesity are presented in the Supplementary  
255 Information (Table S2 and S3).

256

257 Correlation between replicated factors is displayed as a heatmap in Fig S1 (Supplementary  
258 Information). To assess any structure underlying replicated nutrition and lifestyle factors, we  
259 performed a principal component factor analysis to identify common underlying factors. In  
260 men, two principal components (PC) were identified. The first PC mainly consisted of serum  
261 antioxidants (antioxidant PC). The second PC comprised serum vitamin D and vigorous  
262 physical activity (exercise-related PC). In addition to these two factors, a third factor (food  
263 additive PC) was identified in women, which only included aspartame intake. The total

264 variance of replicated variables explained by these principal components in men was 36%  
265 (95% CI: 34-36%) by antioxidant PC and 22% (21-22%) by exercise-related PC. In women,  
266 29% (95% CI: 29-31%) of total variance was explained by antioxidant PC, 16% (15-16%) by  
267 exercise-related PC, and 15% (14-15%) by food additive PC).

268

269 For the final analysis, we obtained estimates for replicated nutrition and lifestyle factors in  
270 relation to abdominal obesity in the overall survey (phase I and phase II) for men and women  
271 (Table 4). In addition to these factors, we calculated estimates for antioxidant PC and  
272 exercise-related PC from the principal component analysis. We found that these two principal  
273 components were inversely associated with abdominal obesity in both sexes (Table 4). In a  
274 sensitivity analysis where we adjusted for BMI, only antioxidant PC was consistently  
275 associated with abdominal obesity in both men and women (Table S4). Associations remain  
276 significant for both principal components when models were adjusted for waist-to-hip ratio  
277 (Table S4).

278

279 When we adjusted for other metabolic disorders as denoted by presence of one or more  
280 components of metabolic syndrome apart from obesity, the results were not altered, and all  
281 replicated factors remained significantly associated to abdominal obesity in men and women  
282 (Table 4). In a multivariable model incorporating all replicated factors, a lack of statistically  
283 significant association with abdominal obesity was observed for serum  $\alpha$ -carotene in men and  
284 women, and for  $\beta$ -cryptoxanthin in women. Other factors and all principal components  
285 identified remained significantly associated with abdominal obesity. The total variance  
286 explained by the multivariable model including replicated nutrition and lifestyle factors was  
287 11% and 17% for men and women, respectively. The total variance explained by replicated

288 factors was 2% and 6% in men and women, respectively. Similar contribution to variance  
289 was found for principal components in the multivariable models

## 290 **Discussion**

291 In a systematic screening of 182 nutrition and lifestyle factors, 5 factors in men and 7 factors  
292 in women were found to have statistically significant associations with abdominal obesity  
293 after applying the EWAS methodology among a representative sample of the U.S.  
294 population. Based on inter-correlation between these factors, three underlying principal  
295 components were identified. Lower odds of being abdominally obese were seen with higher  
296 quantities of factors representing serum antioxidants and exercise in both men and women,  
297 whereas a positive association was observed for aspartame intake in women, but not men.

298

299 Circulating levels of common antioxidants including vitamin A metabolites and vitamin C  
300 have been reported to be inversely associated with general and abdominal obesity [31–35].  
301 Recently, using repeated measurements, longitudinal associations between levels of these  
302 antioxidants and adiposity indicators were observed in postmenopausal women, indicating  
303 lower serum  $\beta$ -carotene and higher  $\gamma$ -tocopherol to be associated with higher WC [36].  
304 However, results from clinical studies have failed to demonstrate benefit of antioxidant  
305 supplementation in prevention of obesity-related diseases such as cardiovascular disease [37]  
306 and breast cancer [38], although confounding by fruit and vegetable consumption may be  
307 implicated. Interestingly, a meta-analysis assessing a total of 78 randomised trials showed  
308 increased mortality with supplementation of  $\beta$ -carotene or vitamin E, and with higher doses  
309 of vitamin A [39]. Our findings support inverse associations between serum antioxidants and  
310 abdominal obesity which was robust against variation in BMI and waist-to-hip ratio. The  
311 contrasting positive association between vitamin A levels and abdominal obesity, albeit not

312 seen in the replication set, may underline the discrepancy between absorbed pro-vitamin A  
313 and the tightly regulated levels of vitamin A [40,41]. In line with this, different associations  
314 between carotenoids and vitamin A levels with respect to other health outcomes such as  
315 mortality have also been noted [42]. Our findings also showed disagreement between dietary  
316 intake and serum levels of antioxidants in relation to obesity. Nevertheless, it is possible that  
317 this discrepancy and the lack of associations for dietary antioxidants that we observed was  
318 due to a lack of precision from measurement error and within-individual variation because  
319 information was obtained by a single 24-hour dietary recall. Alternatively, such discrepancy  
320 may also indicate the implication of physiological regulators of antioxidant metabolism rather  
321 than antioxidant intake on obesity and relevant health outcomes. In support of this,  
322 experimental evidence indicated that circulating carotenoids reduce adiposity through  
323 regulation of adipocyte thermogenesis [43]. These findings may indicate an interplay between  
324 antioxidant metabolism and physiological regulation of adiposity warranting further  
325 investigations.

326

327 The role of physical activity in management of obesity has been well-established [44], as well  
328 as their opposing effects on health outcomes such as cardiovascular death [45]. Similarly,  
329 decreased levels of serum vitamin D among individuals with general and abdominal obesity  
330 have been reported [46–48] but the directionality of this association is unclear. Findings from  
331 a meta-analysis of vitamin D supplementation [49] and a Mendelian randomisation study [50]  
332 suggested that levels of vitamin D decrease secondary to increasing adiposity. Our study  
333 corroborates the inverse relationship between physical activity or serum vitamin D and  
334 abdominal obesity in both men and women. Additionally, from the principal component  
335 analysis, we observed a high correlation between physical activity and serum vitamin D.  
336 Although higher levels of physical activity have been linked to increasing levels of vitamin D

337 [51,52], their mechanistic association is unclear. Adding to the current evidence, we  
338 identified from the principal component analysis that an unobserved PC, which we denoted as  
339 ‘exercise-related’, drove the associations of physical activity and serum vitamin D with  
340 abdominal obesity. One possible explanation is that levels of vitamin D may be a proxy for a  
341 healthier lifestyle which involves outdoor activities. However, it was suggested that sun  
342 exposure and time spent outdoor do not explain the majority of variation in vitamin D levels  
343 [53]. On the other hand, the notion that obesity is followed by decreasing vitamin D levels  
344 [49,50] may indicate a physical activity-obesity-vitamin D regulation axis. Mechanistic  
345 investigations are needed to confirm these plausible pathways.

346

347 Aspartame is a methyl ester of a dipeptide and widely used as a synthetic non-nutritive  
348 sweetener (NNS) [54]. There is evidence that NNSs may interfere glucose and insulin  
349 response by disrupting learned physiological response [55,56]. However, a position statement  
350 by the Academy of Nutrition and Dietetics concluded that aspartame consumption was not  
351 associated with adverse health effects in humans (Grade I evidence) [57]. In the context of  
352 obesity, weight loss and maintenance among obese women have been reported following diet  
353 regimens incorporating aspartame-sweetened food and beverages, which are often part of  
354 diet-related products such as diet soda, compared to those without [58]. Nevertheless, there is  
355 a lack of evidence apart from clinical trials including individuals on weight management  
356 programmes. We found that higher aspartame intake correlated to more prevalent abdominal  
357 obesity in obese women. Although any obesogenic effect of aspartame intake has not been  
358 well-documented, our findings are in line with previous studies suggesting higher risks of  
359 subsequent general and abdominal obesity following use of artificially-sweetened beverages  
360 [59–61]. On the other hand, the positive association observed between aspartame intake and  
361 abdominal obesity in women may also signify certain behavioural patterns secondary to

362 obesity, such as efforts to moderate energy intake [56] and a ‘licensing effect’, since artificial  
363 sweeteners are often a part of diets based on calorie restriction. The latter refers to  
364 disinhibition or ‘licensing’ of unhealthy behaviours following commitment to a self-  
365 perceived healthy behaviour [62,63], a phenomenon increasingly recognised in marketing  
366 research and experimental human studies. Further studies are needed to rule out such reverse  
367 causality, which is important in clarifying the role of aspartame in obesity and obesity-related  
368 outcomes.

369

370 One of the strengths of this study is its generalisability following the use of nationally  
371 representative data of the U.S. population. We were able to adjust for major confounders such  
372 as education and PIR in our analysis. To our knowledge, this is the first study applying  
373 GWAS-like analytical approaches in studying determinants of obesity. Robustness of the  
374 statistical associations between investigated markers and obesity was ascertained through  
375 replication analysis and adjustment for presence of other metabolic factors. The systematic  
376 screening was able to eliminate factors with small effects which may be more prone to bias.  
377 Additionally, this method overcomes the limitation of selective reporting, which may be an  
378 issue with studies focusing on individual exposures. Nevertheless, it is important to address  
379 limitations of this study. NHANES III was set up as a cross-sectional study, thus our analysis  
380 was unable to identify any causality. Some nutrition and lifestyle factors were only measured  
381 in small numbers of the participants and this may have limited statistical power of the  
382 analysis. Many of investigated factors, such as smoking status and dietary assessment, were  
383 self-reported. For dietary assessment, only one 24-hour dietary recall was used. Such  
384 imprecision arising from subjective instruments and potential recall bias [64] may have  
385 resulted in the discrepancy between findings from dietary intake and serum levels of  
386 antioxidants. Therefore, it is necessary to confirm these results with objective measurements



387 such as digitalised instruments to monitor energy balance [65]. Nevertheless, these results  
388 may also indicate a role of physiological factors involved in oxidative stress response  
389 pathways, which may have greater influence than dietary intake of antioxidants in  
390 determining their serum levels. Definition of other metabolic disorders was limited by data  
391 availability in NHANES III. For instance, diabetes was based on fasting glucose and not all  
392 participants were fasting at time of measurements. Although we took into account potential  
393 confounders and inter-correlation between replicated factors, residual confounding may have  
394 occurred. It should also be noted that there were non-replicated factors in this study such as  
395 fat intake and serum cotinine that were individually correlated to abdominal obesity but did  
396 not display  $FDR < 5\%$  or significance in the replication set. Similarly, the association between  
397 aspartame intake and abdominal obesity may not have been gender-specific given a similar  
398 but weaker estimate in men after adjustment for multiple comparisons. These factors may still  
399 be associated, albeit weakly, with abdominal obesity. Furthermore, we were unable to  
400 exclude the potential role of other relevant factors apart from those assessed in NHANES III.  
401 Therefore, obtaining an equivalent definition of ‘genome-wide significance’ as one would be  
402 able to claim in a GWAS analysis may be impractical or otherwise requires more rigorous  
403 and thorough assessments of nutrition and lifestyle determinants.

## 404 **Conclusion**

405 Using a comprehensive screening, our study identified nutrition and lifestyle factors  
406 demonstrating robust associations with abdominal obesity. Future mechanistic investigations  
407 are necessary in order to draw conclusions which may lead to development of suitable  
408 behavioural intervention and public policies aimed to reduce the obesity pandemic.

409 **Acknowledgement**

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