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# Effects of sodium intake and cardiorespiratory fitness on body composition and genetic susceptibility to obesity: results from the Quebec Family Study

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## Abstract

The main aim of this study was to evaluate the effects of Na intake and cardiorespiratory fitness (CRF) on body composition. The study was also intended to assess whether Na intake and/or CRF mediate the genetic susceptibility to obesity. Analyses were performed on a sample of 526 adult participants from the Quebec Family Study for whom a complete data set was available for nutrient and energy intake, CRF and body composition variables. The effects of Na, CRF and their interaction were analysed by comparing sex-specific tertiles using general linear mixed models. In both males and females, we observed a significant effect of Na intake and CRF on all body composition variables. However, in females only, we found that the effect of Na intake on body composition variables varies according to CRF level such that high Na intake was associated with increased body fatness, but only in females with low CRF. This interaction effect remained significant after statistical adjustment for total sugar, fat and energy intake. Using mediation analysis, we also found Na intake and CRF to be significant mediators of the relationship between a polygenic risk score of obesity based on > 500 000 genetic variants and BMI or waist circumference. In conclusion, the current study shows that Na intake influences body composition via mechanisms that interact with aerobic fitness, especially in females. Furthermore, both Na intake and CRF seem to be involved in the expression of the genetic susceptibility to obesity.

**Key words:** **Body composition: Obesity: Energy balance: Micronutrient: Genetic susceptibility**

The association between diet, obesity and its related complications has been traditionally documented by focusing on nutrients or dietary factors that provide dietary energy, i.e. protein, fat, carbohydrate and alcohol. This has led to the consensus that an energy dense/high-fat/high-sugar diet is problematic for the maintenance of energy balance as well as the prevention of obesity and co-morbidities. However, a recent analysis of the Global Burden of Disease Study showed that Na is the nutrient whose variations in intake are the most predictive of the risk of food-related mortality[1].

Na is the main cation of the extracellular fluid and plays a key role in the regulation of extracellular volume and water balance. It is linked to thirst and the angiotensin drinking behaviour[2]. Its acute administration is known to induce hyperphagia in laboratory animals[3],while prolonged Na deficiency stimulates Na appetite[4]. Recently, Kitada *et al.*[5] described a mechanism devoted to salt excretion while preserving body water in the context of high-salt diet. This mechanism is mediated by urea production and transport that provide the osmotic gradient necessary to reabsorb water when dietary salt is excreted. It also involves an increase in glucocorticoid levels and glucocorticoid-driven muscle catabolism and hepatic ketogenesis, although these effects are prevented by an increase in food intake. Furthermore, this hyperphagia is not observed when mice fed a high-salt diet have free access to water. Thus, beyond its ability to promote sufficient intakes of macronutrients and micronutrients, e.g. Ca[6], appetite control seems to influence salt and water balance, especially in individuals having an inadequate water intake.

**Abbreviations:** CRF, cardiorespiratory fitness; PRS, polygenic risk score; QFS, Quebec Family Study; WC, waist circumference.

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The analysis of large population-based studies has also been used to investigate the existence of a possible relationship between Na intake and the proneness to overweight. In Australian children, daily urinary Na was found to be associated with obesity[7]. The adjustment for energy intake, measured with 24-h dietary recall, did not modify this association. The same group also reported a positive relationship between dietary Na intake and fluid consumption. They also observed in consumers of sugar-sweetened beverages that a 390 mg increase in Na predicted an increase of 32 g/d of sugar-sweetened beverages, even after adjustment for relevant confounders such as sex and energy intake[8]. The analysis of data of the UK National Diet and Nutrition Survey 2008/2009 to 2011/2012 collected with a 4-d diary (energy intake) and 24-h urine collection (Na) showed that a 1 g/d increase in salt intake was related to a 28 % increase in the obesity risk[9]. The significance of this relationship persisted after statistical adjustment for energy intake, physical activity and other co-variates. More recently, Zhang *et al.*[10] also examined the Na–obesity relationship by using the 1999–2006 NHANES data. This analysis revealed that for each 1 g/d increment in Na intake, there was an increase of 15 and 24 % in the risk to develop obesity and central obesity, respectively. After stratification for sex and ethnicity, these associations were apparent only in females and in non-Hispanic whites. Globally, these epidemiological observations support the idea of a link between Na intake and obesity. In addition, as further discussed in this paper, the persistence of this association after statistical adjustment for energy intake should not be viewed as an indication that the first law of thermodynamics, which stipulates that body energy varies according to the balance between energy intake and expenditure, is not valid in this context.

It is also relevant to consider physical activity and cardiorespiratory fitness (CRF) in the study of the association between Na intake, obesity and its co-morbidities. In this regard, it was reported that physical activity is significantly, independently and inversely related to salt sensitivity of blood pressure[11], i.e. blood pressure increases to a lesser extent in active people in response to a high Na intake. However, to our knowledge, it is not known whether the Na–obesity relationship is attenuated in fit physically active individuals. Thus, the first objective of this study was to evaluate variations of body composition in relation to Na intake and CRF in the Quebec Family Study (QFS).

It is well established that heredity is a significant contributor to the predisposition to a positive energy balance and excess body fat[12,13]. In this context, the second objective of this study was to examine the role of Na intake and CRF as putative mediators of the relationship between genetic susceptibility to obesity, assessed using a polygenic risk score of obesity, and BMI or waist circumference (WC).

## Methods and measurements

### Participants

The present study is based on data from the QFS (NCT03355729). Detailed information on QFS can be found elsewhere[14,15]. As depicted in Supplementary Fig. S1, the QFS was an observational study with three phases of data collection between 1979 and 2002. All the participants were recruited through the media and were French Canadians living in the Quebec City area. In phase 1, 1630 individuals from 375 families were recruited, irrespective of their body weight. Some of these families included monozygotic or dizygotic twins and/or adopted children. A modification of the sampling procedure was introduced for phases 2 and 3 with the objective of investigating the role of genetic factors in the determinants and health-related consequences of obesity. For that purpose, we started recruiting nuclear families ascertained for obesity (at least one parent and one offspring with a BMI of 32 kg/m$^2$ or higher) and collected DNA samples. In phase 2, 385 subjects from 105 phase 1 families were retested for a second time and 372 subjects from seventy-four families (including 108 relatives from forty-six phase 1 families that were not tested in phase 1) were recruited. In phase 3 (1998–2002), 195 subjects from forty-four families were added, while 204 subjects from phase 1 were tested a third time and 113 subjects were tested a second time. Therefore, the participants with cross-sectional data potentially eligible for this study include 952 subjects (757 from phase 2 and 195 from phase 3) from 223 families. Among these subjects, 939 lymphocyte-derived DNA samples are available and genome-wide genotyping are available for 926 participants. After exclusion of participants with no genome-wide genotype data (*n* 26), aged under 18 years (*n* 44), no nutrient intake data (*n* 104) and no CRF data (*n* 252), the final study sample included 526 healthy adults. For participants with data on phases 2 and 3, the sample selection procedure favoured the phase with less missing data for both nutrient intake and CRF or favoured phase 2 when data were available on both phases. All the participants gave their written consent to participate in the study that was accepted by the ethics committee of Université Laval (2010-075 CG R8/10-12-2021).

### Anthropometry and body composition

Body weight, height and WC were measured by following the standardised guidelines recommended at the Airlie Conference[16]. BMI was also calculated by dividing body weight by height squared.

The hydrostatic weighing technique was used to estimate body composition. Before water immersion, the pulmonary residual volume was measured with the method of Meneely and Kaltreider[17]. The mean of six valid underwater weighing measurements was used to assess body density from which percent body fat was estimated with the Siri equation[18]. Body fat and fat-free mass were then calculated from body weight and percent body fat.

Computed axial tomography was used to measure visceral fat deposition at the level of the fourth and the fifth lumbar vertebrae, as described by Ferland *et al.*[19]. According to Lemieux *et al.*[20], WC also represents a convenient and valid measure of visceral fat.

### Cardiorespiratory fitness

CRF was assessed using a progressive submaximal exercise test performed on a modified Monark cycle ergometer, as previously described[21]. The test included three consecutive 6-minute

workloads at a pedaling frequency of 70 rpm, each separated by a 1-minute rest, during which heart rate was monitored with a standard CM5 electrocardiogram configuration (Quinton Q4000 ECG). The test was designed to elicit a heart rate around 170 bpm at the end of the last workload. The physical working capacity at a heart rate of 150 bpm (PWC150) was then calculated from the linear relation between heart rate and power output and expressed per kilogram of body weight (PWC150/kg) to take into account individual differences in body weight. This measurement, which was found to be highly reproducible and a valid surrogate measure of maximal aerobic power[22], was used as an indicator of CRF in the present study.

### Nutrient intake

Self-reported 3-d dietary records were completed during two weekdays and one weekend day to measure daily nutrient intake. Before completing the diary, participants met the team dietitian who gave instructions on how to describe and record foods. For that purpose, a scale and measuring spoons and cup were left to participants to facilitate the measurement of quantities of ingested foods. Following its completion, the diary was verified by the dietitian who might have some questions to be answered by the participant before recorded foods are subsequently coded. Their nutrient and energy content was calculated by using the 2010 computerised version of the Canadian Nutrient File[23]. The weighted food record procedure was shown to be reproducible[24]. This methodology was also found to provide concordant results with changes in body composition and appetite sensations in the context of a weight-reducing program[25].

### Genetic susceptibility to obesity

Genetic susceptibility to obesity was assessed using a polygenic risk score (PRS). A PRS represents an individual's genetic susceptibility to a trait, calculated according to their genome-wide genotype profile and relevant genome-wide association study data[26]. Genome-wide genotyping of QFS participants was performed using the Illumina 610-Quad chip as described elsewhere[27]. The PRS for obesity was derived using the summary statistics of the most recent genome-wide association study meta-analysis of obesity that quantified the relationship between more than 2·5 million common variants and BMI in over 700 000 individuals[28]. We used the computational tool called LDpred2 for PRS calculation[29], adjusting for the effect size estimates of all variants and accounting for linkage disequilibrium between genetic variants to derive a PRS with independent genetic variants across the genome. A total of 523 101 variants were included in the PRS for obesity.

### Adjustment for misreporting

The plausibility of self-reported energy intake was assessed using the method described by Huang *et al.*[30] where under- and over-reporters of energy intake are defined as those having a ratio of reported energy intake to predicted energy requirements that deviates more than one standard deviation (± 1 SD) calculated from a formula that accounts for measurement error in reported energy intake and predicted energy requirements. Predicted energy requirements were assessed using equations developed by the Institute of Medicine[31]. As an objective measure of physical activity level was not available for all participants, it was assumed that participants are sedentary, as previously done[32]. To account for skewness of energy intake, the ± 1 SD CI were exponentiated using a multiplicative factor of 1[33]. The resulting CI were 0·78 and 1·29, meaning that under- and over-reporters of energy intake were defined as those having a ratio of reported energy intake to predicted energy requirements < 0·78 (11 % of the subjects) and > 1·29 (21 % of the subjects), respectively. The reporting status (i.e. under-reporters, plausible reporters and over-reporters) was considered in all analyses by creating two indicator variables representing underreporting (yes, 1; no, 0) and overreporting (yes, 1; no, 0), as recently recommended[34].

### Statistical analysis

The effects of CRF, Na intake and their interaction on body composition variables were assessed using general mixed linear models implemented in the MIXED procedure of SAS (SAS University Edition, version Oct 2019), whereas the Tukey HSD test was used for a posteriori comparison. Non-independence of family members was taken into account by modelling the covariance parameters for individuals coming from the same family. Analyses were performed separately in males and females using tertiles of CRF and Na intake as independent variables and the under- and over-reporting status as covariables, as described above.

### Mediation analyses

We used a statistical approach called mediation analysis to assess the role of Na intake and CRF as mediators of the relationship between genetic susceptibility to obesity and BMI as well as WC. For that purpose, we used a data sample consisting of a maximum of 750 subjects from QFS phases 2 and 3, as explained previously in a recent paper from our group investigating dietary mediators of genetic susceptibility to obesity[35]. The three mediation models tested in the present study (mediating effect of Na, CRF and joint effects of Na and CRF) are illustrated in Fig. 1. Mediation analysis is used to assess the extent to which the effect of an independent variable X (here, PRS for obesity) on a dependent variable Y (here, BMI or WC) is explained by a hypothesised mediator M (here, Na intake or CRF). The mediation models depicted in Fig. 1 can be represented by the following three linear regressions:

$$Y = iY + cX \quad (1)$$

$$M = iM + aX \quad (2)$$

$$Y = iY + c'X + bM \quad (3)$$

where Y represents the dependent variable (BMI or WC), X represents the independent variable (PRS obesity) and M is the mediating variable (Na or CRF). The path $c$ (estimated by equation 1) represents the total effect of X on Y. The path $a$



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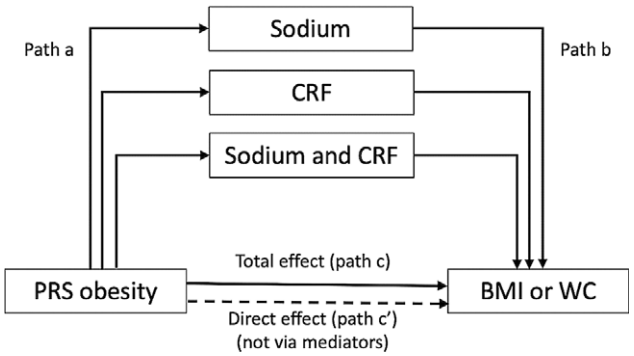


**Fig. 1.** The three mediation models tested in the present study. The models represent the effects of X (PRS of obesity) on Y (BMI or waist circumference (WC)) through 1) sodium intake (sodium), 2) cardiorespiratory fitness (CRF) and 3) joint effects of sodium and CRF. See methods for the description of the various paths.

(estimated by equation 2) represents the strength of the relationship between X and M. The path *c'* (estimated by equation 3) represents the direct effect (not via the mediator) of X on Y when M is added as covariate in the model. The path *b* (estimated by equation 3) represents the effect of M on Y after accounting for the effect of X on Y. The pathway relating X to Y via the mediator M represents the mediated (or indirect) and is quantified by computing the product of *a* and *b* coefficients.

The effects represented by the regression coefficients in equations (1) to (3) were estimated using PROCESS (version 3.4.1, for SAS), a computational tool for path analysis-based mediation analysis[36,37]. PROCESS reports significance of total, direct and indirect effects using both the normal theory *p* values and bootstrapping procedures. We report values from both procedures in the results, but the bootstrap 95 % CI is the method recommended to interpret significance of the indirect effect as no assumption is made about the normality of the distribution of the indirect effect[37]. The indirect effect was thus tested using bootstrapping with the percentile method in 5000 samples of the same sample size as the original cohort. The percentage of mediation was calculated as the ratio of indirect effect to total effect (i.e. $(ab/c) \times 100$). Analyses were conducted on data adjusted for age, sex and misreporting and with further adjustment for energy intake, menopause and smoking.

## Results

The descriptive characteristics of participants categorised by tertiles of Na intake are presented in Table 1. In both males and females, daily Na intake in the lower tertile conformed to dietary recommendations[38], whereas values of the upper tertile were close to the intake threshold considered at risk of Na-related health problems. This table also shows that for both sexes, the upper tertile reported significantly greater daily fat and energy intake than the lower and the middle tertiles. Additionally, fat and energy intake was higher in the middle than in the lower tertile. Body weight, fat mass, fat-free mass, WC and visceral fat were significantly greater in the high than in the low tertile in males and females. Except for fat mass and visceral fat in males, the values of the high tertile were also greater than those observed in the middle tertile in both sexes (Table 1). Finally, it is worthy to emphasise that CRF, as reflected by values of PWC150/kg, was comparable among tertiles in both males and females.

The effects of CRF and Na intake on body composition variables are presented in Table 2. In male subjects, there was a significant effect of CRF on BMI, WC, % body fat, fat mass and visceral fat, whereas no significant effect was found for body weight. Na intake also exerted a significant impact on morphological variables in males, except for % body fat.

Table 2 also shows that all morphological variables were significantly influenced by both CRF and Na intake in females. Furthermore, except for % body fat, a significant interaction between CRF and Na intake was observed in females, indicating that the detrimental effects of Na intake on body fat and fat distribution were less pronounced in fit females compared with those displaying a low CRF level. This interaction effect, illustrated in Fig. 2, shows a much less favourable profile in females classified in the low CRF–high Na subgroup. The statistical significance of this interaction effect persisted after adjustment for total sugar and fat intake or energy intake.

To further document the association between Na intake and the risk of overweight/obesity, we studied the mediating effects of Na intake and CRF on the relationship between a polygenic risk score of obesity and BMI or WC, as described above. The PRS for obesity was significantly ($p < 0{\cdot}0001$) associated with BMI and WC explaining 17·4 % and 13·0 % of the variance in the two traits, respectively (results not shown). The results of mediation analyses for the age-, sex- and misreporting-adjusted data are summarised in Table 3. For both BMI and WC, we observed significant mediation effects of Na intake ($\beta_{\text{indirect}} = 0{\cdot}03 \pm 0{\cdot}01$, 95 % CI (0·02, 0·06) for BMI; $\beta_{\text{indirect}} = 0{\cdot}04 \pm 0{\cdot}01$, 95 % CI (0·02, 0·06) for WC) and CRF ($\beta_{\text{indirect}} = 0{\cdot}04 \pm 0{\cdot}01$, 95 % CI (0·02, 0·07) for BMI; $\beta_{\text{indirect}} = 0{\cdot}04 \pm 0{\cdot}01$, 95 % CI (0·02, 0·06) for WC). The proportion of the effect that is mediated by Na reached 7·1 % and 8·2 % for BMI and WC, respectively, while the corresponding values for CRF were 12·1 and 11·9 %. The results of the multiple mediator model (combined effects of Na and CRF) are illustrated in Fig. 3 for BMI (panel A) and WC (panel B). The results show a significant combined mediating effect of Na and CRF on the relationship between the PRS of obesity and both BMI and WC. The proportion of the effect mediated by joint effects of Na and CRF reached 17·2 % for BMI and 18·5 % for WC. Similar results were obtained when analyses were repeated with further adjustment for energy intake, menopause and smoking (results not shown).

To rule out the possibility that poor diet quality reflected by high Na intake could in part explain the results presented in Tables 2 and 3, we repeated the analyses after further adjustment of the data for either fruit and vegetable consumption or diet quality (results not shown). As explained in a recent paper from our group[35], fruit and vegetable consumption was derived from the food items of the 3-day dietary record. Diet quality was assessed using the Nutrient Rich Food Index 6·3, which measures the nutritional quality of each food based on the proportion of daily reference values provided for six nutrients to encourage and three nutrients to limit. The significant results reported in Table 2 regarding the effects of CRF, Na intake and the

**Table 1.** Nutrient intake and body composition in males and females by groups of sodium intake

| Variable | Tertiles of Na intake | | | | | | |
|---|---|---|---|---|---|---|---|
| | Low (*n* 83) | | Middle (*n* 83) | | High (*n* 83) | | |
| Males | Means | SEM | Means | SEM | Means | SEM | *P* value |
| Age (years) | 39·1 | 1·6 | 37·7 | 1·6 | 37·4 | 1·6 | NS |
| PWC 150/kg | 11·5 | 0·5 | 10·5 | 0·5 | 10·9 | 0·5 | NS |
| Na intake (mg/d) | 2624 | 64 | 3768 | 64 | 5191 | 64 | |
| Fat intake (g/d) | 86·4 | 3·4 | 97·0 | 3·7‡ | 107·5 | 3·6* | < 0·0001 |
| Sugar intake (g/d) | 119·1 | 6·3 | 117·8 | 6·8 | 124·4 | 6·8 | NS |
| Energy intake (kcal/d) | 2409 | 59 | 2557 | 58‡ | 2837 | 58* | < 0·0001 |
| Body weight (kg) | 73·9 | 2·2 | 79·0 | 2·4 | 84·2 | 2·4* | 0·0004 |
| BMI (kg/m$^2$) | 24·5 | 0·7 | 26·3 | 0·7 | 27·7 | 0·7* | 0·0003 |
| Body fat (%) | 20·4 | 1·0 | 21·1 | 1·1 | 22·6 | 1·1 | NS |
| Fat mass (kg) | 15·9 | 1·4 | 17·8 | 1·5 | 20·4 | 1·5† | 0·0285 |
| Fat-free mass (kg) | 58·3 | 1·1 | 61·3 | 1·2 | 63·6 | 1·1* | 0·0002 |
| Waist circumference (cm) | 86·4 | 1·7 | 90·1 | 1·9 | 94·5 | 1·9* | 0·0005 |
| Visceral fat (cm$^2$) | 95·7 | 9·9 | 108·2 | 10·8 | 125·7 | 10·5† | 0·039 |
| Females | Low (*n* 92) | | Middle (*n* 93) | | High (*n* 92) | | |
| Age (years) | 34·5 | 1·4 | 34·4 | 1·4 | 36·5 | 1·4 | NS |
| PWC 150/kg | 7·5 | 0·3 | 6·9 | 0·3 | 6·9 | 0·3 | NS |
| Na intake (mg/d) | 1989 | 70 | 2844 | 69 | 4180 | 70 | – |
| Fat intake (g/d) | 73·7 | 2·9 | 81·4 | 3·0‡ | 90·2 | 3·0* | < 0·0001 |
| Sugar intake (g/d) | 92·5 | 4·8 | 92·3 | 5·0 | 94·3 | 4·9 | NS |
| Energy intake (kcal/d) | 1872 | 44 | 2019 | 45‡ | 2235 | 45* | < 0·0001 |
| Body weight (kg) | 63·4 | 2·3 | 67·7 | 2·3 | 76·1 | 2·3* | < 0·0001 |
| BMI (kg/m$^2$) | 24·7 | 0·9 | 26·0 | 0·9 | 29·3 | 0·9* | < 0·0001 |
| Body fat (%) | 29·0 | 1·2 | 30·3 | 1·3 | 35·0 | 1·3* | < 0·0001 |
| Fat mass (kg) | 19·6 | 1·7 | 21·8 | 1·7 | 28·6 | 1·7* | < 0·0001 |
| Fat-free mass (kg) | 43·9 | 0·8 | 45·9 | 0·8‡ | 48·1 | 0·8* | 0·0002 |
| Waist circumference (cm) | 75·9 | 1·9 | 80·4 | 2·0‡ | 87·6 | 2·0* | < 0·0001 |
| Visceral fat (cm$^2$) | 75·4 | 7·4 | 81·3 | 7·5 | 100·5 | 7·4* | 0·0103 |

NS: non-significant.
Values are means ± SEM after adjustment for age and misreporting.
PWC 150/kg: Power work capacity at 150 heart beats expressed per kg of body weight.
* High significantly different from low and middle.
† High significantly different from low.
‡ Middle significantly different from low.

CRF–Na intake interaction remained the same after further adjustment for NRF6·3 or fruit and vegetable consumption. Similarly, all mediating effects reported in Table 3 for BMI and WC remained significant.

## Discussion

The study of the relationship between dietary factors and the risk of obesity has been traditionally oriented towards the impact of macronutrients and other dietary factors providing energy such as alcohol. However, our research and that of others have shown that micronutrients such as Ca also affect energy balance and body composition[39–41] and may even be more related to the risk of excess body weight compared with high fat or alcohol consumption[42]. In the present study, we have pursued the investigation of body weight-related effects of micronutrients by focussing on the potential link between Na intake and body composition. Our results confirmed those obtained in previous population-based studies having demonstrated a positive association between Na intake and body weight and fat[7–10,43]. We also report for the first time a significant interaction effect between Na intake and CRF in females according to which the detrimental effects of high Na intake on adiposity are more pronounced in females displaying a low fitness level. Finally, this study gave us the opportunity to extend our research pertaining to the genetics of obesity by showing that Na intake and CRF are significant mediators of the relationship between a polygenic risk score of obesity and BMI or WC.

The mechanisms explaining the effects of Na on body homeostasis have been mostly studied to understand the increased risk of high blood pressure and CVD that may result from excess Na intake. With respect to the Na–obesity relationship, the available literature is less abundant but nevertheless permits to propose plausible explanations of the potential obesogenic role of excess Na intake. The first hypothesis that is worthy of consideration is related to the drinking habits that allow to compensate for the thirst induced by high Na intake[2]. In high Na consumers, an increase in Na intake was found to predict an increase in sugar intake[8]. The experience of culinary art also provides a potential explanation of the link between Na intake and body fat. Indeed, the usual practice in fine cuisine relies on high-fat foods such as cream to exert a tuning effect on food texture and flavor, e.g. salty taste, that increases palatability and may promote overconsumption. These observations are compatible with the fact that an increase in Na intake in this study was related to an increase in fat intake in both sexes. On the other hand, it is also relevant to indicate that the statistical adjustment for both

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**Table 2.** Effects of cardiorespiratory fitness and sodium intake on body composition in males and females

| | Low CRF | | | Mid CRF | | | High CRF | | | *P*-values | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Variable | Low NA | Mid Na | High Na | Low Na | Mid Na | High Na | Low Na | Mid Na | High Na | CRF | Na | CRF x Na interaction |
| Males | 23≤ N ≤31 | 23≤ N ≤27 | 20≤ N ≤25 | 18≤ N ≤24 | 25≤ N ≤34 | 20≤ N ≤26 | 22≤ N ≤28 | 18≤ N ≤22 | 27≤ N ≤32 | | | |
| Weight (kg) | 78·9 ± 3·0 | 82·8 ± 3·2 | 83·8 ± 3·4 | 69·9 ± 3·3 | 78·1 ± 3·1 | 87·9 ± 3·3 | 72·3 ± 3·1 | 75·7 ± 3·4 | 81·0 ± 3·1 | NS | 0·0003 | NS |
| BMI (kg/m$^2$) | 26·0 ± 0·9 | 27·6 ± 1·0 | 28·4 ± 1·0 | 24·0 ± 1·0 | 26·1 ± 0·9 | 28·6 ± 1·0 | 23·8 ± 0·9 | 25·3 ± 1·0 | 26·3 ± 0·9 | 0·009 | 0·0003 | NS |
| WC (cm) | 91·1 ± 2·4 | 93·2 ± 2·5 | 95·9 ± 2·7 | 84·0 ± 2·6 | 89·5 ± 2·5 | 96·4 ± 2·6 | 84·1 ± 2·5 | 87·5 ± 2·7 | 91·2 ± 2·5 | 0·007 | 0·0004 | NS |
| Body fat (%) | 24·3 ± 1·3 | 24·0 ± 1·4 | 25·3 ± 1·5 | 19·9 ± 1·5 | 20·6 ± 1·4 | 23·8 ± 1·5 | 18·0 ± 1·4 | 18·7 ± 1·5 | 18·8 ± 1·4 | < 0·0001 | NS | NS |
| Fat mass (kg) | 20·8 ± 1·8 | 21·7 ± 2·0 | 22·4 ± 2·1 | 13·9 ± 2·0 | 16·7 ± 1·9 | 22·2 ± 2·1 | 13·3 ± 1·9 | 15·0 ± 2·1 | 16·6 ± 1·9 | < 0·0001 | 0·0197 | NS |
| AVF (cm$^2$) | 128·2 ± 13·3 | 131·2 ± 14·0 | 144·6 ± 15·0 | 90·6 ± 14·6 | 107·6 ± 14·1 | 132·6 ± 14·1 | 76·8 ± 13·9 | 84·1 ± 15·2 | 102·0 ± 13·5 | < 0·0001 | 0·0400 | NS |
| Females | 25≤ N ≤27 | 33≤ N ≤38 | 25≤ N ≤28 | 25≤ N ≤28 | 22≤ N ≤29 | 29≤ N ≤35 | 23≤ N ≤37 | 21≤ N ≤26 | 27≤ N ≤29 | | | |
| Weight (kg) | 70·5 ± 3·1 | 72·0 ± 2·8 | 90·5 ± 3·2 | 66·0 ± 3·1 | 70·3 ± 3·3 | 72·8 ± 2·9 | 59·9 ± 2·9 | 63·7 ± 3·2 | 67·7 ± 3·1 | < 0·0001 | < 0·0001 | 0·013 |
| BMI (kg/m$^2$) | 27·9 ± 1·1 | 27·7 ± 1·0 | 35·2 ± 1·2 | 25·7 ± 1·1 | 27·3 ± 1·2 | 27·6 ± 1·1 | 23·0 ± 1·1 | 24·1 ± 1·2 | 26·2 ± 1·1 | < 0·0001 | < 0·0001 | 0·002 |
| WC (cm) | 81·7 ± 2·6 | 83·0 ± 2·4 | 100·6±2·4 | 79·1 ± 2·6 | 84·7 ± 2·8 | 84·6 ± 2·4 | 73·0 ± 2·5 | 76·9 ± 2·7 | 80·1 ± 2·6 | < 0·0001 | < 0·0001 | 0·001 |
| Body fat (%) | 34·3 ± 1·6 | 33·3 ± 1·5 | 42·4 ± 1·7 | 30·7 ± 1·6 | 33·1 ± 1·8 | 33·8 ± 1·5 | 25·7 ± 1·5 | 26·2 ± 1·6 | 30·2 ± 1·6 | < 0·0001 | < 0·0001 | NS |
| Fat mass (kg) | 26·0 ± 2·2 | 25·4 ± 2·0 | 40·8 ± 2·3 | 21·4 ± 2·1 | 24·7 ± 2·3 | 26·2 ± 2·0 | 16·6 ± 2·1 | 18·3 ± 2·2 | 21·5 ± 2·1 | < 0·0001 | < 0·0001 | 0·002 |
| AVF (cm$^2$) | 97·5 ± 9·9 | 88·7 ± 8·9 | 143·1 ± 10·2 | 77·4 ± 10·0 | 95·5 ± 11·1 | 95·5 ± 9·5 | 67·1 ± 10·3 | 72·1 ± 10·6 | 73·2 ± 9·6 | < 0·0001 | 0·0100 | 0·008 |

Values are means ± SEM after adjustment for age and misreporting.
AVF, area of visceral fat; CRF, cardiorespiratory fitness; Na, Na intake; WC, waist circumference.

total sugar and fat intake did not eliminate the significance of the association between Na intake and morphological indicators, which suggests that other factors contribute to the association between Na intake and body weight stability.

The analysis of the NHANES data has repeatedly shown that the statistical significance of the Na–-obesity relationship is mostly obtained in females[10,43]. In this regard, the results of the present study extend this finding by highlighting an interaction effect between Na intake and aerobic fitness on body fat only in females. Specifically, this effect reflects that the enhancing effect of Na intake on body weight and abdominal fat accumulation is much greater in females displaying a low aerobic fitness, as illustrated in Fig. 1. From a statistical standpoint, this effect is robust since its high statistical significance persisted after adjustment for either total sugar, fat or energy intake. This observation also raises the question as to why aerobic fitness, which provides a better picture of the long-term print of physical activity than reported actual physical activity participation[44], offers a protective effect against weight gain in female high Na consumers. Up to now, there is no clear answer to this question, but the recently reported research of Kitada *et al.*[5] is worthy of consideration in this context. They found that an increase in food intake can prevent hepatic ketogenesis and glucocorticoid-driven muscle catabolism being linked to a mechanism aiming at water conservation via dietary salt excretion and mediated by variations in urea production. In this regard, it was demonstrated that the rate of urea reincorporated into protein is significantly increased during and after exercise of different intensities[45]. This agrees with the observation that exercise is an effective strategy to prevent muscle atrophy and to protect against glucocorticoid-induced muscle wasting, especially in Type II fibres[46]. Taken together, these observations suggest that exercise could replace increased energy intake regarding the prevention of muscle catabolism induced by glucocorticoids. This hypothesis obviously deserves further investigation that might ultimately confirm that muscle catabolism is linked to water and Na balance and could be prevented by a switch from hyperphagia to an agent promoting energy expenditure such as exercise. Furthermore, research is also needed to explain why this effect is more detectable in females than in males.

The use of data of the QFS also gave us the opportunity to extend our research pertaining to the genetics of obesity. At its beginning, the QFS revealed the existence of a significant familial resemblance for body fat and related anthropometric indicators[12,47]. Accordingly, it was subsequently used to examine the association between candidate genes and the proneness to fat gain. A relevant example for the present study was the demonstration that the polymorphism of the glucocorticoid receptor gene is associated with variations in abdominal fat[48] and predicts changes in body weight and fat over time, especially in females[49]. More recently, we performed mediation analyses in participants of QFS and showed that disinhibition and hunger behaviours were significant mediators of the genetic susceptibility of obesity, assessed using a genetic risk score, on BMI and WC[50]. We pursued these analyses in the present study by testing the mediating effects of daily Na intake and CRF on the relationship between a PRS of obesity and variations in BMI or WC. Na intake and

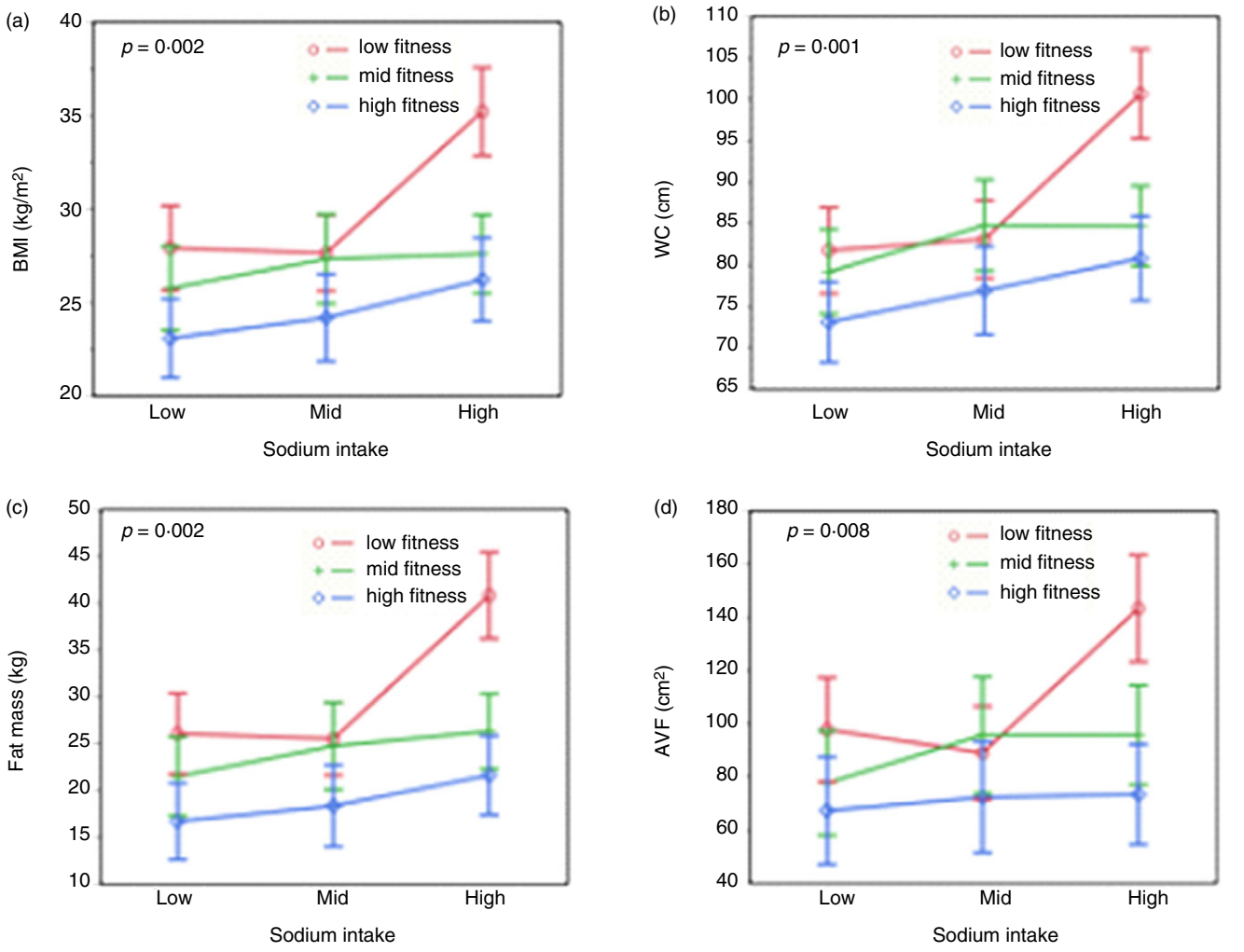


**Fig. 2.** Effect of sodium intake on body composition in females according to fitness level. Figure presents the age- and reporting status adjusted values for BMI (panel A), waist circumference (panel B), fat mass (panel C) and abdominal visceral fat (panel D). Groups of sodium intake and fitness are defined based on sex-specific tertiles of the age-adjusted data of each variable. The *p* value reported is the one corresponding to the effect of interaction.

CRF were found to be significant mediators explaining approximately 8 % and 12 %, respectively, of the PRS–BMI/WC association. We also observed that approximately 18 % of the effect of the obesity PRS on BMI and WC could be explained by the combined mediating effects of Na intake and CRF. Our finding of the mediating effect of Na intake on body fatness is in agreement with a recent Mendelian randomisation study that showed a causal relationship between salt intake and BMI[51]. These results support the role of Na intake as a determinant of obesity and its relevance in a clinical setting since the prevention of excess intake likely contributes to attenuate the genetic susceptibility to obesity.

The measurement of food intake, be it by dietary recalls and diaries, imposes a limitation on the interpretation of the Na–body composition relationship in the present study as it was the case in other population-based studies that documented the existence of this association[7–10,43]. Indeed, even if the 3-d dietary record used in the present study has been found to be a reliable procedure[24], it cannot provide data that are totally representative of usual nutrient and energy intake. This is explained by errors of measurement, including day-to-day variation in food intake reported by participants and the fact that foods coded in the nutrient files may not be perfectly representative of reported foods. However, the adjustment made for misreporting in the present study contributed to reduce this bias. The corollary of these observations is that even if a relationship such as that is potentially linking Na and body fat is adjusted for daily energy intake, it is likely that its contribution to the relationship is not entirely withdrawn by the statistical adjustment. Furthermore, it is worthy to remind that variations in body fat over time result from fluctuations in energy balance, i.e. not energy intake *per se*. Taken together, these observations indicate that it would be unjustified to consider that the first law of thermodynamics is not involved in the effect of a nutrient not containing energy such as Na on the predisposition to obesity.

Despite the statistical adjustments of nutrient intake data for misreporting and the demonstration of a mediation role of Na intake on the PRS–BMI relationship, the results of the study cannot be generalised to the entire population. Indeed, the QFS was



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**Table 3.** Mediating effects of sodium and CRF on the association between the obesity PRS and measures of obesity*

| | BMI | | | | Waist circumference | | | |
|---|---|---|---|---|---|---|---|---|
| | *β* | SE | 95 % CI | *P* value | *β* | SE | 95 % CI | *P* value |
| Mediation through Na Na † | | | | | | | | |
| Total effect | 0·49 | 0·03 | 0·43, 0·55 | < 0·0001 | 0·44 | 0·03 | 0·38, 0·50 | < 0·0001 |
| Direct effect (not via Na) | 0·46 | 0·03 | 0·40, 0·51 | < 0·0001 | 0·41 | 0·03 | 0·35, 0·46 | < 0·0001 |
| Indirect effect (via Na) | 0·03 | 0·01 | 0·02, 0·06 | 0·0002 | 0·04 | 0·01 | 0·02, 0·06 | 0·0001 |
| % mediation | 7·1 | | | | 8·2 | | | |
| Mediation through CRF‡ | | | | | | | | |
| Total effect | 0·35 | 0·03 | 0·29, 0·42 | < 0·001 | 0·33 | 0·03 | 0·26, 0·39 | < 0·0001 |
| Direct effect (not via CRF) | 0·31 | 0·03 | 0·25, 0·37 | < 0·0001 | 0·29 | 0·03 | 0·22, 0·35 | < 0·0001 |
| Indirect effect (via CRF) | 0·04 | 0·01 | 0·02, 0·07 | 0·002 | 0·04 | 0·01 | 0·02, 0·06 | 0·002 |
| % mediation | 12·1 | | | | 11·9 | | | |
| Mediation through Na and CRF‡ | | | | | | | | |
| Total effect | 0·33 | 0·03 | 0·26, 0·39 | < 0·0001 | 0·31 | 0·03 | 0·24, 0·37 | < 0·0001 |
| Direct effect (not via Na and CRF) | 0·27 | 0·03 | 0·21, 0·33 | < 0·0001 | 0·25 | 0·03 | 0·18, 0·31 | < 0·0001 |
| Total indirect effect (via Na and CRF)§ | 0·06 | 0·01 | 0·03, 0·09 | | 0·06 | 0·01 | 0·03, 0·09 | |
| Specific indirect effect (via Na) | 0·03 | 0·01 | 0·01, 0·04 | 0·005 | 0·03 | 0·01 | 0·01, 0·05 | 0·004 |
| Specific indirect effect (via CRF) | 0·03 | 0·01 | 0·02, 0·05 | 0·001 | 0·03 | 0·01 | 0·01, 0·05 | 0·002 |
| % mediation (total) | 17·2 | | | | 18·5 | | | |
| % mediation (Na) | 7·3 | | | | 8·8 | | | |
| % mediation (CRF) | 9·9 | | | | 9·7 | | | |

CRF, cardiorespiratory fitness; PRS, polygenic risk score.
* Values are standardised regression coefficients (*β*) ± standard errors (SE). All analyses performed on age- and sex-adjusted data with further adjustment for misreporting for mediation models including Na.
† *n* 750.
‡ *n* 500.
§ *P* values for the total indirect effect in multiple mediation model not provided by PROCESS.

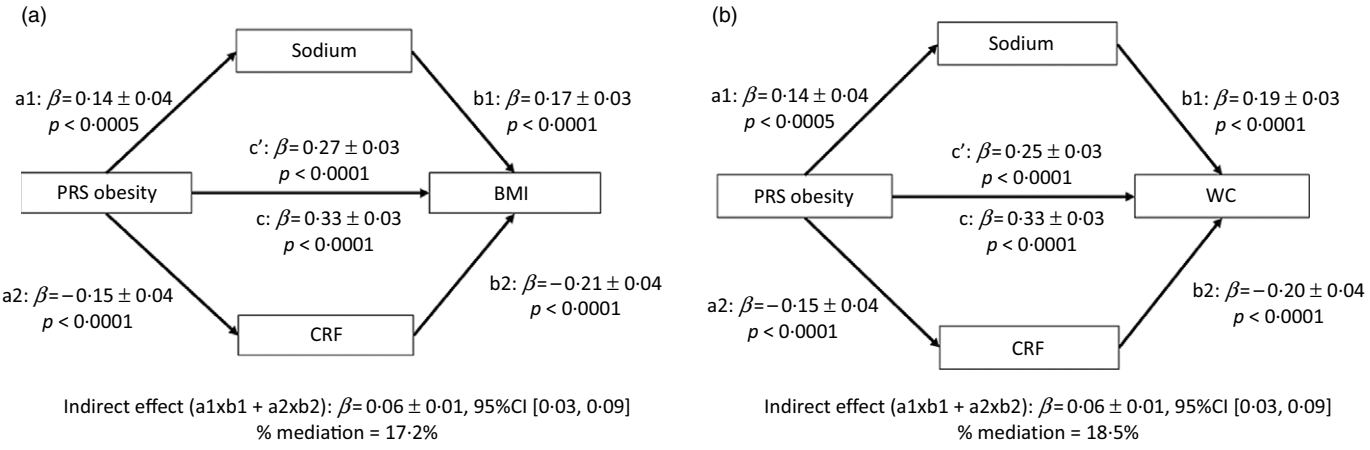


**Fig. 3.** Combined mediating effects of sodium intake (sodium) and cardiorespiratory fitness (CRF) on the association between the PRS of obesity and measures of BMI (panel A) and waist circumference (panel B). Standardised regression coefficients (*β*) are presented for each path of the model on data adjusted for age, sex and misreporting. The combined mediating effect of sodium and CRF is represented by the sum of indirect specific effects for sodium (a1 × b1) and CRF (a2 × b2).

based on a voluntary participation leading to the recruitment of a study sample that may not be entirely representative of the general population.

In conclusion, the present study provides additional evidence that high Na intake may partly explain the proneness to obesity, especially in females. The results also revealed the existence of an interaction effect between Na intake and CRF in females suggesting that an increased aerobic capacity exerts a protective effect against the obesogenic effect of high Na intake. Finally, mediation analyses showed that Na intake and CRF are significant mediators of the genetic susceptibility to obesity. From a clinical standpoint, the present study and others support the idea that beyond the prevention of hypertension and metabolic complications, it is relevant to avoid high Na intake to facilitate body weight stability.

## Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S0007114522000666

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