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Sex-specific effects of vegetarian diet on adiponectin levels and insulin sensitivity in healthy non-obese individuals

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ABSTRACT

Objectives: The beneficial influence of a vegetarian diet in reducing the risk for metabolic syndrome has been demonstrated. However, adiponectin production and secretion are scarcely studied in vegetarians, despite their important role in recovering metabolic homeostasis by reducing visceral obesity, inflammation, and insulin resistance. The aim of this study was to evaluate the effect of a vegetarian diet on serum adiponectin levels and its association with the established biomarkers of insulin sensitivity and inflammation in healthy, non-obese individuals.

Methods: Adiponectin, C-reactive protein, uric acid, glucose, insulin, lymphocyte and polymorphonuclear cell counts were determined in the blood of sex- and age-matched healthy vegetarian (n = 40) and omnivore (n = 36) individuals. The homeostatic model assessment (HOMA-2) calculator was used for the β-cell function (HOMA2-%B) and insulin resistance index (HOMA2-IRI) estimation.

Results: Adiponectin levels were significantly higher in female vegetarians than the respective omnivore controls ($P = 0.03$), whereas no dietary-associated difference was observed in men. HOMA2-%B was significantly higher in vegetarians than in omnivore controls ($P = 0.04$), whereas no diet-dependent differences were found in insulin, HOMA2-IRI, inflammatory, and metabolic biomarkers. Multiple regression analysis showed that adiponectin levels were significantly predicted by the type of diet only in women ($P = 0.042$), whereas no associations were found in men.

Conclusions: A vegetarian diet resulted in improved β-cell function. Favorable adiponectin and insulin sensitivity responses in women reveal a distinct effect of diet-to-metabolic homeostasis, indicating an interesting pattern of sexual dimorphism regarding the beneficial metabolic effect of a vegetarian diet.

Introduction

It is generally considered that a vegetarian diet, if appropriately planned and conducted, may provide both adequate nutrition and health benefits, particularly in reducing the risks for chronic non-communicable diseases [1]. Metabolic syndrome (MetS), a cluster of metabolic abnormalities involving insulin resistance (IR), dyslipidemia, hypertension, and abdominal obesity, represents a significant risk factor in most prevalent chronic diseases, such as diabetes, cancer, and cardiovascular disease (CVD) [2]. Considering the pivotal role of obesity in the pathogenesis of MetS, preventive health care strategies aimed at tackling global epidemics of high-risk conditions recognized dietary interventions as the critical component [3]. Various dietary regimens with restricted calorie intake were found to be effective in reducing body weight and alleviating diverse molecular components of MetS [4,5]. The results of the Adventist Health Study 2 showed that a vegetarian diet was associated with a more favorable metabolic risk profile and lower incidence of MetS in the general adult population [6].

Adipose tissue, particularly its visceral compartment, serves not only as a body energy depot, but also as an essential endocrine organ producing adipokines—bioactive peptides acting as crucial molecular regulators of body weight and energy homeostasis [7]. Deregulation of adipokine metabolism triggers biochemical abnormalities intertwined in MetS. Among adipokines, adiponectin—a 30 kDa protein comprising 244 amino acids—plays a prominent

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protective metabolic role due to its ability to improve insulin sensitivity and reduce inflammation and endothelial dysfunction [8]. Adiponectin is structurally similar to the C1 q complement factor and circulates at relatively high concentrations in three major forms: trimers, hexamers, and high-molecular-weight (HMW) multimers. The consistent evidence from human studies indicates a significantly lower adiponectin level in overweight/obese individuals [7,8]. It was hypothesized that adiponectin might be a key molecular link between obesity and MetS. Thus, interventions aimed at improving adiponectin levels and action became a very attractive research field, including both the pharmacologic and lifestyle approach.

Adiponectin levels can be modulated by lifestyle interventions, such as exercise and diet. In a meta-analysis including 52 studies, Silva et al. [9] reported on the favorable effect of specific dietary patterns on adiponectin recovery. Fish-rich diet and ω-3-supplementation, fiber supplementation, and combined low-calorie diet and exercise were found to be the most effective dietary patterns associated with both weight loss and recovery of adiponectin levels. Thus far, the collected evidence on the effect of a vegetarian/vegan diet on adiponectin levels is scarce and related to distinct clinical entities, such as children and individuals with diabetes. The vegetarian diet was reported to elicit an improvement in the anti-inflammatory adipokine profile in prepubertal children, although no difference in adiponectin levels per se was found [10]. In a 24-wk randomized trial, Kahleova et al. demonstrated that a calorie-restricted vegetarian diet was superior to a conventional diabetic diet in the improvement of insulin sensitivity and adiponectin levels in obese individuals with type 2 diabetes [11].

This study aimed to evaluate the effect of a vegetarian diet on serum adiponectin levels and its association with the established biomarkers of insulin sensitivity and inflammation in healthy, non-obese individuals.

Methods and materials

Study participants

This case–control study included healthy non-obese adult vegetarians and age- and sex-matched non-vegetarian individuals who served as controls. Inclusion criteria were as follows:

- Non-obese adults (body mass index [BMI] <30 kg/m^2; 18–60 y of age) with no medical history of or pharmacologic treatment for chronic illness/condition, and clinical or laboratory signs of acute infection at the time of the study;
- Vegetarian/vegan diet for the vegetarian and mixed diet for the non-vegetarian group, respectively; and
- Non-pregnant and non-lactating women.

Individuals with a history of exposure to ionizing radiation or corticosteroid treatment in the previous 6 mo or to antibiotics in the previous 3 mo were excluded from the study.

Study participants provided a detailed report on their lifestyle and dietary habits in the form of a standardized questionnaire based on the non-quantitative food frequency questionnaire (FFQ), as described in detail previously [12].

The study was approved by the Ethics Committee of the Institute of Medical Research and Occupational Health, Zagreb, Croatia. The participants were informed in detail about the study, and those willing to participate gave their informed consent.

Sampling procedure

Blood samples were obtained by phlebotomy the morning after an overnight fast using vacuum tubes with and without appropriate anticoagulants (Becton Dickinson, Franklin Lakes, NJ, USA). Blood sampling was carried out during a 3-mo winter period to avoid the confounding effect of seasonal variability in nutrition factors and sun exposure. The blood samples were processed according to preanalytical protocols including centrifugation (3000*g*, 10 min) and separation of serum samples that were either immediately analyzed (serum glucose, uric acid, C-reactive protein [CRP], white blood cells [WBCs], lymphocytes, neutrophils) or aliquoted and stored (−80°C) for the laboratory determination of adiponectin and insulin concentrations.

Laboratory analysis

Serum glucose and uric acid concentrations were determined by the reference hexokinase and enzymatic colorimetric uricase methods, respectively (AU680 Chemistry System, Beckman Coulter, Brea, CA, USA). Latex-enhanced immunoturbidimetric procedure with a dynamic range of 0.2 to 160 mg/L was used for the high-sensitivity CRP measurement (AU680 Chemistry System, Beckman Coulter). Lymphocyte and polymorphonuclear cell (PMNC) counts were determined in fresh whole-blood samples anticoagulated with K3 EDTA by an automated blood counter (Advia120, Siemens Healthineers, USA).

Fasting serum insulin was determined by an automated chemiluminescent immunoassay (Advia Centaur XP, Siemens Healthineers, Tarrytown, NY) standardized against World Health Organization (WHO) first IRP 66/304 reference material with a total imprecision expressed as coefficient of variation (CV) of 4.89%.

Estimation of insulin sensitivity and β-cell function

Homeostasis model assessment HOMA2 Calculator (version 2.2.2, Diabetes Trials Unit, University of Oxford, UK) was used to estimate β-cell function (HOMA2-%B) and insulin resistance index (HOMA2-IRI) from fasting glucose and insulin concentrations [13]. HOMA2 is a dedicated algorithm that estimates steady state β-cell function and insulin sensitivity as percentages of a healthy reference population. The IRI is a reciprocal of the estimated insulin sensitivity.

Adiponectin analysis

Total serum adiponectin was measured by a validated automated immunoturbidimetric assay (Randox Laboratories, Crumlin, UK) with declared assay range of 0.7 to 28.1 mg/L and within-and total-run CVs of 1.6% and 1.9%, respectively. Aliquots of frozen sera were thawed at room temperature, vortexed, and centrifuged before the analysis, which was carried out in the same series of single samples on the AU680 Chemistry System (Beckman Coulter).

Statistical analysis

After testing for normality, normally distributed continuous data were expressed as mean ± SD, whereas the median ± interquartile range (IQR) was used for the expression of the data that were not normally distributed. Differences in continuous variables between the vegetarian and non-vegetarian groups were analyzed with the Student's *t* test or Mann–Whitney test, as appropriate. A χ^2 test was used for the assessment of differences between categorical variables. Multivariate regression analysis was carried out to evaluate associations between variables. Statistical analyses were performed using MedCalc Statistical Software version 18.11.6 (MedCalc Software bvba, Ostend, Belgium) statistical software. $P < 0.05$ was considered statistically significant.

Sample size calculation was based on the absolute change of adiponectin levels between the vegetarian and omnivore control groups. A change of 0.5 SD was considered biologically relevant. With α error probability of 0.05 and power of 0.8, a total sample size of 10 samples per group was estimated (G*Power v. 3.1.9.2).

Results

Seventy-six adults meeting the inclusion criteria and willing to participate were included in the study. All were white, lived in the same geographic region (Zagreb metropolitan area), and shared similar patterns of education and physical activity. The control group (n = 36; 23 women) reported adherence to a Mediterranean-type mixed diet, whereas the vegetarian group (n = 40; 24 women) included 10 vegans and 30 lacto-ovo vegetarians. The composition of the diet of each study group was described in detail previously [12]. The average period of vegetarian dietary practice was 8.85 ± 4.69 y (range 3–20 y). The percentage of active smokers was the same in both groups (17.5%). There was no statistically significant difference regarding vitamin, minerals, and ω-3 fatty acid supplements taken between the groups ($P > 0.05$, not shown). Moderate physical activity (≤150 min/wk) was reported by all the participants. Population characteristics are given in Table 1. The groups did not differ regarding age, BMI, and sex distribution ($P = 0.58$, $P = 0.57$, and $P = 0.82$, respectively). As expected, the men had a significantly higher BMI than the women ($P < 0.0001$, Table 2).

Table 1
General, anthropometric and biochemical characteristics of the study groups according to dietary habits

	Vegetarians (n = 40)	Controls (n = 36)	*P*-value
Age (y)	30 (19–55)	30 (22–59)	0.58
M/F (n)	16/24	13/23	0.82
BMI (kg/m^2)	22.4 ± 2.6	22.8 ± 3	0.57
Adiponectin (mg/L)	10.1 [6.8–13.1]	9.2 [6–12.2]	0.22
WBC (× 10^9/L)	5.4 [4.9–6.9]	6 [5.2–7]	0.20
PMNC (× 10^9/L)	3.35 ± 0.99	3.46 ± 1.14	0.64
Lymphocytes (× 10^9/L)	1.71[1.46–2.08]	2.03 [1.46–2.43]	0.19
hs-CRP (mg/L)	0.40 [0.20–1.08]	0.50 [0.30–1.48]	0.19
Serum uric acid (μmol/L)	226 ± 63	240 ± 69	0.35
Fasting glucose (mmol/L)	4.9 ± 0.5	5 ± 0.4	0.66
Fasting insulin (pmol/L)	41.3 [36.2–56.9]	51.2 [37.8–71.3]	0.07
HOMA2-IRI	0.90 [0.80–1.20]	1.10 [0.80–1.50]	0.06
HOMA2-%B	115.5 ± 42.9	91 ± 35	0.04
Vegetarian practice duration (y)	9 (3–20)	–	–

BMI, body mass index; HOMA2-IRI, homeostatic model assessment 2-insulin resistance index; HOMA2-%B, homeostatic model assessment 2-β cell function; hs-CRP, high-sensitivity C-reactive protein; PMNC, polymorphonuclear cell; WBC, white blood cell
Data expressed as median (range); mean ± SD; median [interquartile range]
To emphasize a statistically significant value. The value is in bold since the *P* value is lower then 0.05, but it can be un-bold.

Inflammatory and metabolic biomarkers

Inflammatory biomarkers—lymphocytes, PMNC, and serum high-sensitivity CRP (hs-CRP)—did not differ between the two groups. The level of serum uric acid—a recognized metabolic biomarker with antioxidant properties—also did not differ (Table 1). Also, no significant difference was found in a separate analysis according to sex and dietary habits in either of the inflammatory or metabolic biomarkers (Table 2), although serum uric acid level was significantly lower in women than men in the entire study cohort ($P < 0.001$).

Glycemia, insulin resistance, and β-cell function

Fasting serum glucose concentration was not significantly affected by dietary habits in neither the entire group (Table 1) nor in the sex-associated subgroups (Table 2). On the other hand, HOMA2-estimated v function (HOMA2-%B) was significantly higher in vegetarians than in omnivore controls ($P = 0.04$; Table 1).

Significantly higher insulin and HOMA2-IRI were found in the men than in the women in the entire study cohort ($P = 0.02$; Table 2). Sex-specific analysis showed that female vegetarians had significantly lower fasting insulin and HOMA2-IRI, as well as HOMA2-%B, than omnivore controls ($P = 0.02$; Table 2). No differences in these biomarkers were observed in male vegetarians when compared with sex-specific omnivore controls ($P = 0.77$, $P = 0.59$, and $P = 0.44$, respectively).

Adiponectin

Adiponectin levels did not differ between the vegetarian and omnivore participants ($P = 0.19$) but were significantly higher in the women than in the men in the entire study cohort (11.7 [9.9–14.6] versus 6.6 [4.9–8.3] mg/L; $P < 0.001$). Furthermore, significantly higher adiponectin levels were found in female vegetarians when compared with omnivore controls ($P = 0.03$), although there was no difference in male participants ($P = 0.79$). The results are presented in Table 1 and Figure 1.

Associations between variables

Simple Spearman's rank correlation analysis in the entire study cohort detected significant negative correlation between adiponectin and BMI ($r = -0.445$, $P = 0.0001$), serum uric acid ($r = -0.477$, $P < 0.0001$), age ($r = -0.230$, $P = 0.044$), CRP ($r = -0.275$, $P = 0.02$), and fasting plasma glucose ($r = -0.233$, $P = 0.043$). These variables, together with sex and type of diet, were included in a linear regression model, which predicted adiponectin levels (F-ratio = 3.676, $R^2 = 0.3545$, $P < 0.0001$), with sex and type of diet adding significantly to the prediction ($P = 0.001$ and $P = 0.049$, respectively). Sex-specific multiple regression analysis showed that adiponectin levels were significantly predicted by the type of diet in women, but not in men ($P = 0.006$ and $P = 0.296$, respectively). At the same time, BMI predicted adiponectin levels in male participants ($P = 0.005$). Also, fasting serum insulin and HOMA2-IRI were significantly predicted by BMI only ($P = 0.002$), whereas no influence of sex, type of diet, or any of the inflammatory or metabolic parameters could be demonstrated.

Discussion

In this study, we investigated the influence of a vegetarian diet on serum adiponectin levels and its association with IR and the established inflammatory and metabolic biomarkers in healthy non-obese adults. Serum adiponectin levels were significantly higher in female, but not in male vegetarians compared with omnivore controls. Also, the vegetarian diet improved biomarkers of IR and β-cell function in the women only. Finally, as assessed by multiple linear regression analysis, the type of diet was able to independently predict adiponectin levels in the women, indicating an interesting and previously not-evidenced pattern of gender dimorphism regarding the beneficial metabolic effect of a vegetarian diet.

The benefits of a vegetarian diet in improving health and reducing the risks for adverse health outcomes have been extensively researched. A recent systematic review and meta-analysis of observational studies has shown a significantly reduced risk for both incidence and mortality from ischemic heart disease and the incidence of total cancer associated with a vegetarian diet [14]. However, the benefits regarding total cardiovascular and cerebrovascular morbidity and all-cause mortality, which are associated with obesity and MetS, could not be demonstrated, probably due to substantial differences in response to the vegetarian diet observed in heterogeneous study populations. A previous study showed that a mixed Mediterranean diet might offer better micronutritional status and antioxidant protection, as well as a lower level of genome damage than a vegetarian diet in healthy non-obese individuals [12]. Nevertheless, IR was found to be ameliorated by vegetarian [15] as well as a vegan diet [16], suggesting potential benefits in the prevention of diabetes and cardiometabolic diseases.

Some reports have indicated that weight loss itself, rather than the type of diet, may be responsible for favorable metabolic effects, including adiponectin recovery in an obese population [17]. Chiang et al. reported that a lacto-ovo-vegetarian diet was associated with a reduced risk for MetS and IR in female Buddhists [18]. The results of the present case–control study, conducted with comparable participants regarding common confounding factors (age, BMI, physical activity, duration of vegetarian practice), demonstrate for the first time that the vegetarian diet elicits a protective metabolic effect in women but not in men. The present results suggested the existence of sex-specific mechanism(s) responsible for improved adiponectin and insulin sensitivity response.

Table 2
General, anthropometric, and biochemical characteristics of the study population according to sex

	Women			Men		
	Vegetarians	Controls	Total	Vegetarians	Controls	Total
N	24	23	47	16	13	29
Age (y)	30 (19–55)	29 (22–59)	29 (19–59)	33 (25–49)	32 (25–42)	32 (25–49)
BMI (kg/m^2)	21.8 ± 2.3	21.3 ± 2.5	21.5 ± 2.4	23.8 ± 2.7	25.1 ± 2	24.3 ± 2.5*
WBC (× 10^9/L)	5.7 [5–6.8]	6 [5.3–7.2]	5.9 [5.1–7]	5.1 [4.9–7.2]	5.8 [4.6–7]	5.4 [4.8–7]
PMNC (× 10^9/L)	3.32 ± 0.86	3.60 ± 1.22	3.45 ± 1.05	3.39 ± 1.18	3.28 ± 0.99	3.34 ± 1.08
Lymphocytes (× 10^9/L)	1.84 [1.56–2.03]	2.06 [1.58–2.45]	1.90 [1.38–2.35]	1.50 [1.57–2.34]	1.57 [1.40–2.28]	1.54 [1.38–2.15]
hs-CRP (mg/L)	0.40 [0.20–0-98]	0.50 [0.18–1.30]	0.50 [0.20–1.05]	0.40 [0.15–1.15]	0.75 [0.40–1.50]	0.55 [0.30–1.40]
Serum uric acid (μmol/L)	193 ± 47	203 ± 40	197 ± 44	276 ± 48	302 ± 62	288 ± 55*
Fasting glucose (mmol/L)	4.8 ± 0.4	4.9 ± 0.4	4.8 ± 0.4	5 ± 0.6	5.1 ± 0.5	5 ± 0.5
Fasting insulin (pmol/L)	38.4† [35.1–46.4]	49.9 [37.7–63.8]	42.5 [36.2–53.4]	57 [37.9–69.9]	57 [42–73.8]	57‡ [38,.4–73.3]
HOMA2-IRI	0.80† [0.75–0.95]	1.10 [0.80–1.30]	0.90 [0.80–1.10]	1.20 [0.83–1.68]	1.30 [0.80–1.70]	1.20‡ [0.80–1.63]
HOMA2-%B	124† [102–135]	91 [75–125]	113 [90–132]	86 [67–123]	81 [61–118]	83 [63–123]
Vegetarian practice duration (y)	8 (3–20)	–	–	10 (3–20)	–	–

BMI, body mass index; HOMA2-IRI, homeostatic model assessment 2-insulin resistance index; HOMA2-%B, homeostatic model assessment 2-β cell function; hs-CRP, high-sensitivity C-reactive protein; PMNC, polymorphonuclear cell; WBC, white blood cell
Data expressed as median (range); mean ± SD; median [interquartile range]
*$P < 0.0001$ vs women.
†$P = 0.02$ vs omnivore controls.
‡$P = 0.03$ vs women.

Sex differences in circulating adiponectin levels are well known. Higher circulating adiponectin levels in women than men have been consistently reported in both lean and obese adults [19,20], as well as in individuals with MetS [21]. As recently evidenced by Ohman-Hanson et al., sex differences in adiponectin levels develop during puberty and reach their peak in adulthood [22]. They are consistent throughout one's life and present in the geriatric population as well [23]. Differences in body fat depositions and testosterone concentration have been postulated as biological factors determining the sexual dimorphism of circulating adiponectin levels, positively associated with whole body insulin sensitivity [19,24]. Elevated adiponectin is likely to provide general health benefits by exerting pleiotropic effects that involve improvement in insulin sensitivity, as well as anti-inflammatory and antiapoptotic actions mediated by specific adiponectin receptors expressed in various tissues [25]. Recent evidence on the sex-specific association of adiponectin with clinical indices of heart failure indicate that women are more susceptible to adverse cardiac outcomes due to hypoadiponectinemia than men [26]. Thus, interventions aimed at improving adiponectin levels seem desirable goals in the prevention of adverse health outcomes, particularly in women.

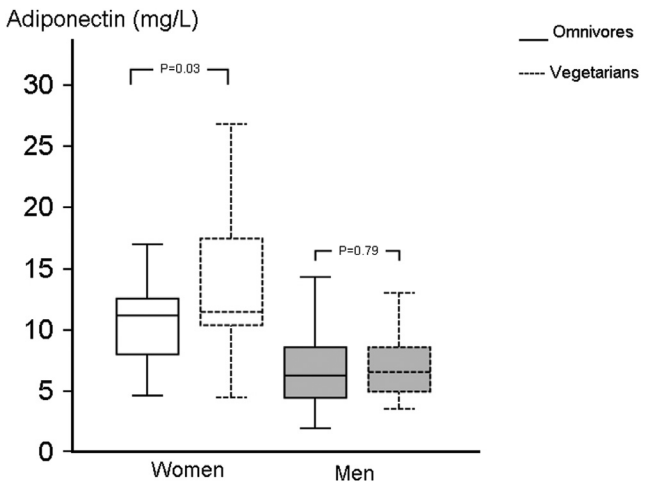

Fig. 1. Serum adiponectin levels in omnivore controls and vegetarians according to sex.
Mann-Whitney *U* test. Data expressed as median [interquartile range].

An array of clinical evidence indicates that women are less prone to IR than men due to specific differences in body composition and energy balance [27]. Men have more lean mass and less adipose tissue than women of equal BMI, but also have an unfavorable distribution of body fat with metabolically active visceral and hepatic fat prevailing over peripheral and subcutaneous adipose tissue, which is a predominant feature in women. Unequal body fat distribution, together with differences in adipokines and sex hormones, stimulate complex molecular mechanisms responsible for the sex-specific differences in insulin sensitivity. The results of this study, showing higher fasting insulin and HOMA2-IRI in men than women, regardless of the type of diet, are in accord with previous reports. Participants in the present study were non-obese, with no differences between the vegetarian and omnivore group regarding BMI, age, and sex distribution. However, at a similar fasting plasma glucose level, omnivore individuals had a significantly higher fasting insulin and IRI, indicating that they needed to produce more insulin to maintain a physiologic euglycemic set-point (5 mmol/L). Again, the beneficial effect of a vegetarian diet was observed in women only. At the same time, no diet-dependent differences were found men males who had higher fasting insulin and HOMA2-IRI regardless of diet. This finding corroborates the well-established evidence of a more pronounced susceptibility to MetS and suggests that a vegetarian diet may not offer protection toward IR in men.

There were several limitations to the present study. The size of the study population was relatively small, and the study included individuals of a single ethnicity and homogenous lifestyle/education level. We did not assess body composition, including fat mass percentage. Furthermore, cross-sectional design could not provide an insight into causal relationships, and single sampling may have introduced a bias due to the effect of biological variability on biomarker levels. Total adiponectin was measured instead of a biologically active HMW form. However, ample evidence indicates a similar association of both adiponectin forms with clinical outcomes [28]. A homogenous study population and standardized approach regarding the seasonality of sampling provided well-matched case–control groups for comparisons.

Conclusions

Despite the aforementioned limitations, the study offered novel evidence on the sexual dimorphism regarding the metabolic benefits of a vegetarian diet in comparison to Mediterranean-type mixed diet in healthy non-obese adults. The vegetarian diet was independently associated with elevated adiponectin levels, followed by reduced fasting insulin and improved insulin sensitivity and β-cell function in women. At the same time, there was no such effect in men. The present results suggested that women may benefit more from a vegetarian diet, whereas some other lifestyle modifications (e.g., exercise) might better serve men in attaining and maintaining metabolic health. Recent evidence from genome-wide association studies of the female-specific genetic variants, which may improve the prediction of MetS, identified sex-associated differences as an essential issue for the prevention and treatment of MetS and associated chronic diseases [29]. The sexual dimorphism observed in this study supports the concept of a personalized approach in designing appropriate lifestyle measures aimed to improve health and reduce cardiometabolic risks in the general population. Longitudinal studies in larger cohorts of women are warranted to assess health benefits from the vegetarian diet in attaining and maintaining metabolic health.

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