

## CLINICAL STUDY

# Gender differences in serum high-molecular-weight adiponectin levels in metabolic syndrome

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## Abstract

**Objective:** The objective of this study was to estimate gender-specific associations between metabolic syndrome (MS) and high-molecular-weight (HMW) adiponectin in an Estonian adult population.

**Methods:** Plasma HMW adiponectin was measured in 458 subjects (191 men) who participated in a population-based cross-sectional multicenter study ( $n=495$ ) on the prevalence of metabolic disorders in Estonia. MS was defined according to National Cholesterol Education Program Adult Treatment Panel III criteria.

**Results:** Median HMW adiponectin levels ( $\mu\text{g/ml}$ ) were significantly lower among all subjects with MS compared with subjects without MS: 2.1 vs 2.8 in men ( $P=0.002$ ) and 3.1 vs 5.1 in women ( $P<0.001$ ). In a fully adjusted, logistic regression model containing HMW adiponectin, homeostasis model assessment of insulin resistance (HOMA-IR), BMI, and age, HMW adiponectin was significantly associated with MS only in women. Comparison of HMW adiponectin and HOMA-IR as markers for MS indicated that HOMA-IR predicted MS better than did HMW adiponectin in both genders. However, after adjusting for age and BMI, HOMA-IR was a significantly better predictor only in men. HMW adiponectin and HOMA-IR predicted the presence of MS at the same level in women. Areas under the receiver operating characteristic curves for HMW adiponectin and HOMA-IR were 0.833 vs 0.88 in men ( $P=0.02$ ) and 0.897 vs 0.907 in women ( $P=0.5$ ).

**Conclusions:** These data suggest that the association between low HMW adiponectin levels and presence of MS might be stronger in women compared with men.

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## Introduction

Metabolic syndrome (MS) is a cluster of metabolic risk factors associated with at least a twofold increase in risk of developing cardiovascular disease and a fivefold increase in risk for type 2 diabetes mellitus (1, 2, 3). According to the latest international consensus, the presence of any three of the following five risk factors constitutes a diagnosis of MS (1): elevated waist circumference (population- and country-specific definitions); triglycerides  $\geq 1.7$  mmol/l or drug treatment for elevated triglycerides; HDL-cholesterol  $< 1.0$  mmol/l for men or  $< 1.3$  mmol/l for women, or drug treatment for reduced HDL-cholesterol; blood pressure  $\geq 130/85$  mmHg, or antihypertensive drug treatment and fasting glucose  $\geq 5.6$  mmol/l; or drug treatment of elevated blood glucose.

The prevalence of the MS is increasing globally, without any universal, gender-specific prevalence differences (4). We recently estimated the weighted prevalence of MS according to the National Cholesterol Education Program (NCEP) Adult Treatment Panel

(ATP) III criteria (5) to be 26% among Estonian adults. Rates for men and women were 29 and 24% respectively (6).

Abdominal adiposity and insulin resistance (IR) appear to be at the core of the development of MS, although it is still unclear whether IR is a unifying pathophysiological mechanism of MS (4). Adipose tissue is an active endocrine organ that releases a large number of bioactive mediators (adipokines) modulating hemostasis, blood pressure, lipid and glucose metabolism, inflammation, and atherosclerosis (7). Adipokines, such as adiponectin, leptin, resistin, and visfatin, provide an important link between obesity, IR, and related inflammatory disorders (8). Among various adipokines, adiponectin stands out due to its abundant expression in adipose tissue and inverse relationship with IR (7), MS (7, 9), and type 2 diabetes (7, 10, 11, 12). In plasma, adiponectin circulates as a low-molecular-weight trimer, a middle-molecular-weight hexamer, and high-molecular-weight (HMW) 12- to 18-mer (7). HMW adiponectin is the most active form of the hormone, and a better predictive power of HMW

adiponectin compared with total adiponectin for glucose intolerance, IR, and MS has been demonstrated in humans (7, 12, 13, 14).

More recent studies about associations between HMW adiponectin and MS come mainly from Asia (15, 16, 17, 18) and the United States (19). The SWAN study from the United States showed significant racial–ethnic differences in circulating adipokine levels. Women of Caucasian origin had higher levels of total and HMW adiponectin compared with women of African-American, Chinese, and Japanese origin (20). However, there are no data available about associations between HMW adiponectin and MS in Europe.

Previous studies (21, 22, 23, 24) have convincingly shown that males have significantly lower levels of adiponectin than females. Data are scant as to whether this gender dimorphism results in any consequences in cardiometabolic conditions in females vs males. A recent study from Finland showed a greater reduction in total adiponectin levels in women compared with men among subjects with both MS and elevated blood pressure (23). The Dutch Hoorn Study demonstrated that the relationship between high total adiponectin level and lower risk of impaired glucose metabolism and type 2 diabetes was stronger among women than men in a group of 50- to 70-year-old subjects (11). However, no gender difference was revealed in the association of total adiponectin with cardiovascular risk factors in German subjects aged 55–74 years (KORA survey 2000) (24). Thus, data on gender-specific associations between adiponectin (especially HMW adiponectin) levels and cardiometabolic risk factors are rather limited so far.

The aims of this general population study were to assess the levels and gender differences in HMW adiponectin levels in subjects with MS and to compare the utility of HMW adiponectin and IR to predict MS in male vs female populations.

## Materials and methods

A population-based cross-sectional multicenter study on the prevalence of metabolic disorders and associated risk factors was conducted between November 2008 and May 2009 in three different counties of Estonia. The study population consisted of randomly selected adults, aged 20–74 years, from four general practices. Study participants were representative of the general Estonian population in terms of age and gender. An invitation letter about the study was sent to each participant. The total response rate was 53.2%, resulting in a total study population of 495 subjects.

On the day of the study, subjects visited their GPs in the morning between 0800 and 1100 h after an overnight fast (lasting at least 10 h). An informed consent form was signed, and blood pressure, waist circumference, height, and weight were measured with participants wearing their indoor clothes without shoes.

Blood pressure was measured using a mercury sphygmomanometer after the patient had been sitting for at least 5 min. The mean of three consecutive measurements was used for analysis, with at least a 3-min interval between each measurement. A face-to-face clinical interview was conducted to assess other medical conditions and cardiovascular risk factors.

Fasting plasma HMW adiponectin was measured in 458 subjects (191 men) in plasma samples that had been stored at  $-80^{\circ}\text{C}$  for a maximum of 2.5 years and had never been thawed. HMW adiponectin was detected by Adiponectin (Multimeric) ELISA (ALPCO Diagnostics, Salem, NH, USA) and by automatic ELISA Triturus analyzer (Grifols International, Barcelona, Spain). Intra-assay coefficient of variation for HMW adiponectin ELISA was 4.8% ( $n=9$ ), and interassay coefficient of variation was 6.9% ( $n=7$ ). Plasma glucose was measured by the hexokinase method. Total cholesterol, HDL-cholesterol, and triglycerides were measured using an enzymatic colorimetric assay (COBAS INTEGRA 800 plus analyzer; Roche). Plasma insulin was measured using a chemiluminescent assay (Immulite 2000 analyzer; Siemens Healthcare Diagnostics, Deerfield, IL, USA).

MS was diagnosed by having at least three of the five NCEP ATP III criteria (5). IR was estimated using homeostasis model assessment (HOMA):  $\text{HOMA-IR} = \text{fasting glucose (mmol/l)} \times \text{fasting insulin (mU/l)} / 22.5$ . IR was defined as the upper quartile of HOMA-IR in the whole study group (exempting subjects with previously known diabetes mellitus). The threshold for the whole study group was 1.92 (2.04 and 1.82 for men and women respectively). The study was approved by the University of Tartu Ethics Review Committee on Human Research.

## Statistical analysis

Descriptive statistics as medians and interquartile ranges were calculated for the continuous variables. The Mann–Whitney  $U$  test was used for comparisons between different groups. Linear regression analysis with logarithmic HMW adiponectin levels was used for trend analysis over continuous age (adjusted for gender) and for examining association between HMW adiponectin and gender (adjusted for waist circumference, BMI, and use of diabetes, antihypertensive, and lipid-lowering medicines). Multiple logistic regression analysis was used to calculate the odd ratios (ORs) and 95% CI for MS risk factors. Receiver operating characteristic (ROC) curves were generated to compare the ability of HMW adiponectin and HOMA-IR to discriminate between subjects with and without MS. The pROC package in R was used to compare the area under the ROC curves (AUROC), according to DeLong's method.  $P$  values were considered statistically significant at the 0.05 level. Statistical analysis was performed using R software version 2.1.

**Table 1** Gender-specific characteristics of study subjects. Data presented as mean  $\pm$  s.d.

Characteristics	Men <i>n</i> =191	Women <i>n</i> =267	<i>P</i> value	Total <i>n</i> =458
Age (years)	47.4 $\pm$ 14.5	49.0 $\pm$ 14.6	NS	48.3 $\pm$ 14.6
Waist (cm)	97.7 $\pm$ 13.6	90.4 $\pm$ 16.1	<0.001	93.5 $\pm$ 15.5
BMI (kg/m <sup>2</sup> )	27.9 $\pm$ 5.3	28.6 $\pm$ 6.7	NS	28.3 $\pm$ 6.2
Systolic blood pressure (mmHg)	133.3 $\pm$ 15.8	126.8 $\pm$ 17.3	<0.001	129.5 $\pm$ 17.0
Diastolic blood pressure (mmHg)	84.1 $\pm$ 9.7	79.5 $\pm$ 9.6	<0.001	81.4 $\pm$ 9.9
Cholesterol (mmol/l)	5.6 $\pm$ 1.2	5.8 $\pm$ 1.2	0.02	5.7 $\pm$ 1.2
Triglycerides (mmol/l)	1.37 $\pm$ 0.77	1.25 $\pm$ 0.65	NS	1.30 $\pm$ 0.70
HDL-cholesterol (mmol/l)	1.40 $\pm$ 0.43	1.64 $\pm$ 0.45	<0.001	1.54 $\pm$ 0.46
Fasting glucose (mmol/l)	5.6 $\pm$ 0.9	5.4 $\pm$ 0.8	<0.001	5.5 $\pm$ 0.8
2-h glucose during OGTT (mmol/l)	5.7 $\pm$ 2.7	5.7 $\pm$ 2.1	NS	5.7 $\pm$ 2.3
Fasting insulin (mU/l)	6.72 $\pm$ 6.41	6.14 $\pm$ 4.79	NS	6.38 $\pm$ 5.52
HOMA-IR	1.75 $\pm$ 1.85	1.52 $\pm$ 1.35	NS	1.62 $\pm$ 1.58
HMW adiponectin ( $\mu$ g/ml) <sup>a</sup>	2.5 (1.5–3.8)	4.6 (2.9–6.5)	<0.001	3.5 (2.1–5.6)
Impaired fasting glucose <sup>b</sup>	9 (4.7)	12 (4.5)	NS	21 (4.6)
Impaired glucose tolerance <sup>b</sup>	22 (11.5)	22 (8.2)	NS	44 (9.6)
Diabetes <sup>b</sup>	19 (9.9)	20 (7.5)	NS	39 (8.5)
Metabolic syndrome <sup>b</sup>	57 (29.8)	71 (26.6)	NS	128 (27.9)

<sup>a</sup>Data presented as median (interquartile range).

<sup>b</sup>Data presented as *n* (%).

## Results

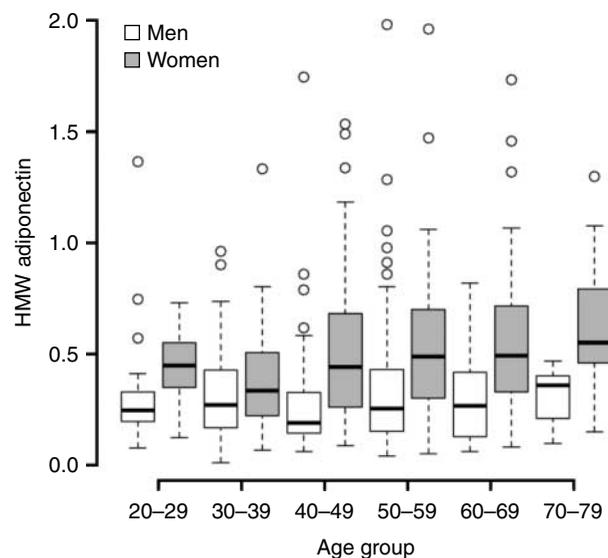
The main characteristics of the study subjects are presented in Table 1. The median HMW adiponectin level ( $\mu$ g/ml) was significantly higher ( $P < 0.001$ ) in women than in men (4.6, 2.9–6.5 vs 2.5, 1.5–3.8; median, interquartile range respectively). This gender difference in HMW adiponectin levels also remained significant after adjustment for waist circumference, BMI, and use of diabetes, antihypertensive, and lipid-lowering medicines. The median HMW adiponectin levels in 10-year age groups in the whole study group showed an increase in older age groups for both genders (Fig. 1). There was a significant positive association between HMW adiponectin and age according to trend analysis ( $P = 0.01$ ). The median (interquartile range) HMW adiponectin level was significantly lower for both genders among subjects with MS compared with those without MS: 2.1 (1.3–3.0) vs 2.8 (1.7–4.3) in men ( $P = 0.002$ ) and 3.1 (2.1–4.8) vs 5.1 (3.5–6.9) in women ( $P < 0.001$ ). The median (interquartile range) HOMA-IR was significantly higher in both genders among subjects with MS compared with those without MS: 2.53 (1.54–3.98) vs 0.76 (0.47–1.27) in men ( $P < 0.001$ ) and 2.45 (1.45–3.52) vs 0.89 (0.49–1.37) in women ( $P < 0.001$ ). The median (interquartile range) HMW adiponectin level was significantly lower in both genders in insulin-resistant subjects compared with those without IR: 1.9 (0.9–2.8) vs 2.8 (1.7–4.2) in men ( $P < 0.001$ ) and 3.0 (2.1–4.7) vs 5.1 (3.5–6.8) in women ( $P < 0.001$ ). HMW adiponectin remained significantly inversely related to MS in women, even after controlling for age, BMI, and HOMA-IR (Table 2).

The predictive value of HMW adiponectin for MS was significantly lower than that of HOMA-IR. The crude AUROC for HMW adiponectin and HOMA-IR were 0.64 vs 0.864 in men ( $P < 0.001$ ) and 0.702 vs 0.839 in

women ( $P = 0.0008$ ) (Fig. 2). After adjustment for age and BMI, the predictive value of HMW adiponectin remained lower than that of HOMA-IR only in men but became equal with HOMA-IR in women. AUROCs for HMW adiponectin and HOMA-IR in men were 0.833 vs 0.88 ( $P = 0.02$ ) and 0.897 vs 0.907 in women ( $P = 0.5$ ) (Fig. 3).

## Discussion

The current study revealed that the association between low HMW adiponectin levels and presence of MS might be stronger in women compared with men. In line with previous studies, our results confirmed a clear gender



**Figure 1** HMW adiponectin ( $\mu$ g/ml) level (mean, interquartile range) in 10-year age groups in the Estonian adult population.

**Table 2** Gender-specific multiple logistic regression analysis to estimate risk factors for metabolic syndrome in an Estonian adult population.

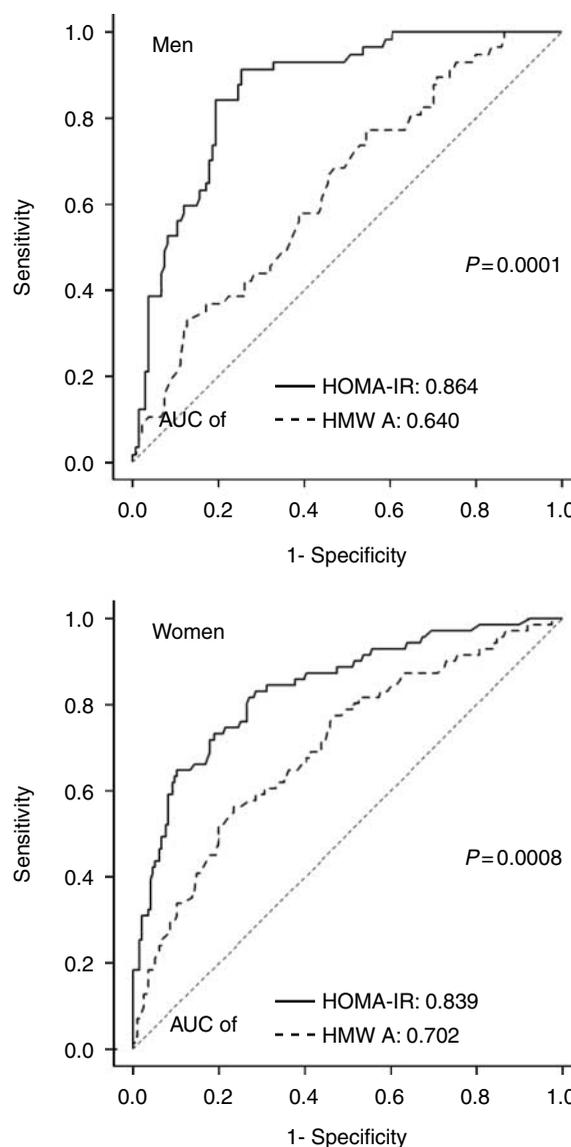
Risk factors	Men			Women		
	OR	95% CI	P value	OR	95% CI	P value
HMW-A ( $\mu\text{g/ml}$ )	0.86	0.70–1.07	NS	0.77	0.65–0.90	0.01
Age (years)	1.03	0.99–1.06	NS	1.10	1.06–1.14	0.001
HOMA-IR	1.58	1.20–2.08	0.01	2.41	1.59–3.65	0.001
BMI ( $\text{kg/m}^2$ )	1.18	1.07–1.29	0.001	1.17	1.09–1.25	0.001

OR, odds ratio; NS, nonsignificant ( $P$  value  $\geq 0.05$ ); HMW-A, high-molecular-weight adiponectin; HOMA-IR, homeostasis model assessment insulin resistance index.

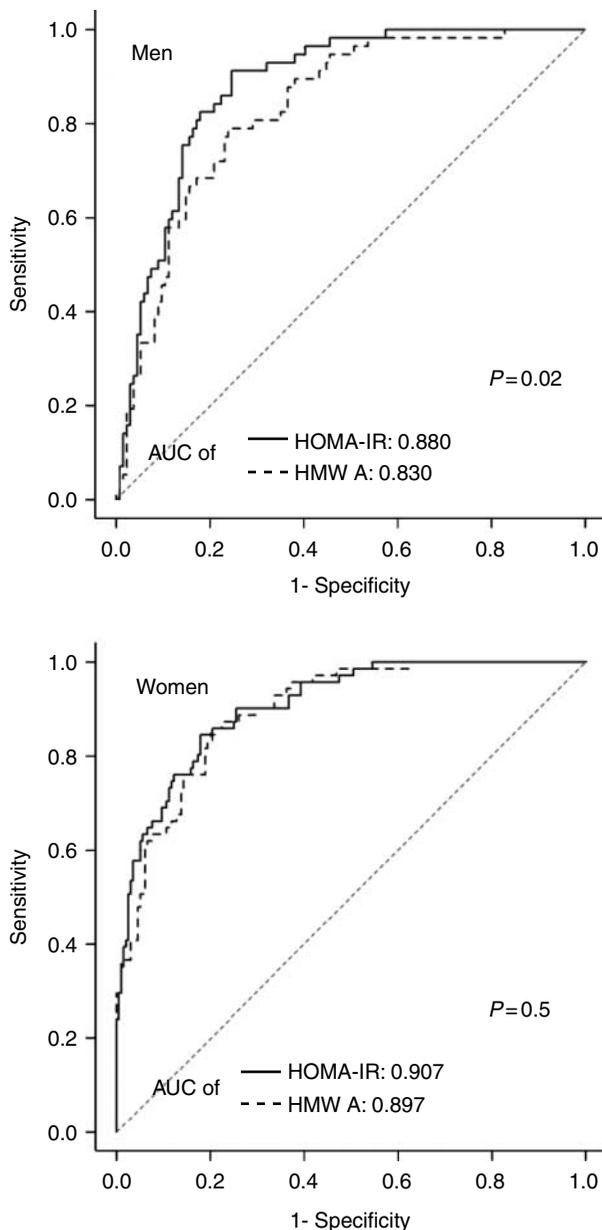
difference in adiponectin levels. The median HMW adiponectin level was significantly higher for women compared with men. This is believed to be primarily attributed to the inhibitory effects of the male hormone testosterone on adiponectin, selectively reducing the circulating levels of HMW adiponectin by inhibiting its secretion from adipocytes (22). Previous studies have shown that the concentration of HMW adiponectin in females was significantly higher than that in males, whereas there were no gender differences for the other two forms (21, 22). Considering that women have higher HMW adiponectin levels compared with men, we wondered whether the association between HMW adiponectin and MS could also be stronger in women.

Indeed, gender-specific logistic regression analysis revealed that, after adjustment for age, BMI, and HOMA-IR, HMW adiponectin remained significantly associated with MS only in women. Similarly, a recent study from Finland in subjects with elevated blood pressure also demonstrated that after adjustment for BMI, the association between total adiponectin and the presence of MS was statistically significant in women but not in men (23). Another value of our study is the analysis of the association between HMW adiponectin and MS in a general population sample. We believe that our study population of 495 randomly selected subjects is truly representative of the general Estonian population (1.29 million inhabitants in 2011). Furthermore, comparison of HOMA-IR and HMW adiponectin as markers for predicting MS in an Estonian adult population showed a gender-specific difference. At first, HOMA-IR as a marker for IR was superior to HMW adiponectin to predict the presence of MS in both genders (estimated by AUROC). This result was in line with a Japanese study where HOMA-IR predicted the presence of MS better than HMW adiponectin (AUC 0.75 vs 0.67 respectively) in subjects without medications for hypertension, diabetes, or dyslipidemia (15).

The current study, after adjustments for age and BMI, found that HOMA-IR in men remained a better predictor for MS compared with HMW adiponectin. By contrast, there was no difference between the predictive powers of HOMA-IR and HMW adiponectin for MS in women. To detect the presence of MS, HMW adiponectin was a better predictor in women than in men in all



**Figure 2** Gender-specific comparison of predictive values (ROC curves) between HMW adiponectin and HOMA-IR for the presence of metabolic syndrome. ROC, receiver operating characteristic; HMW, high-molecular-weight; HOMA-IR, homeostasis model assessment insulin resistance index; AUC, area under the curve.



**Figure 3** Gender-specific comparison of predictive values (ROC curves) between HMW adiponectin and HOMA-IR for the presence of metabolic syndrome (adjusted for age and BMI). ROC, receiver operating characteristic; HMW, high-molecular-weight; HOMA-IR, homeostasis model assessment insulin resistance index; AUC, area under the curve.

logistic regression models. Therefore, these results demonstrate a tighter relationship between HMW adiponectin and MS in women.

Associations between HMW adiponectin levels and the presence of MS have been studied previously in Japanese (9, 15), Caucasian American (19), Japanese American (25), Thai (17), Korean (18), and Chinese subjects (16). No similar European population-based surveys assessing the association between HMW

adiponectin and MS have been performed, to the best of our knowledge. Associations between total adiponectin and various metabolic parameters in different population subgroups have been addressed in earlier Estonian studies (26, 27), but the current study is the first one estimating serum HMW adiponectin level in a general population-based survey.

This population-based cross-sectional study also showed that, as expected, MS among an Estonian adult population was characterized by lower levels of serum HMW adiponectin and higher levels of IR assessed by HOMA-IR. Accordingly, a strong inverse correlation between IR and HMW adiponectin levels was observed.

It is well established that MS increases the risk of heart disease in both genders, although it seems to elicit a greater impact on women (28). MS is a stronger predictor of cardiovascular disease in women than in men (29), and the effect of MS on left ventricular function and hypertrophy is greater in women than in men (30). Dysregulation of adipocytokines is believed to play an important role in atherosclerosis, hypertension, and their sequelae. Data from experimental (cell culture and animal) studies indicate that adiponectin may be a central factor in imbalance between pro- and anti-inflammatory adipocytokines by suppressing the expression of pro-inflammatory tumor necrosis factor, interleukin-6, and interferon- $\gamma$  and by enhancing the expression of interleukin-10 and interleukin-1 receptor antagonists (8).

Furthermore, the direction of causality in the relationship between IR and hypoadiponectinemia in humans is not entirely clear. Combined human and experimental data suggest that a bidirectional relationship between these two atherogenic factors may exist (12). Considering the current findings about gender differences between HMW adiponectin and MS, we propose that hypoadiponectinemia may be more strongly associated with MS in women than in men. Further studies are necessary to confirm these findings in other populations and elucidate whether adiponectin can influence pathogenetic mechanisms of cardiometabolic diseases in a gender-specific manner in humans.

## Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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## Author contribution statement

T Eglit contributed to data collection, data analysis, drafted, and critically reviewed the manuscript. M Lember designed the study, contributed to data collection, data analysis, data interpretation, and

critical review of the manuscript. I Ringmets contributed to data analysis and data interpretation. T Rajasalu contributed to the design of the study, data collection, data analysis, data interpretation; drafted; and critically reviewed the manuscript. All authors have read and approved the final manuscript.

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