

RESEARCH ARTICLE

Circulating adiponectin mediates the association between omentin gene polymorphism and cardiometabolic health in Asian Indians

Karani Santhanakrishnan Vimalaswaran^{1,2*}, Dhanasekaran Bodhini³, Juanjie Jiang¹, Kandaswamy Ramya³, Deepa Mohan⁴, Coimbatore Subramanian Shanthi Rani⁵, Nagarajan Lakshmipriya⁶, Vasudevan Sudha⁶, Rajendra Pradeepa⁷, Ranjit Mohan Anjana⁷, Viswanathan Mohan⁷, Venkatesan Radha³



1 Department of Food and Nutritional Sciences, Hugh Sinclair Unit of Human Nutrition, University of Reading, Reading, United Kingdom, **2** Institute for Food, Nutrition, and Health, University of Reading, Reading, United Kingdom, **3** Department of Molecular Genetics, Madras Diabetes Research Foundation, Chennai, India, **4** Department of Epidemiology, Madras Diabetes Research Foundation, Chennai, India, **5** Department of Clinical Epidemiology, Madras Diabetes Research Foundation, Chennai, India, **6** Department of Foods, Nutrition and Dietetics Research, Madras Diabetes Research Foundation, Chennai, India, **7** Department of Diabetology, Madras Diabetes Research Foundation & Dr. Mohan's Diabetes Specialities Centre, IDF Centre of Excellence in Diabetes Care, & ICMR Centre for Advanced Research on Diabetes, Gopalapuram, Chennai, India

* v.karani@reading.ac.uk

OPEN ACCESS

Citation: Vimalaswaran KS, Bodhini D, Jiang J, Ramya K, Mohan D, Shanthi Rani CS, et al. (2021) Circulating adiponectin mediates the association between omentin gene polymorphism and cardiometabolic health in Asian Indians. *PLoS ONE* 16(5): e0238555. <https://doi.org/10.1371/journal.pone.0238555>

Editor: Narasimha Reddy Parine, King Saud University, SAUDI ARABIA

Received: August 14, 2020

Accepted: March 15, 2021

Published: May 12, 2021

Copyright: © 2021 Vimalaswaran et al. This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability Statement: All relevant data are within the manuscript and its [Supporting Information](#) files.

Funding: The Chennai Willingdon Corporate Foundation supported the CURES field studies. The funder had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

Competing interests: The authors have declared that no competing interests exist.

Abstract

Background

Plasma omentin levels have been shown to be associated with circulating adiponectin concentrations and cardiometabolic disease-related outcomes. In this study, we aim to examine the association of omentin gene polymorphism with serum adiponectin levels and cardiometabolic health status using a genetic approach, and investigate whether these associations are modified by lifestyle factors.

Methods

The study included 945 normal glucose tolerant and 941 unrelated individuals with type 2 diabetes randomly selected from the Chennai Urban Rural Epidemiology Study (CURES), in southern India. Study participants were classified into cardiometabolically healthy and unhealthy, where cardiometabolically healthy were those without hypertension, diabetes, and dyslipidemia. Fasting serum adiponectin levels were measured by radioimmunoassay. The omentin A326T (rs2274907) single nucleotide polymorphism (SNP) was screened by polymerase chain reaction-restriction fragment length polymorphism and direct sequencing.

Results

The 'A' allele of the omentin SNP was significantly associated with lower adiponectin concentrations after adjusting for age, sex, body mass index (BMI), waist circumference (WC)

and cardiometabolic health status ($p = 1.90 \times 10^{-47}$). There was also a significant association between circulating adiponectin concentrations and cardiometabolic health status after adjusting for age, sex, BMI, WC and Omentin SNP ($p = 7.47 \times 10^{-10}$). However, after adjusting for age, sex, BMI, WC and adiponectin levels, the association of 'A' allele with cardiometabolic health status disappeared ($p = 0.79$) suggesting that adiponectin serves as a mediator of the association between omentin SNP and cardiometabolic health status. There were no significant interactions between the SNP and dietary factors on adiponectin levels and cardiometabolic health status ($p > 0.25$, for all comparisons).

Conclusions

Our findings show that adiponectin might function as a mechanistic link between omentin SNP and increased risk of cardiometabolic diseases independent of common and central obesity in Asian Indians. Before strategies to promote adiponectin modulation could be implemented, further studies are required to confirm the molecular mechanisms involved in this triangular relationship between omentin gene, adiponectin and cardiometabolic diseases.

Introduction

The prevalence of cardiometabolic diseases, such as type 2 diabetes (T2D), dyslipidemia, and hypertension, is rapidly increasing in Asian Indians leading to increased morbidity and mortality [1,2]. Despite lower body mass index (BMI), Asian Indians are characterised by increased plasma insulin levels, insulin resistance, increased waist circumference, excess visceral fat, lower high-density lipoprotein cholesterol (HDL-c), increased triglyceride levels and higher proportion of small dense low-density lipoprotein cholesterol (LDL-c) [2,3]. In addition, Asian Indians have low adiponectin levels [3], an adipokine with insulin-sensitizing, anti-apoptotic, and anti-inflammatory properties, which has shown to play an important role in the pathogenesis of dyslipidemia by affecting HDL-c and LDL-c metabolism [4–6].

Omentin, also referred as intelectin-1, is another adipocytokine that is highly expressed in human visceral fat tissue [7]. *In vitro* and animal studies have shown that omentin enhances insulin action in human adipocytes and has beneficial effects on cardiovascular system [8,9]. Majority of the studies have shown that circulating levels of omentin are decreased in individuals with obesity and T2D [10–13] and positively associated with flow-mediated vasodilatation [14,15] suggesting a protective role of human omentin on cardiometabolic health. Even though omentin and adiponectin have been shown to have anti-inflammatory and cardioprotective effects, only a few studies have examined the physiological link between these adipokines in relation to cardiometabolic diseases [16,17].

Several studies have demonstrated an association of omentin gene single nucleotide polymorphism (SNP), A326T (rs2274907), in the exon 4 with cardiometabolic disease-related traits. A study in a South Asian population ($N = 350$) [18] has shown a significant association between the SNP rs2274907 and coronary artery disease. In addition, a study in 168 Iranians showed an association of this SNP with BMI and T2D [19]. Furthermore, a study in 495 Central-Europeans showed that the T allele of the SNP rs2274907 was associated with lowest average energy intake (7877 ± 2780 J/day) [20]. However, a few small studies have failed to show a significant association between the SNP and cardiometabolic traits [21,22], which could be

either due to insufficient statistical power or differences in genetic heterogeneity. To date, there are no genetic studies to establish the triangular molecular link between omentin, adiponectin and cardiometabolic health status. Given that genetic associations are less prone to confounding [23,24], in the present study, we have used an extensively studied missense polymorphism, rs2274907, in the omentin gene, as a genetic instrument to test for its association with serum adiponectin levels and cardiometabolic health status in up to 1,886 individuals from an Asian Indian population. In addition, we have tested for the interaction of this genetic variant with lifestyle factors such as diet and physical activity on adiponectin levels and cardiometabolic health.

Materials and methods

Study population

The study participants were chosen from the urban component of the Chennai Urban Rural Epidemiology Study (CURES), a cross-sectional epidemiological study conducted on a representative sample of the population of Chennai in Southern India [25]. The details of the study has been published elsewhere [25] and is briefly outlined in Fig 1. Briefly, in phase 1, 26,001 individuals were recruited based on a systematic random sampling technique. Participants with self-reported diabetes taking drug treatment for diabetes were classified as “known diabetes”. All individuals with known diabetes ($n = 1,529$) were invited to visit the center for detailed studies. In addition, every 10th individual of the 26,001 individuals without known diabetes was invited to undergo oral glucose tolerance tests using a 75-g oral glucose load (dissolved in 250 ml of water) (Phase 3 of CURES). Those who were confirmed by oral glucose tolerance test to have 2-h plasma glucose value ≥ 11.1 mmol/l (200 mg/dl) based on World

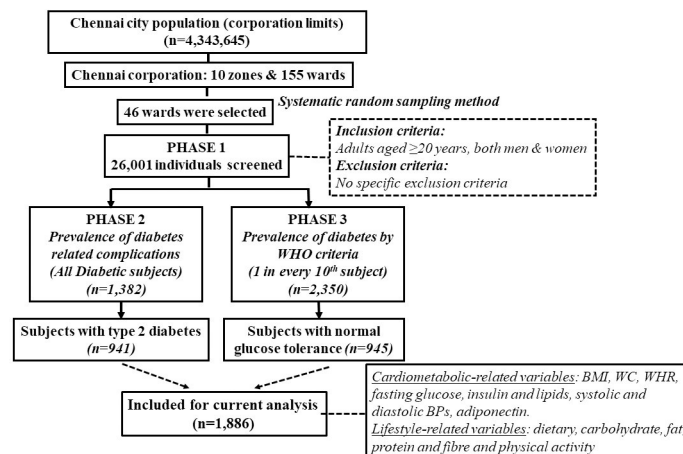


Fig 1. Flow diagram describing the selection of study participants. The Chennai Urban Rural Epidemiology Study (CURES) is a large ongoing epidemiological study on a representative population of Chennai. Briefly, the city of Chennai is divided into 155 corporation wards representing a socioeconomically diverse group. In Phase 1 of CURES, individuals from 46 corporation wards were screened by a systematic sampling technique. The sample distribution in each ward within these zones is based on the proportion of their population in that zone. A probabilistic proportionate sampling was adopted to select the number of individuals seen in each ward. Furthermore, within each ward, every third lane or road, following the right-hand rule, was surveyed. A total of 26,001 individuals aged ≥ 20 years were screened. Phase 2 of CURES deals with studies on the prevalence of microvascular and macrovascular complications of diabetes in subjects with self-reported diabetes from Phase 1 of the study. In Phase 3 of CURES, every tenth subject recruited in Phase 1 ($n = 2,600$), was invited to the tertiary care centre for diabetes for an OGTT; known diabetic subjects had fasting and postprandial glucose tests. For the current article, analysis was computed in randomly selected 941 individuals with diabetes from Phase 2 and 945 individuals with normal glucose tolerance from Phase 3, totalling to 1,886 individuals.

<https://doi.org/10.1371/journal.pone.0238555.g001>

Health Organization (WHO) consulting group criteria were labelled as “newly detected diabetes” and those with 2-h plasma glucose value < 7.8 mmol/l (140 mg/dl) as being normal glucose tolerant (NGT) [26]. For the present study, 945 NGT and 941 unrelated individuals with T2D and genetic data were included. Written informed consent was obtained from all study participants, and the study was approved by the Madras Diabetes Research Foundation Institutional Ethics Committee. There were no minors involved in the study.

Phenotype measurements

Anthropometric measurements including weight, height, and waist circumference (WC) were obtained using standardized techniques. The BMI was calculated as weight (in kg) divided by the square of height (in m). Blood pressure was recorded in the sitting position in the right arm to the nearest 2mmHg using the mercury sphygmomanometer (Diamond Deluxe BP apparatus, Pune, India). Two readings were taken 5 minutes apart and mean of two was taken as the blood pressure.

Venous blood samples were collected in EDTA-containing vacutainer tubes (for plasma and whole blood) and plain tubes without additives (for serum) by experienced phlebotomists in all participants for biochemical and genetic analyses. Whole blood samples were aliquoted in port tubes and stored in a deep freezer at -20°C for genetic analysis. The remaining blood samples collected in the EDTA and plain tubes were centrifuged to separate the plasma and serum within 1 hour of collection. After measurement of biochemical parameters on the day of blood sample collection, the remaining serum and plasma were aliquoted into cryotubes and stored in a deep freezer at -80°C for future research analysis. Biochemical analyses were done on a Hitachi-912 Auto Analyzer (Hitachi, Mannheim, Germany) using kits supplied by Roche Diagnostics (Mannheim). Fasting plasma glucose (glucose oxidase–peroxidase method), serum cholesterol (cholesterol oxidase-phenol-4-amino-antipyrene peroxidase method), serum triglycerides (glycerol phosphatase oxidase-phenol-4-amino-antipyrene peroxidase method), and HDL-c (direct method; polyethylene glycol-pretreated enzymes) were measured. LDL-c was calculated using the Friedewald formula [27]. Glycated haemoglobin (HbA1c) was estimated by high-performance liquid chromatography using a Variant™ machine (Bio-Rad, Hercules, CA, USA). Serum insulin concentration was estimated using an enzyme-linked immunosorbent assay (Dako, Glostrup, Denmark).

Assessment of serum adiponectin concentrations

Fasting adiponectin levels were measured using radioimmunoassay (Cat. No. HADP-61HK, Linco Research, St Charles, MO, USA). The intra-assay and the inter-assay co-efficient of variation were 3.8 and 7.4 per cent respectively and the lower detection limit was 1 ng/ml [28]. Adiponectin data was available for 1,205 samples.

Dietary intake and physical activity assessments

Dietary intakes were assessed using a previously validated and published [29] interviewer administered semi-quantitative food frequency questionnaire (FFQ) containing 222 food items to estimate food intake over the past year. A detailed description of the development of FFQ and the data on reproducibility and validity had been published [29]. A validated self-report questionnaire was used to measure physical activity [30]. For the present study, only a subset of the study population ($N = 513$) had data on dietary intake and physical activity.

Definitions

Study participants were classified into cardiometabolically healthy (N = 370) and unhealthy (N = 1,516), where cardiometabolically healthy were those without hypertension, diabetes, and dyslipidemia [31]. Hypertension was diagnosed in all subjects who were on drug treatment for hypertension or if the blood pressure \geq 140/90 mmHg [32]. National Cholesterol Education Programme guidelines were used to define those with and without dyslipidemia [33].

SNP genotyping

The SNPrs2274907 was genotyped by polymerase chain reaction on a GeneAmp PCR system 9700 thermal cycler (Applied Biosystems, Foster City, CA) using the primers, forward: 5' CCT CTGCAGATCCAAAGGTG 3' and reverse: 5' CCGCACTGAGAATGGTGTTA 3'. The PCR amplicons were digested with AccI restriction enzyme (New England Biolabs, Inc., Beverly, MA) and the resulting products were electrophoresed on a 3% agarose gel (S1 Fig). Based on the analysis of 200 blind duplicates (20%), there was 100% concordance in the genotyping. Furthermore, a few variants were confirmed by direct sequencing with an ABI 310 genetic analyzer (Foster City, CA). The SNP was in Hardy Weinberg equilibrium (HWE) (P = 0.59).

Statistical analyses

Descriptive statistics are presented as means and SD for continuous variables and as percentages for categorical variables. To test whether the observed genotype counts were in HWE, a goodness-of-fit chi-square test was performed. Student t test as appropriate was used to compare groups for continuous variables. Given the low frequency of the rare homozygotes, dominant model was used (comparing individuals with common homozygous genotypes with the combined group of rare homozygotes and heterozygotes). The genetic associations with the continuous and categorical outcomes were examined using linear and logistic regression models, respectively, adjusting for age, sex, BMI and serum adiponectin, wherever appropriate. Interactions between the SNP and dietary intake were assessed by including an interaction term in the linear and logistic regressions. All analyses were carried out using SPSS, version 26. A P value <0.05 was considered to be statistically significant.

Power calculation

Given that there are no previously reported effect sizes for the associations and interactions pertaining to the Omentin SNP and adiponectin concentrations in the Asian Indian population, we were unable to perform a prospective power calculation. However, based on the most significant associations observed in the present study, we performed a retrospective power calculation using QUANTO software, Version 1.2.4 (May 2009). We performed power calculations in the form of least detectable effects based on the assumption of significance levels and powers of 5 and 80%, respectively. At 80% power, the minimum detectable effect was beta 1.50 $\mu\text{g/mL}$ (adiponectin concentrations) for a SNP with minor allele frequency of 21% in the case-control analysis (N = 1,204).

Results

Associations between cardiometabolic health status and clinical and biochemical parameters

In the present study, 80.3% of the individuals were cardiometabolically unhealthy with significantly higher BMI, WC, fasting plasma glucose, insulin, total serum cholesterol, LDL-c,

triglycerides, systolic and diastolic blood pressures and HbA1c and lower HDL-c and serum adiponectin concentrations ($p < 9.6 \times 10^{-9}$ for all comparisons) (Table 1).

There was a significant association between circulating adiponectin concentrations and cardiometabolic health status after adjusting for age, sex, BMI, WC and Omentin SNP rs2274907, where cardiometabolically unhealthy individuals had 2.00 $\mu\text{g}/\text{mL}$ decrease in adiponectin concentrations compared to the control group ($p = 7.47 \times 10^{-10}$).

Association between the SNP and serum adiponectin concentrations

The Omentin SNP rs2274907 was significantly associated with serum adiponectin concentrations after adjusting for age, sex, BMI, WC and cardiometabolic health status ($p = 1.90 \times 10^{-47}$), where 'A' allele carriers (AT + AA) had significantly lower levels of adiponectin (means \pm SE: $4.2 \pm 2.7 \mu\text{g}/\text{mL}$) compared to those with TT genotype (means \pm SE: $8.9 \pm 4.5 \mu\text{g}/\text{mL}$) (Fig 2).

Association between the SNP and cardiometabolic health status

After adjusting for age, sex, BMI and WC, there was a significant association between the 'A' allele of the SNP rs2274907 and increased risk of cardiometabolic health status, where 'A' allele carriers had 1.35 times increased risk of being cardiometabolically unhealthy compared to TT

Table 1. Clinical and biochemical characteristics of the participants from the CURES study.

Clinical and biochemical parameters	Cardiometabolically healthy (N = 370)	Cardiometabolically Unhealthy (N = 1,516)	P value
Age (years)	37 \pm 13	47 \pm 13	3.41 x 10 ⁻³⁶
Sex (men/women)	111/259	736/780	1.27 x 10 ^{-10**}
Body mass index (kg/m ²)	22.1 \pm 4.8	24.9 \pm 4.4	3.39 x 10 ⁻²²
Waist circumference (cm)	79 \pm 12	89 \pm 11	1.58 x 10 ⁻⁴¹
Waist-hip ratio	0.85 \pm 0.09	0.92 \pm 0.08	1.32 x 10 ⁻⁴⁹
Fasting plasma glucose (mg/dl)	84 \pm 8	134 \pm 67	1.30 x 10 ⁻¹⁴⁶
Fasting serum insulin ($\mu\text{IU}/\text{mL}$)	7.6 \pm 5.2	10.1 \pm 6.5	4.33 x 10 ⁻¹³
Systolic blood pressure (mmHg)	116 \pm 16	126 \pm 20	5.46 x 10 ⁻²⁴
Diastolic blood pressure (mmHg)	73 \pm 10	77 \pm 11	2.77 x 10 ⁻⁹
Total serum cholesterol (mg/dl)	162 \pm 20	196 \pm 43	3.20 x 10 ⁻⁹²
Serum triglycerides (mg/dl)	79 \pm 25	163 \pm 109	4.68 x 10 ⁻¹³⁷
Low-density lipoprotein cholesterol (mg/dl)	97 \pm 18	122 \pm 37	6.55 x 10 ⁻⁷²
High-density lipoprotein cholesterol (mg/dl)	50 \pm 7	41 \pm 10	5.98 x 10 ⁻⁶¹
Glycated hemoglobin (%)	5.5 \pm 0.4	7.6 \pm 2.4	7.23 x 10 ⁻¹⁷⁹
Fasting serum adiponectin ($\mu\text{g}/\text{mL}$)	9.9 \pm 5.6	7.4 \pm 4.3	9.60 x 10 ⁻⁹
Total energy intake (kcal)	2655 \pm 579	2813 \pm 919	0.12
Carbohydrate energy (%)	65 \pm 7	65 \pm 6	0.97
Protein energy (%)	11 \pm 1	11 \pm 1	0.35
Fat energy (%)	23 \pm 5	23 \pm 5	0.47
Fibre (g/day)	30 \pm 8	33 \pm 12	0.07
Physical activity levels (Sedentary %/ Moderately active %/ Physically active %)	81/ 18/ 1	82/ 15/ 3	0.52**

Data shown are represented as means \pm SD, wherever appropriate.

*P values generated from an independent samples 't' test for the differences in the means/proportions between cardiometabolically healthy and unhealthy participants.

** P value generated from a chi-square test.

<https://doi.org/10.1371/journal.pone.0238555.t001>

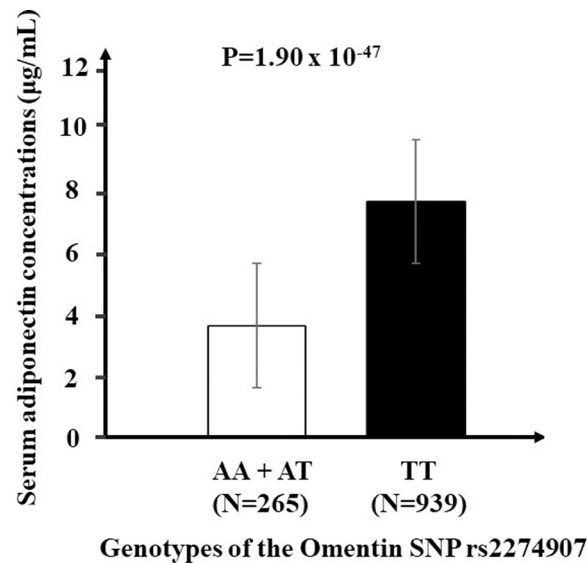


Fig 2. Association between omentin SNP rs2274907 with serum adiponectin concentrations. After adjusting for age, sex, BMI, WC and cardiometabolic health status, the 'A' allele carriers (AA + AT) have significantly lower levels of serum adiponectin concentrations compared to those with TT genotype ($p = 1.90 \times 10^{-47}$). Abbreviations: BMI, Body mass index; WC, waist circumference; SNP, Single nucleotide polymorphism.

<https://doi.org/10.1371/journal.pone.0238555.g002>

homozygotes ($p = 0.03$). However, after adjusting for age, sex, BMI, WC and adiponectin concentrations, the 'A' allele was not associated with cardiometabolic health status ($P = 0.79$) (Fig 3).

There was also no significant difference in the genotype and allele frequencies of the SNP between cardiometabolically unhealthy and healthy individuals under an additive ($p = 0.31$) and a dominant ($p = 0.40$) model (SI Table).

Interaction between SNP and adiponectin concentrations on cardiometabolic health status

To test if the association between the SNP and cardiometabolic health status is modified by serum adiponectin concentrations, we examined the interaction between the SNP and

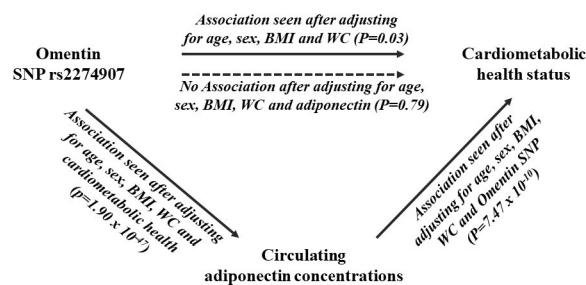


Fig 3. Diagram showing the role of circulating adiponectin as an intermediate predictor between omentin SNP and cardiometabolic health status. One-sided arrows with unbroken lines represent significant associations and one-sided arrows with broken lines represent lack of associations. There is a significant association between the omentin SNP rs2274907 and lower serum adiponectin concentrations after adjusting for age, sex, BMI, WC and cardiometabolic health status ($p = 1.90 \times 10^{-47}$). There is a significant association between serum adiponectin concentrations and cardiometabolic health status after adjusting for age, sex, BMI, WC and SNP rs2274907 ($p = 7.47 \times 10^{-10}$). There is no association between the omentin SNP rs2274907 and cardiometabolic health status after adjusting for age, sex, BMI, WC and serum adiponectin concentrations ($p = 0.79$). Abbreviations: BMI, Body mass index; WC, waist circumference; SNP, Single nucleotide polymorphism.

<https://doi.org/10.1371/journal.pone.0238555.g003>

adiponectin on cardiometabolic health status. There was no evidence for a significant interaction ($p_{\text{interaction}} = 0.24$) suggesting that adiponectin is unlikely to modify the effect of the SNP on cardiometabolic health status.

Interaction between SNP and lifestyle factors on adiponectin concentrations and cardiometabolic health status

There was no significant interaction between the SNP and lifestyle factors such as carbohydrate energy %, fat energy %, protein energy %, dietary fibre intake and physical activity levels on adiponectin concentrations and cardiometabolic health status ($P > 0.25$, for all comparisons), respectively (Table 2).

Discussion

Our study provides the first evidence for the role of circulating adiponectin as a mechanistic link in the association between omentin SNP rs2274907 and cardiometabolic health independent of common and central obesity in this Asian Indian population. In this study, we observed a strong cross-sectional association between the omentin SNP and serum adiponectin concentrations, even after accounting for the potential confounders including cardiometabolic health status. Similarly, a strong association was seen between adiponectin concentrations and cardiometabolic health status after adjusting for the confounders including the omentin SNP. However, the association between 'A' allele of the omentin SNP rs2274907 and cardiometabolic health disappeared after adjusting for serum adiponectin concentrations, which suggests that the association is likely to be mediated through circulating adiponectin. Hence, modulating adiponectin concentrations through lifestyle interventions might be an effective approach to overcome the genetic risk of cardiometabolic diseases.

Adiponectin, an adipokine with 244 amino acids, is synthesized by adipocytes and has been shown to stimulate the glucose uptake in skeletal muscles and decrease the hepatic glucose synthesis [34], whereas omentin, a 313-amino-acid-long polypeptide adipokine, is mainly synthesized by visceral adipose tissue and is involved in cellular energy homeostasis and vascular tone regulation [8]. Both animal and human studies have demonstrated a positive correlation between omentin and adiponectin concentrations [12,35–37]. However, there is no study, to date, that has examined the genetic variants in omentin gene with serum adiponectin concentrations. The present study has examined the A326T (SNP rs2274907), which is a single nucleotide missense polymorphism in the exon-4 of the Omentin 1 gene, which substitutes valine instead of aspartic acid at position 109 (Val109Asp or V109D). Even though the position 109 is located outside the fibrinogen domain of Omentin protein, several studies have reported

Table 2. Interactions between the Omentin SNP rs2274907 and lifestyle factors on adiponectin concentrations and cardiometabolic health status.

<i>P values for the interactions between the Omentin SNP and dietary factors on serum adiponectin concentrations**</i>				
SNP* Carbohydrate energy %	SNP* Protein energy %	SNP* Fat energy %	SNP* Fibre (g) [†]	SNP* physical activity
0.77	0.37	0.57	0.98	0.95
<i>P values for the interactions between the Omentin SNP and dietary factors on cardiometabolic health status***</i>				
SNP* Carbohydrate energy %	SNP* Protein energy %	SNP* Fat energy %	SNP* Fibre (g) [†]	SNP* physical activity
0.87	0.26	0.14	0.30	0.69

**P values obtained from linear regression analysis after adjusting for age, sex, body mass index, waist circumference and cardiometabolic health status.

*** Data are p values obtained from logistic regression analysis after adjusting for age, sex, body mass index, waist circumference and adiponectin concentrations.

[†] Adjusted for age, sex, body mass index, waist circumference, adiponectin concentrations and total energy intake.

SNP, Single Nucleotide Polymorphism.

<https://doi.org/10.1371/journal.pone.0238555.t002>

association of the SNP rs2274907 with cardiometabolic diseases [18–22,38] suggesting that the SNP might be in linkage disequilibrium (LD) with another causative variant. Interestingly, a study in 4,200 North Indians that had examined 207 common genetic variants in proximal promoter and untranslated regions of genes on 1q21–23 and 20q13 identified omentin SNP rs1333062 as one of the top signals for T2D [38]; this SNP in the 3' flank region of omentin gene is in complete LD with Val109Asp—SNP rs2274907 ($D' = 1.0$ and $r^2 = 1.0$ for Gujarati Indians in Houston, Texas population from HapMap data). Although the amino acid position 109 does not represent a completely conserved consensus position [5], the direct adjacent site at 108 contains a highly conserved amino acid (alanine) and hence, the proximity of the substituted amino acid at 109 position to the highly conserved amino acid at 108 might be of functional relevance.

Our study has shown that the minor 'A' allele of the omentin SNP rs2274907 is associated with cardiometabolic health under the mediation of circulating adiponectin levels. The effect of the minor allele on chronic disease outcomes has also been demonstrated in other ethnic groups including Pakistani (N = 350) [18], Iranian (N = 168 & 282) [22,39] and Turkish (N = 87) [40] populations. However, a couple of small studies, one in a Caucasian population (N = 390) and one in an Indian population (N = 500) [41], failed to provide an evidence of an association of the SNP with T2D [21]. These discrepancies are likely to be due to the existence of genetic heterogeneity across different ethnic groups and insufficient statistical power to detect small effect sizes. To date, the present study has been the largest (N = 1,886) to explore the association of the omentin SNP rs2274907 with cardiometabolic diseases. While majority of the studies have shown 'T' allele as the minor allele [18,22,39,40], the dbSNP database shows 'A' allele as the minor allele except for some of the Asian, African and European populations, which is indicative of a significant genetic heterogeneity (https://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?do_not_redirect&rs=rs2274907) [42]. However, 'A' allele is the minor allele in our study and the dbSNP database for GIH population (Gujarati Indians in Houston, Texas, USA). This suggests that future large studies focusing on omentin SNP rs2274907 is highly warranted in each ethnic group to understand the ethnic-specific role of the variant in cardiometabolic diseases.

Several studies have implicated hypoadiponectinemia in the pathogenesis of T2D and cardiovascular diseases [43–45]. Higher concentrations of adiponectin have been shown to decrease the cardiometabolic risk [46,47], given its role in promoting anti-inflammatory effects, improving insulin sensitivity, increasing glucose uptake by the cells and producing endothelial nitric oxide [48,49]. While some studies have shown adiponectin as an independent risk factor for cardiometabolic diseases [44,50], there are a few studies that have shown adiponectin as a mediator of the cross-talk between adipose tissue and cardiovascular system [51]. Furthermore, a few studies have also explained the role of adiponectin as a mediator in the relationship between omentin and cardiometabolic diseases [35,52]. These studies suggest that omentin could be classified under the growing group of adipokines including adiponectin which might have cardioprotective effects [53]. These mechanistic studies are in line with our genetic association study in Asian Indians, where circulating adiponectin levels seem to serve as a mediator in conferring the genetic risk of cardiometabolic diseases. A previous study in a Spanish population has shown a significant association of the minor allele of the omentin SNP rs12409609, which is in complete LD with SNP rs2274907, with low omentin gene expression [54]. Given the positive correlation between plasma omentin and adiponectin levels [12,35–37], it is possible that low omentin expression might contribute to the reduction in adiponectin levels, which, in turn, could possibly increase the cardiometabolic risk among 'A' allele carriers. However, mechanistic studies are required to confirm the triangular relationship between omentin gene, adiponectin and cardiometabolic risk.

Our study findings are suggestive of the fact that modulation of adiponectin levels might be an effective strategy to overcome the genetic risk of cardiometabolic diseases. Previous studies have examined the impact of lifestyle modifications and drug therapies to improve the circulating adiponectin concentrations [55–57]. A few studies have shown that weight loss [58] and combined diet control and physical exercise [59] can increase plasma levels of adiponectin, while smoking [60] and increasing activity of the sympathetic nervous system [61] can decrease the adiponectin concentrations. Drugs such as renin-angiotensin system blocking agents [62], peroxisome proliferator activated receptor (PPAR)-alpha agonists [63], PPAR-gamma agonists [64] and hypoglycemic drugs [65] have been shown to improve adiponectin concentrations. To understand whether modifying the lifestyle could overcome the genetic risk of hypoadiponectinemia and cardiometabolic diseases, we investigated the SNP-lifestyle interactions and found that none of the interactions were statistically significant. The lack of interaction could be a result of the small sample size and insufficient statistical power to detect the small effect sizes of the interactions.

The main strength of the study is the large sample size from a well characterised population, which is representative of the city of Chennai, and the study is sufficiently powered to detect the genetic associations. The other strength is the use of a validated FFQ, which has shown high reproducibility and validity for total carbohydrates and dietary fibre. However, our study has a few limitations which need to be acknowledged. We performed a cross-sectional study and hence, we are unable to infer causality between the SNP, adiponectin concentrations and cardiometabolic disease outcomes. Furthermore, as the study is based on 1,886 randomly selected diabetic participants and those with NGT, extrapolating these results to the general population should be done with caution. However, the selection process has ensured that the study subjects are representative of the population. Although confounders were adjusted in our regression analyses, we cannot exclude the residual confounding due to unknown factors. Another limitation is the recall bias from FFQ which cannot be ruled out. Even though our study is sufficiently powered to detect the genetic associations, the sample size is small for detecting significant gene-lifestyle interactions, which might be the reason for the lack of significant interactions. Furthermore, omentin protein or mRNA expression levels were not assessed in the study and hence, it is not possible to confirm whether the SNP has any influence on the omentin gene expression. Finally, given that the outcome is a multifactorial trait, the present study has examined only one genetic variant from the omentin gene; however, this is the only coding region variant that has been extensively studied in the gene. Future studies should focus on using a tagSNP approach which will be an effective strategy for the study of genetic level variation of complex diseases such as cardiometabolic traits [66].

In summary, we have identified a robust association between the omentin SNP and serum adiponectin concentrations and the latter with cardiometabolic disease outcomes, suggesting that adiponectin could be a pathogenic mediator of the genetic susceptibility towards cardiometabolic disease outcomes. These findings suggest that targeting adiponectin might be beneficial in overcoming the genetic risk of cardiometabolic diseases. Hence, lifestyle interventions and drug therapies to increase adiponectin levels could serve as effective tools in preventing cardiometabolic diseases in Asian Indians. However, mechanistic studies are required to confirm this epidemiological relationship before strategies to promote adiponectin modulation could be implemented.

Supporting information

S1 Fig. RFLP gel photograph of rs2274907 A/T polymorphism in the omentin gene.
(TIF)

S1 Table. Association between the Omentin SNP rs2274907 and cardiometabolic health status.

(DOCX)

Acknowledgments

We thank all study participants for their cooperation. Dr. Karani S Vimalleswaran acknowledges support from the British Nutrition Foundation (BNF). This is the 157th paper from CURES (CURES- 157).

Author Contributions

Conceptualization: Karani Santhanakrishnan Vimalleswaran.

Data curation: Deepa Mohan, Rajendra Pradeepa.

Formal analysis: Karani Santhanakrishnan Vimalleswaran, Dhanasekaran Bodhini, Juanjie Jiang, Kandaswamy Ramya.

Funding acquisition: Karani Santhanakrishnan Vimalleswaran, Viswanathan Mohan, Venkatesan Radha.

Investigation: Karani Santhanakrishnan Vimalleswaran, Juanjie Jiang.

Methodology: Karani Santhanakrishnan Vimalleswaran, Kandaswamy Ramya, Coimbatore Subramanian Shanthi Rani, Nagarajan Lakshmipriya, Vasudevan Sudha, Rajendra Pradeepa, Viswanathan Mohan, Venkatesan Radha.

Project administration: Rajendra Pradeepa, Ranjit Mohan Anjana, Viswanathan Mohan.

Resources: Ranjit Mohan Anjana.

Software: Karani Santhanakrishnan Vimalleswaran.

Supervision: Karani Santhanakrishnan Vimalleswaran, Viswanathan Mohan, Venkatesan Radha.

Writing – original draft: Karani Santhanakrishnan Vimalleswaran.

Writing – review & editing: Karani Santhanakrishnan Vimalleswaran, Dhanasekaran Bodhini, Deepa Mohan, Coimbatore Subramanian Shanthi Rani, Nagarajan Lakshmipriya, Vasudevan Sudha, Rajendra Pradeepa, Ranjit Mohan Anjana, Viswanathan Mohan, Venkatesan Radha.

References

1. Volgman AS, Palaniappan LS, Aggarwal NT, Gupta M, Khandelwal A, Krishnan AV, et al. Atherosclerotic Cardiovascular Disease in South Asians in the United States: Epidemiology, Risk Factors, and Treatments: A Scientific Statement From the American Heart Association. *Circulation*. 2018; 138(1): e1–e34. Epub 2018/05/26. <https://doi.org/10.1161/CIR.0000000000000580> PMID: 29794080.
2. Patel SA, Shivashankar R, Ali MK, Anjana RM, Deepa M, Kapoor D, et al. Is the "South Asian Phenotype" Unique to South Asians?: Comparing Cardiometabolic Risk Factors in the CARRS and NHANES Studies. *Glob Heart*. 2016; 11(1):89–96 e3. Epub 2016/04/23. <https://doi.org/10.1016/j.gheart.2015.12.010> PMID: 27102026; PubMed Central PMCID: PMC4841915.
3. Mohan V, Deepa R. Adipocytokines and the expanding 'Asian Indian Phenotype'. *J Assoc Physicians India*. 2006; 54:685–6. Epub 2007/01/11. PMID: 17212014.
4. Izadi V, Farabad E, Azadbakht L. Epidemiologic evidence on serum adiponectin level and lipid profile. *Int J Prev Med*. 2013; 4(2):133–40. Epub 2013/04/02. PMID: 23543874; PubMed Central PMCID: PMC3604843.

5. Rahbar AR, Nabipour I. The relationship between dietary lipids and serum visfatin and adiponectin levels in postmenopausal women. *Endocr Metab Immune Disord Drug Targets*. 2014; 14(2):84–92. Epub 2014/05/29. <https://doi.org/10.2174/1871530314666140527143009> PMID: 24867620.
6. Zhang T, Chen J, Tang X, Luo Q, Xu D, Yu B. Interaction between adipocytes and high-density lipoprotein: new insights into the mechanism of obesity-induced dyslipidemia and atherosclerosis. *Lipids Health Dis*. 2019; 18(1):223. Epub 2019/12/18. <https://doi.org/10.1186/s12944-019-1170-9> PMID: 31842884; PubMed Central PMCID: PMC6913018.
7. Du Y, Ji Q, Cai L, Huang F, Lai Y, Liu Y, et al. Association between omentin-1 expression in human epicardial adipose tissue and coronary atherosclerosis. *Cardiovasc Diabetol*. 2016; 15:90. Epub 2016/06/30. <https://doi.org/10.1186/s12933-016-0406-5> PMID: 27352781; PubMed Central PMCID: PMC4924240.
8. Yang RZ, Lee MJ, Hu H, Pray J, Wu HB, Hansen BC, et al. Identification of omentin as a novel depot-specific adipokine in human adipose tissue: possible role in modulating insulin action. *Am J Physiol Endocrinol Metab*. 2006; 290(6):E1253–61. Epub 2006/03/15. <https://doi.org/10.1152/ajpendo.00572.2004> PMID: 16531507.
9. Greulich S, Chen WJ, Maxhera B, Rijzewijk LJ, van der Meer RW, Jonker JT, et al. Cardioprotective properties of omentin-1 in type 2 diabetes: evidence from clinical and in vitro studies. *PLoS One*. 2013; 8(3):e59697. Epub 2013/04/05. <https://doi.org/10.1371/journal.pone.0059697> PMID: 23555749; PubMed Central PMCID: PMC3612072.
10. de Souza Batista CM, Yang RZ, Lee MJ, Glynn NM, Yu DZ, Pray J, et al. Omentin plasma levels and gene expression are decreased in obesity. *Diabetes*. 2007; 56(6):1655–61. Epub 2007/03/03. <https://doi.org/10.2337/db06-1506> PMID: 17329619.
11. Elsaid NH, Sadik NA, Ahmed NR, Fayez SE, Mohammed NAE. Serum omentin-1 levels in type 2 diabetic obese women in relation to glycemic control, insulin resistance and metabolic parameters. *J Clin Transl Endocrinol*. 2018; 13:14–9. Epub 2018/07/20. <https://doi.org/10.1016/j.jcte.2018.05.003> PMID: 30023310; PubMed Central PMCID: PMC6047309.
12. Pan X, Kaminga AC, Wen SW, Acheampong K, Liu A. Omentin-1 in diabetes mellitus: A systematic review and meta-analysis. *PLoS One*. 2019; 14(12):e0226292. Epub 2019/12/11. <https://doi.org/10.1371/journal.pone.0226292> PMID: 31821362; PubMed Central PMCID: PMC6903756.
13. As Habi A, Sadeghi M, Arab A, Hajianfar H. The association between omentin and diabetes: a systematic review and meta-analysis of observational studies. *Diabetes Metab Syndr Obes*. 2019; 12:1277–86. Epub 2019/08/27. <https://doi.org/10.2147/DMSO.S206981> PMID: 31447571; PubMed Central PMCID: PMC6683169.
14. Cimen AR, Cerit ET, Iyidir OT, Karakus R, Uyar BB, Toruner FB, et al. Serum Omentin-1 Levels and Endothelial Dysfunction in Obesity. *Acta Endocrinol (Buchar)*. 2017; 13(2):138–43. Epub 2017/04/01. <https://doi.org/10.4183/aeb.2017.138> PMID: 31149164; PubMed Central PMCID: PMC6516446.
15. Hayashi M, Morioka T, Hatamori M, Kakutani Y, Yamazaki Y, Kurajoh M, et al. Plasma omentin levels are associated with vascular endothelial function in patients with type 2 diabetes at elevated cardiovascular risk. *Diabetes Res Clin Pract*. 2019; 148:160–8. Epub 2019/01/15. <https://doi.org/10.1016/j.diabres.2019.01.009> PMID: 30641171.
16. Lau DC, Dhillon B, Yan H, Szmitek PE, Verma S. Adipokines: molecular links between obesity and atherosclerosis. *Am J Physiol Heart Circ Physiol*. 2005; 288(5):H2031–41. Epub 2005/01/18. <https://doi.org/10.1152/ajpheart.01058.2004> PMID: 15653761.
17. Weschenfelder C, Schaan de Quadros A, Lorenzon Dos Santos J, Bueno Garofallo S, Marcadenti A. Adipokines and Adipose Tissue-Related Metabolites, Nuts and Cardiovascular Disease. *Metabolites*. 2020; 10(1). Epub 2020/01/17. <https://doi.org/10.3390/metabo10010032> PMID: 31940832; PubMed Central PMCID: PMC7022531.
18. Nazar S, Zehra S, Azhar A. Association of single Nucleotide Missense Polymorphism Val109Asp of Omentin-1 gene and coronary artery disease in Pakistani population: Multicenter study. *Pak J Med Sci*. 2017; 33(5):1128–33. Epub 2017/11/17. <https://doi.org/10.12669/pjms.335.13110> PMID: 29142551; PubMed Central PMCID: PMC5673720.
19. Jamshidi J, Ghanbari M, Asnaashari A, Jafari N, Valizadeh GA. Omentin Val109Asp polymorphism and risk of coronary artery disease. *Asian Cardiovasc Thorac Ann*. 2017; 25(3):199–203. Epub 2017/03/23. <https://doi.org/10.1177/0218492317699752> PMID: 28325076.
20. Splichal Z, Bienertova-Vasku J, Novak J, Zlamal F, Tomandl J, Tomandlova M, et al. The common polymorphism Val109Asp in the omentin gene is associated with daily energy intake in the Central-European population. *Nutr Neurosci*. 2015; 18(1):41–8. Epub 2014/02/21. <https://doi.org/10.1179/1476830513Y.0000000100> PMID: 24552613.
21. Schaffler A, Zeitoun M, Wobser H, Buechler C, Aslanidis C, Herfarth H. Frequency and significance of the novel single nucleotide missense polymorphism Val109Asp in the human gene encoding omentin in Caucasian patients with type 2 diabetes mellitus or chronic inflammatory bowel diseases. *Cardiovasc*

- Diabetol. 2007; 6:3. Epub 2007/02/14. <https://doi.org/10.1186/1475-2840-6-3> PMID: 17295929; PubMed Central PMCID: PMC1802733.
22. Khoshi A, Bajestani MK, Shakeri H, Goodarzi G, Azizi F. Association of Omentin rs2274907 and FTO rs9939609 gene polymorphisms with insulin resistance in Iranian individuals with newly diagnosed type 2 diabetes. *Lipids Health Dis.* 2019; 18(1):142. Epub 2019/06/16. <https://doi.org/10.1186/s12944-019-1085-5> PMID: 31200723; PubMed Central PMCID: PMC6570836.
 23. Berry DJ, Vimalaewaran KS, Whittaker JC, Hingorani AD, Hypponen E. Evaluation of genetic markers as instruments for Mendelian randomization studies on vitamin D. *PLoS One.* 2012; 7(5):e37465. Epub 2012/05/26. <https://doi.org/10.1371/journal.pone.0037465> PMID: 22629401; PubMed Central PMCID: PMC3357436.
 24. Vimalaewaran KS. A nutrigenetics approach to study the impact of genetic and lifestyle factors on cardiometabolic traits in various ethnic groups: findings from the GeNuIne Collaboration. *Proc Nutr Soc.* 2020; 79(2):194–204. Epub 2020/02/01. <https://doi.org/10.1017/S0029665119001186> PMID: 32000867
 25. Deepa M, Pradeepa R, Rema M, Mohan A, Deepa R, Shanthirani S, et al. The Chennai Urban Rural Epidemiology Study (CURES)—study design and methodology (urban component) (CURES-I). *J Assoc Physicians India.* 2003; 51:863–70. Epub 2004/01/09. PMID: 14710970.
 26. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med.* 1998; 15(7):539–53. Epub 1998/08/01. [https://doi.org/10.1002/\(SICI\)1096-9136\(199807\)15:7<539::AID-DIA668>3.0.CO;2-S](https://doi.org/10.1002/(SICI)1096-9136(199807)15:7<539::AID-DIA668>3.0.CO;2-S) PMID: 9686693.
 27. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem.* 1972; 18(6):499–502. Epub 1972/06/01. PMID: 4337382.
 28. Vimalaewaran KS, Radha V, Ramya K, Babu HN, Savitha N, Roopa V, et al. A novel association of a polymorphism in the first intron of adiponectin gene with type 2 diabetes, obesity and hypoadiponectinemia in Asian Indians. *Hum Genet.* 2008; 123(6):599–605. Epub 2008/05/10. <https://doi.org/10.1007/s00439-008-0506-8> PMID: 18465144.
 29. Sudha V, Radhika G, Sathya RM, Ganesan A, Mohan V. Reproducibility and validity of an interviewer-administered semi-quantitative food frequency questionnaire to assess dietary intake of urban adults in southern India. *Int J Food Sci Nutr.* 2006; 57(7–8):481–93. Epub 2006/12/13. <https://doi.org/10.1080/09637480600969220> PMID: 17162327.
 30. Mohan V, Sandeep S, Deepa M, Gokulakrishnan K, Datta M, Deepa R. A diabetes risk score helps identify metabolic syndrome and cardiovascular risk in Indians—the Chennai Urban Rural Epidemiology Study (CURES-38). *Diabetes Obes Metab.* 2007; 9(3):337–43. Epub 2007/03/30. <https://doi.org/10.1111/j.1463-1326.2006.00612.x> PMID: 17391160.
 31. Ahl S, Guenther M, Zhao S, James R, Marks J, Szabo A, et al. Adiponectin Levels Differentiate Metabolically Healthy vs Unhealthy Among Obese and Nonobese White Individuals. *J Clin Endocrinol Metab.* 2015; 100(11):4172–80. Epub 2015/09/25. <https://doi.org/10.1210/jc.2015-2765> PMID: 26401592; PubMed Central PMCID: PMC4702448.
 32. Mohan V, Deepa M, Farooq S, Datta M, Deepa R. Prevalence, awareness and control of hypertension in Chennai—The Chennai Urban Rural Epidemiology Study (CURES-52). *J Assoc Physicians India.* 2007; 55:326–32. Epub 2007/09/12. PMID: 17844691.
 33. Expert Panel on Detection E, Treatment of High Blood Cholesterol in A. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA.* 2001; 285(19):2486–97. Epub 2001/05/23. <https://doi.org/10.1001/jama.285.19.2486> PMID: 11368702.
 34. Lappas M, Yee K, Permezel M, Rice GE. Release and regulation of leptin, resistin and adiponectin from human placenta, fetal membranes, and maternal adipose tissue and skeletal muscle from normal and gestational diabetes mellitus-complicated pregnancies. *J Endocrinol.* 2005; 186(3):457–65. Epub 2005/09/02. <https://doi.org/10.1677/joe.1.06227> PMID: 16135665.
 35. Nishimura M, Morioka T, Hayashi M, Kakutani Y, Yamazaki Y, Kurajoh M, et al. Plasma omentin levels are inversely associated with atherosclerosis in type 2 diabetes patients with increased plasma adiponectin levels: a cross-sectional study. *Cardiovasc Diabetol.* 2019; 18(1):167. Epub 2019/12/07. <https://doi.org/10.1186/s12933-019-0973-3> PMID: 31805941; PubMed Central PMCID: PMC6894467.
 36. Yan P, Liu D, Long M, Ren Y, Pang J, Li R. Changes of serum omentin levels and relationship between omentin and adiponectin concentrations in type 2 diabetes mellitus. *Exp Clin Endocrinol Diabetes.* 2011; 119(4):257–63. Epub 2011/03/05. <https://doi.org/10.1055/s-0030-1269912> PMID: 21374544.
 37. de Castro CA, da Silva KA, Rocha MC, Sene-Fiorese M, Nonaka KO, Malavazi I, et al. Exercise and Omentin: Their Role in the Crosstalk Between Muscle and Adipose Tissues in Type 2 Diabetes Mellitus

- Rat Models. *Front Physiol.* 2018; 9:1881. Epub 2019/01/23. <https://doi.org/10.3389/fphys.2018.01881> PMID: 30666216; PubMed Central PMCID: PMC6330355.
38. Tabassum R, Mahajan A, Dwivedi OP, Chauhan G, Spurgeon CJ, Kumar MV, et al. Common variants of SLAMF1 and ITLN1 on 1q21 are associated with type 2 diabetes in Indian population. *J Hum Genet.* 2012; 57(3):184–90. Epub 2012/01/27. <https://doi.org/10.1038/jhg.2011.150> PMID: 22277902.
 39. Kohan L, Safarpur M, Abdollahi H. Omentin-1 rs2274907 and resistin rs1862513 polymorphisms influence genetic susceptibility to nonalcoholic fatty liver disease. *Mol Biol Res Commun.* 2016; 5(1):11–7. Epub 2016/11/16. PMID: 27844016; PubMed Central PMCID: PMC5019329.
 40. Yoruk U, Yaykasli KO, Ozhan H, Memisogullari R, Karabacak A, Bulur S, et al. Association of omentin Val109Asp polymorphism with coronary artery disease. *Anadolu Kardiyol Derg.* 2014; 14(6):511–4. Epub 2013/12/29. <https://doi.org/10.5152/akd.2013.4932> PMID: 24370683.
 41. Rathwa N, Patel R, Pramanik Palit S, Jadeja SD, Narwaria M, Ramachandran AV, et al. Circulatory Omentin-1 levels but not genetic variants influence the pathophysiology of Type 2 diabetes. *Cytokine.* 2019; 119:144–51. Epub 2019/03/26. <https://doi.org/10.1016/j.cyto.2019.03.011> PMID: 30909150.
 42. Vimalleswaran KS. Comment: "Evaluation of the Association of Omentin 1 rs2274907 A>T and rs2274908 G>A Gene Polymorphisms with Coronary Artery Disease in Indian Population: A Case Control Study". *J Pers Med.* 2020; 10(4). Epub 2020/10/30. <https://doi.org/10.3390/jpm10040190> PMID: 33113755; PubMed Central PMCID: PMC7712587.
 43. Spranger J, Kroke A, Mohlig M, Bergmann MM, Ristow M, Boeing H, et al. Adiponectin and protection against type 2 diabetes mellitus. *Lancet.* 2003; 361(9353):226–8. Epub 2003/01/28. [https://doi.org/10.1016/S0140-6736\(03\)12255-6](https://doi.org/10.1016/S0140-6736(03)12255-6) PMID: 12547549.
 44. Iwashima Y, Katsuya T, Ishikawa K, Ouchi N, Ohishi M, Sugimoto K, et al. Hypoadiponectinemia is an independent risk factor for hypertension. *Hypertension.* 2004; 43(6):1318–23. Epub 2004/05/05. <https://doi.org/10.1161/01.HYP.0000129281.03801.4b> PMID: 15123570.
 45. Laughlin GA, Barrett-Connor E, May S, Langenberg C. Association of adiponectin with coronary heart disease and mortality: the Rancho Bernardo study. *Am J Epidemiol.* 2007; 165(2):164–74. Epub 2006/11/15. <https://doi.org/10.1093/aje/kwk001> PMID: 17101706; PubMed Central PMCID: PMC2642645.
 46. Pischon T, Girman CJ, Hotamisligil GS, Rifai N, Hu FB, Rimm EB. Plasma adiponectin levels and risk of myocardial infarction in men. *JAMA.* 2004; 291(14):1730–7. Epub 2004/04/15. <https://doi.org/10.1001/jama.291.14.1730> PMID: 15082700.
 47. Schulze MB, Shai I, Rimm EB, Li T, Rifai N, Hu FB. Adiponectin and future coronary heart disease events among men with type 2 diabetes. *Diabetes.* 2005; 54(2):534–9. Epub 2005/01/29. <https://doi.org/10.2337/diabetes.54.2.534> PMID: 15677512.
 48. Hattori Y, Suzuki M, Hattori S, Kasai K. Globular adiponectin upregulates nitric oxide production in vascular endothelial cells. *Diabetologia.* 2003; 46(11):1543–9. Epub 2003/10/11. <https://doi.org/10.1007/s00125-003-1224-3> PMID: 14551684.
 49. Robinson K, Prins J, Venkatesh B. Clinical review: adiponectin biology and its role in inflammation and critical illness. *Crit Care.* 2011; 15(2):221. Epub 2011/05/19. <https://doi.org/10.1186/cc10021> PMID: 21586104; PubMed Central PMCID: PMC3219307.
 50. Ai M, Otokozawa S, Asztalos BF, White CC, Cupples LA, Nakajima K, et al. Adiponectin: an independent risk factor for coronary heart disease in men in the Framingham offspring Study. *Atherosclerosis.* 2011; 217(2):543–8. Epub 2011/07/12. <https://doi.org/10.1016/j.atherosclerosis.2011.05.035> PMID: 21741045; PubMed Central PMCID: PMC3662557.
 51. Li FY, Cheng KK, Lam KS, Vanhoutte PM, Xu A. Cross-talk between adipose tissue and vasculature: role of adiponectin. *Acta Physiol (Oxf).* 2011; 203(1):167–80. Epub 2010/11/11. <https://doi.org/10.1111/j.1748-1716.2010.02216.x> PMID: 21062420.
 52. Herder C, Ouwens DM, Carstensen M, Kowall B, Huth C, Meisinger C, et al. Adiponectin may mediate the association between omentin, circulating lipids and insulin sensitivity: results from the KORA F4 study. *Eur J Endocrinol.* 2015; 172(4):423–32. Epub 2015/03/04. <https://doi.org/10.1530/EJE-14-0879> PMID: 25733068.
 53. Niersmann C, Carstensen-Kirberg M, Maalmi H, Holleccek B, Roden M, Brenner H, et al. Higher circulating omentin is associated with increased risk of primary cardiovascular events in individuals with diabetes. *Diabetologia.* 2020; 63(2):410–8. Epub 2019/11/11. <https://doi.org/10.1007/s00125-019-05017-2> PMID: 31705160.
 54. Genre F, Rueda-Gotor J, Remuzgo-Martinez S, Pulito-Cueto V, Corrales A, Mijares V, et al. Omentin: a biomarker of cardiovascular risk in individuals with axial spondyloarthritis. *Sci Rep.* 2020; 10(1):9636. Epub 2020/06/17. <https://doi.org/10.1038/s41598-020-66816-x> PMID: 32541676; PubMed Central PMCID: PMC7295748.

55. Han SH, Quon MJ, Kim JA, Koh KK. Adiponectin and cardiovascular disease: response to therapeutic interventions. *J Am Coll Cardiol*. 2007; 49(5):531–8. Epub 2007/02/06. <https://doi.org/10.1016/j.jacc.2006.08.061> PMID: 17276175.
56. Lopez-Jaramillo P. The Role of Adiponectin in Cardiometabolic Diseases: Effects of Nutritional Interventions. *J Nutr*. 2016; 146(2):422S–6S. Epub 2016/01/15. <https://doi.org/10.3945/jn.114.202432> PMID: 26764331.
57. Mirmiran P, Hosseini S, Hosseinpour-Niazi S, Azizi F. Legume consumption increase adiponectin concentrations among type 2 diabetic patients: A randomized crossover clinical trial. *Endocrinol Diabetes Nutr*. 2019; 66(1):49–55. Epub 2018/09/30. <https://doi.org/10.1016/j.endinu.2018.07.003> PMID: 30266593.
58. Hotta K, Funahashi T, Arita Y, Takahashi M, Matsuda M, Okamoto Y, et al. Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. *Arterioscler Thromb Vasc Biol*. 2000; 20(6):1595–9. Epub 2000/06/10. <https://doi.org/10.1161/01.atv.20.6.1595> PMID: 10845877.
59. Monzillo LU, Hamdy O, Horton ES, Ledbury S, Mullooly C, Jarema C, et al. Effect of lifestyle modification on adipokine levels in obese subjects with insulin resistance. *Obes Res*. 2003; 11(9):1048–54. Epub 2003/09/16. <https://doi.org/10.1038/oby.2003.144> PMID: 12972674.
60. Iwashima Y, Katsuya T, Ishikawa K, Kida I, Ohishi M, Horio T, et al. Association of hypoadiponectinemia with smoking habit in men. *Hypertension*. 2005; 45(6):1094–100. Epub 2005/05/18. <https://doi.org/10.1161/01.HYP.0000169444.05588.4c> PMID: 15897361.
61. Fasshauer M, Klein J, Neumann S, Eszlinger M, Paschke R. Adiponectin gene expression is inhibited by beta-adrenergic stimulation via protein kinase A in 3T3-L1 adipocytes. *FEBS Lett*. 2001; 507(2):142–6. Epub 2001/10/31. [https://doi.org/10.1016/s0014-5793\(01\)02960-x](https://doi.org/10.1016/s0014-5793(01)02960-x) PMID: 11684087.
62. Koh KK, Quon MJ, Han SH, Ahn JY, Jin DK, Kim HS, et al. Vascular and metabolic effects of combined therapy with ramipril and simvastatin in patients with type 2 diabetes. *Hypertension*. 2005; 45(6):1088–93. Epub 2005/05/11. <https://doi.org/10.1161/01.HYP.0000166722.91714.ba> PMID: 15883229.
63. Chinetti G, Zawadski C, Fruchart JC, Staels B. Expression of adiponectin receptors in human macrophages and regulation by agonists of the nuclear receptors PPARalpha, PPARgamma, and LXR. *Biochem Biophys Res Commun*. 2004; 314(1):151–8. Epub 2004/01/13. <https://doi.org/10.1016/j.bbrc.2003.12.058> PMID: 14715259.
64. Yu JG, Javorschi S, Hevener AL, Kruszynska YT, Norman RA, Sinha M, et al. The effect of thiazolidinediones on plasma adiponectin levels in normal, obese, and type 2 diabetic subjects. *Diabetes*. 2002; 51(10):2968–74. Epub 2002/09/28. <https://doi.org/10.2337/diabetes.51.10.2968> PMID: 12351435.
65. Tsunekawa T, Hayashi T, Suzuki Y, Matsui-Hirai H, Kano H, Fukatsu A, et al. Plasma adiponectin plays an important role in improving insulin resistance with glimepiride in elderly type 2 diabetic subjects. *Diabetes Care*. 2003; 26(2):285–9. Epub 2003/01/28. <https://doi.org/10.2337/diacare.26.2.285> PMID: 12547850.
66. Wang S, Liu G., Wang X., Zhang Y., He S., Zhang Y. TagSNP-set selection for genotyping using integrated data. *Future Generation Computer Systems*. 2021; 115:327–34.