Triglyceridemic Waist Phenotypes as Risk Factors for Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis

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Abstract: *Introduction*: Triglyceride waist phenotypes, which combine high triglyceride levels and central obesity, have recently emerged as an area of interest in metabolic disease research.

Objective: To conduct a systematic review (SR) with meta-analysis to determine if triglyceride waist phenotypes are a risk factor for T2DM.

Materials: SR with meta-analysis of cohort studies. The search was conducted in four databases: PubMed/Medline, Scopus, Web of Science, and EMBASE. Participants were classified into four groups, based on triglyceride level and waist circumference (WC): 1) Normal WC and normalConduct triglyceride level (NWNT); 2) Normal WC and high triglyceride level (NWHT), 3) Altered WC and normal triglyceride level (EWNT) and 4) Altered WC and high triglyceride level (EWHT). For the meta-analysis, only studies whose measure of association were presented as Hazard ratio (HR) along with 95% confidence intervals (CI95%) were used.

Results: Compared to people with NWHT, a statistically significant association was found for those with NWHT (HR: 2.65; CI95% 1.77–3.95), EWNT (HR: 2.54; CI95% 2.05–3.16) and EWHT (HR: 4.41; CI95% 2.82–6.89).

Conclusions: There is a clear association between triglyceride waist phenotypes and diabetes, according to this SR and meta-analysis. Although central obesity and high triglyceride levels are associated with a higher risk of the aforementioned disease, their combination appears to pose an even greater risk. Therefore, in the clinical setting, it is important to consider this when assessing the risk of diabetes.

Keywords: Diabetes mellitus, triglycerides, waist circumference, hypertriglyceridemic waist, systematic review (source: MeSH NLM).

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a metabolic disorder characterized by elevated blood glucose levels due to insulin abnormalities [1]. T2DM is a serious complication that could lead to heart disease, neuropathy, blindness, kidney failure, and even lower limb amputation [2].

T2DM is a major public health problem globally. In the United States, an average of 10.5% suffer from diabetes, with a higher prevalence among racial and ethnic minorities [3]; in Europe, 59 million, corresponding to 9.8% of adults [4]; in China, according to recent information, almost 10.9% [5], and in Latin America, 8% [6].

Triglyceride waist phenotypes, which encompass central obesity and high triglyceride levels, are increasingly becoming an area of interest in the study of metabolic diseases over several years [7-9]. Although several studies have indicated that these phenotypes may be a risk factor for T2DM [10-12], others have suggested the opposite [13,14]. Thus, their exact role in the etiology of T2DM remains a topic of debate that needs further investigation.

The association between these variables could be a topic of scientific and clinical interest, as this marker can be used for the prediction of diabetes. Therefore, in this paper, a systematic review (SR) with meta-analysis was developed to establish whether triglyceride waist phenotypes are a risk factor for T2DM.

METHODS

This research consists of a systematic review (SR) with a meta-analysis of cohort studies. The PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) was followed to establish the structure of this study [15].

Search Strategy

This manuscript was developed using search strategies in four databases: PubMed/Medline, Scopus, Web of Science, and EMBASE. The key search terms

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Table 1: Description of the Studies Included in the Systematic Review

First Author, year	Country	Follow up time (mean or median)	Sample	Population (selection criteria)	Sex (% female)	Age	Definition of waist triglyceridemia phenotype				Prevalence of waist triglyceridemia phenotype (%)	Incidence of diabetes (%)	Diagnostic criteria for diabetes (any of the following options)	Association measure	Adjustment variables
							WC used for HTGW detection (cm)		TG used for HTGW detection						
							Male	Female	Male	Female					
Zhang 2012	China	3 years	2908	Persons aged 20 years and older were eligible and were enrolled when they participated in their annual health examination. At baseline, subjects with prediabetes and subjects with diabetes or with a history of diabetes were excluded.	32.70%	NWNT: 50.1 ± 16.3 NWHT: 50.0 ± 12.9 EWNT: 52.3 ± 15.34 EWHT: 50.6 ± 13.0	≥90	≥80	≥1.7 mm/L	≥1.7 mm/L	NWNT: 55.78% NWHT: 17.02% EWNT: 14.72% EWHT: 12.48%	NWNT: 0.52% NWHT: 0.41% EWNT: 0.48% EWHT: 0.79%	FPG ≥7.0 mmol/L	Hazard ratio Men NWNT: Reference NWHT: 1.55 (0.69 - 3.49) EWNT: 3.37 (1.43 - 7.96) EWHT: 4.46 (1.88-10.60) Women NWNT: Reference NWHT: 3.66 (0.88-15.31) EWNT: 1.71 (0.46-6.44) EWHT: 4.64 (1.20-17.97)	Age, body mass index, systolic blood pressure, total cholesterol and HDL-cholesterol
He 2013	China	15 years	687	People who have diabetes were excluded.	41.92%	50	≥ 90 cm	≥ 80 cm	≥1.7 mm/L	≥1.7 mm/L	EWHT: 11.79%	EWHT: 8.3%	1) Self-reported 2) FPG ≥ 7.0 mmol/L	Hazard ratio EWHT: 4.1 (2.4-7.0)	Age, sex, total cholesterol, elevated blodd pressure, HDL-cholesterol, fasting plasma glucose and smoking
Han 2014	Korea	4 years	2900	People who have diabetes or missing data, especially for WC and lipid profiles were excluded.	28.30%	44.3 ± 6.5	≥90 cm	≥85 cm	≥1.7 mm/L	≥1.7 mm/L	NWNT: 61.72% NWHT: 21.21% EWNT: 8.79% EWHT: 8.28%	NWNT: 2.2% NWHT: 4.1% EWNT: 6.% EWHT: 8.3%	1) HbA1c ≥ 6.5% 2) FPG ≥ 7.0 mmol/L 3) OGTT ≥ 11.1 mmol/L	Hazard ratio NWNT: Reference NWHT: 1.39 (0.77–2.23) EWNT: 2.25 (1.20–3.82) EWHT: 1.57 (0.82–2.60)	age, sex, total cholesterol, systolic blood pressure, alcohol drinking history and fasting plasma glucose
Janghorbani 2016	Iran	7.3 years	1865	People who have diabetes were excluded.	73.90%	43 ± 0.15	≥ 102 cm	≥ 88 cm	≥1.7 mm/L	≥1.7 mm/L	NWNT: 37.1% NWHT: 24.6% EWNT: 19.2% EWHT: 19.1%	NWNT: 21.4% NWHT: 26.1% EWNT: 27.9% EWHT: 24.6%	1) FPG ≥ 7.0 mmol/L 2) OGTT ≥ 11.1 mmol/L To confirm the diagnosis, a repeated abnormal measurement was necessary on another day	Odds ratio NWNT: Reference NWHT: 1.67 (1.05–2.64) EWNT: 1.63 (0.98–2.71) EWHT: 1.26 (0.72–2.18)	Age, sex, fasting plasma glucose, cholesterol, LDL-Cholesterol and body mass index

Xu 2020	China	7.7 years	15717	People who have diabetes or missing data were excluded.	58.18%	52:70 ± 11:58	≥ 90 cm	≥ 80 cm	≥1.7 mm/L	≥1.7 mm/L	NWNT: 54.81% NWHT: 21.98% EWNT: 10.14% EWHT: 13.08%	NWNT: 2.45% NWHT: 7.79% EWNT: 6.03% EWHT: 14.16%	1) Self-reported 2) FPG ≥ 7.0 mmol/L 3) Consumption of glucose-lowering drugs or on insulin treatment	Hazard ratio Men NWNT: Reference NWHT:4.07 (3.01-5.50) EWNT: 2.21 (1.58-3.07) EWHT: 5.98 (4.49-7.95) Women NWNT: Reference NWHT: 3.214(2.50-4.36) EWNT: 3.05 (2.13-4.37) EWHT: 6.30 (4.89-8.11)	Age, smoking status, drinking status, physical activity, family history of T2DM, family income, and education
Chen D 2021	China	4 years	6918	People who were under 45 years old, or missing data, especially for WC and lipid profiles were excluded.	53.87	NWNT: 59.6 ± 9.3 NWHT: 58.0 ± 8.7 EWNT: 59.0 ± 9.2 EWHT: 58.6 ± 8.8	≥ 90 cm	≥ 85 cm	≥1.7 mm/L	≥1.7 mm/L	NWNT: 50.51% NWHT: 9.71% EWNT: 26.45% EWHT: 13.33%	NWNT: 6.6% NWHT: 8.2% EWNT: 13.3% EWHT: 18.4%	1) Self-reported 2) FPG ≥ 7.0 mmol/L 3) Consumption of glucose-lowering drugs or on insulin treatment 4) HbA1c ≥ 6.5% 5) casual plasma glucose ≥ 11.1 mmol/L	Risk ratio NWNT: Ref. NWHT: 1.06 EWNT: 1.58 EWHT: 1.91	Age, sex, education background, current smoking, drinking status, area of residence, marital status, systolic blood pressure, body mass index and fasting plasma glucose
Chen G 2021	China	7 years	7397	People who were under 45 years old, or missing data, especially for WC and lipid profiles were excluded.	53.40%	25–49 years (19.4%) 50–59 years (35.7%) 60–69 years (29.5%) ≥ 70 years (15.4%)	≥ 90 cm	≥ 85 cm	≥1.7 mm/L	≥1.7 mm/L	NWNT: 51.9 % NWHT/EWNT: 35.1 % EWHT: 13 %	NWNT: 8.05 % NWHT/EWNT: 13.50 % EWHT: 19.73 %	1) Self-reported 2) FPG ≥ 7.0 mmol/L 3) Consumption of glucose-lowering drugs or on insulin treatment 4) HbA1c ≥ 6.5% 5) casual plasma glucose ≥ 11.1 mmol/L	Hazard ratio NWNT: Reference NWHT/EWNT: 1.28 (1.06-1.54) EWHT: 1.61 (1.26-2.06)	Age, sex, education, marital status, region, body mass index, smoking, drinking , systolic blood pressure, diastolic blood pressure, total cholesterol, HDL-C, and LDL-C

Table 2: Assessment of the Quality of the Included Studies using the Newcastle-Ottawa Scale for Cohort Studies

Authors, year	Selection				Comparatibility		Outcome				
	Representativenes of the exposed cohort	Selection of the non-exposed cohort	Exposure Ascertainment	Outcome not present at the start of the study	Study controls for sex and age	Study controls for any additional important factor	Assement of outcome	Length of follow-up	Adequacy of follow up	Score	Overall Judgement
Zhang 2012			*	*	*	*	*	*	*	7	Low risk
He 2013			*	*	*	*	*	*	*	7	Low risk
Han 2014			*	*	*	*	*	*	*	7	Low risk
Janghorbani 2016			*	*	*	*	*	*	*	7	Low risk
Xu 2020	*	*	*	*	*	*	*	*	*	9	Low risk
Chen D 2021	*	*	*	*	*	*	*	*	*	9	Low risk
Chen G 2021	*	*	*	*	*	*	*	*	*	9	Low risk

"diabetes" and "hypertriglyceridemic waist" were used. The specific search strategies used for each database are available in Supplementary Material 1.

Selection Criteria

Studies were included for analysis if they met the following criteria: 1) cohort study, 2) if blood glucose metrics were evaluated, such as fasting plasma glucose, two-hour plasma glucose level during an oral glucose tolerance test, or HbA1c, 3) where triglycerides were evaluated and abdominal waist was measured, 4) incidence of diabetes mellitus was reported, 5) the association of HTGW as a risk of diabetes was reported as adjusted odds ratios (ORs), relative risks (RRs), or hazard ratios (HRs) along with 95% confidence intervals (CI 95%).

Diabetes was defined as impaired fasting glucose, according to the criteria of the American Diabetes Association (ADA) definition, fasting plasma glucose (FPG) ≥ 7.0 mmol/L (≥126 mg/dL) [16], 2-hour plasma glucose (OGTT) ≥ 11.1 mmol/L (≥200 mg/dL) [16], or elevated hemoglobin A1c (HbA1c) (≥ 6.5%) [16].

Participants were classified into four groups, based on triglyceride level and waist circumference: 1) normal waist circumference and normal triglyceride level (NWNT), 2) normal waist circumference and high triglyceride level (NWHT), 3) enlarged waist circumference and normal triglyceride level (EWNT), and 4) enlarged waist circumference and high triglyceride level (EWHT).

Research studies were excluded if: 1) they were letters to the editor, conference proceedings abstracts, protocols, or review studies, 2) articles that did not provide inferential statistics and measures of association, and 3) articles that did not have abstracts and full text in Spanish or English.

Study Selection

Rayyan software (https://rayyan.qcri.org) was used for the storage of articles found in each of the examined information repositories. The two researchers proceeded, autonomously, to examine the titles and abstracts of the manuscripts. If there was consensus among them for the inclusion of a manuscript, it was included; otherwise, it was excluded. In case of any discrepancy, a meeting was held among the co-authors to reach an agreement on the manuscript in question.

At a later stage, the full text of all selected articles was reviewed. In an Excel file, it was noted whether each study should be included or not. This operation was developed in the same way as the process described above.

Data Extraction and Qualitative Analysis

The scientific manuscripts that were selected moved on to the data extraction phase, for which a Microsoft Excel 2022 form was used. The following information was collected from each chosen article: first author, year, country, follow-up time, population (selection criterion), sample size, sex (% female), age, definition of triglyceride waist phenotype, prevalence of triglyceride waist phenotype, incidence of diabetes, diagnostic criterion for diabetes, measure of association used, adjustment variables.

Risk of Bias Assessment

Three reviewers independently analyzed the risk of bias in each of the chosen studies, discussing their findings until reaching an agreement. For this, the New Castle Ottawa (NCO) risk of bias tool for cohort studies [17] was used. Basically, the NCO assesses the level of risk of a manuscript based on three primary criteria: 1) study selection, which evaluates the representativeness of the sample, the choice of the non-exposed, and the confirmation of the exposure, 2) comparability, which examines whether the researchers have adequately controlled confounding factors in the study design or analysis, 3) outcomes, which reviews how the outcomes were evaluated, the duration of participant follow-up, and whether losses during follow-up were taken into account. Each criterion is evaluated according to a series of subcriteria and stars are awarded to studies that meet these subcriteria. Studies that obtained ≥ 7 stars were considered to have a low risk of bias.

Quantitative Analysis

Analyses were performed with RevMan 5.3. The variables of interest were worked on in a dichotomized way. The outcome was the incidence of diabetes. For the meta-analysis, only studies whose measure of association were presented as HRs were used. Due to the nature of the included studies, results were reported through the DerSimonian and Laird random effects models.

The I2 statistic estimate was used to assess heterogeneity among the included cohort studies [18].

Significant heterogeneity was considered if I2 > 50% [19]. Publication bias was not evaluated, as the manuscripts found did not exceed the required minimum (10).

RESULTS

Eligible Studies

507 manuscripts were found in the database search. After removing the duplicates, which were 256, we reviewed 251 records, of which we reviewed full-text documents of 44 of them, to finally include 7 articles [11-14, 20-22]. No additional articles were found. See Figure **1**.

Study Characteristics

All evaluated studies were from the Asian continent. Five were conducted in China [11,12,20-22]; one in Iran [12], and another in Korea [14]. The total number of participants was 38,392 and ranged from 687 to 15,717. The follow-up time ranged from three to 15 years.

Three studies had the percentage of female sex around 50% [12,20,21], while the work of Han *et al*. [14] had the lowest percentage (28.30%) and that of Jangorbani *et al*., the highest value of all (73.90%).

All manuscripts evaluated each of these phenotypes, except for the study by He *et al*. [22], which only evaluated the EWHT form (through the classic terminology of hypertriglyceridemic waist or HTGW) and the study by Chen G [21], which combined NWHT/EWNT as a single variable.

In relation to this, only in the work of Janghorbani and Amini *et al*. [13] they used the cut-off points of The Third Report of the National Cholesterol Education Program Adult Treatment Panel III (ATPIII) [23]. It was identified that the criteria for measuring WC varied between genders. For men, a cut-off point of ≥ 90 cm was used. However, in the case of women, this cut-off

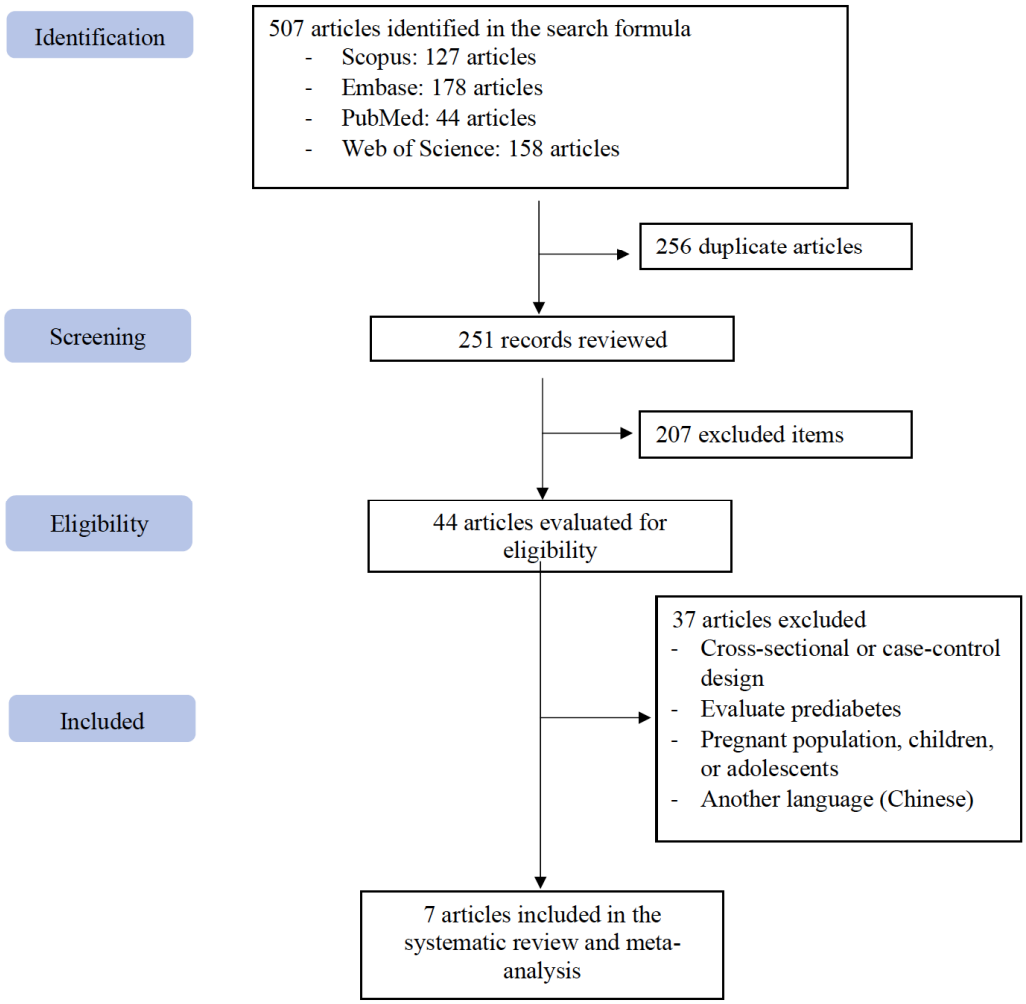

Figure 1: Flowchart.

point varied: it ranged from ≥ 80 cm to ≥ 85 cm. Regarding hypertriglyceridemia, uniformity was observed in the studies; all used a level of ≥1.7 mm/L as a diagnostic criterion.

Risk of Bias Assessment

All studies presented a low level of bias (score from 7 to 9). Those by Zhang M *et al*. [11], He S *et al*. [22], Han KJ *et al*. [14] and Janghorbani and Amini [13] presented a lower score level in the selection domain, as they used non-representative samples, both for the exposed and non-exposed cohort.

Meta-Analysis of the Association between Obesity and Prediabetes

For the meta-analysis, only studies that used the hazard ratio as a measure of association and that evaluated the four phenotypes were included. Thus, four studies were finally included [11,12,14,20]. Those by Xu M *et al*. [12] and Zhang M *et al*. [11] evaluated both men and women.

Figure **2** shows that, compared to people with NWHT, a statistically significant association was found for those with NWHT (HR: 2.65; CI 95% 1.77 – 3.95), EWNT (HR: 2.54; CI 95% 2.05 – 3.16) and EWHT (HR: 4.41 (CI 95% 2.82 – 6.89). Figure **3** shows how the measure of association varies according to the phenotype.

Regarding the heterogeneity of the studies, measured through I2, it was 70%, 0%, and 75% in the works evaluating NWNT versus NWHT, versus EWNT, and versus EWHT, respectively.

DISCUSSION

The results of this systematic review show a geographical trend in the development of the evaluated works, which come from the Asian continent. The

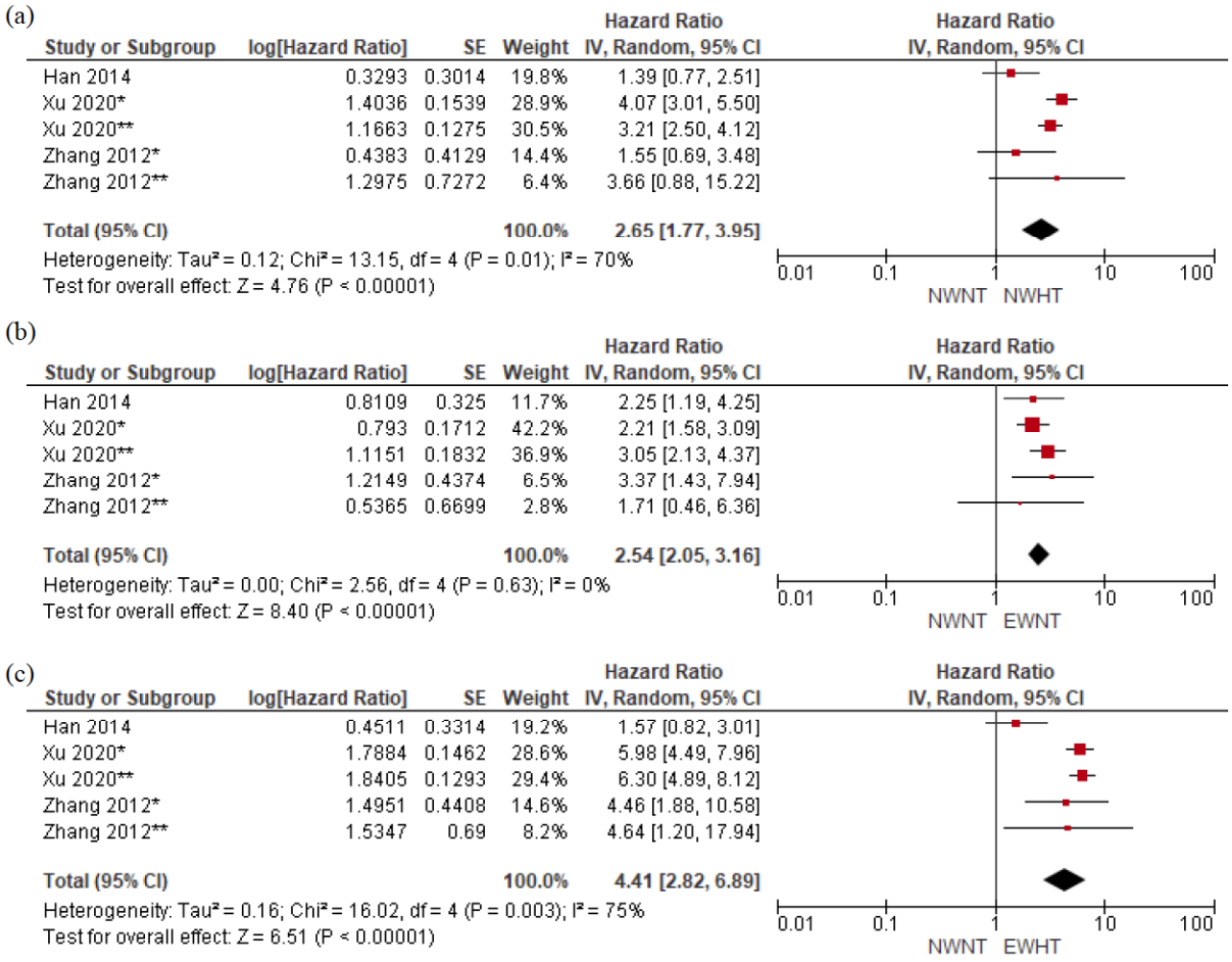

Figure 2: Meta-analysis for the association of NWHT (**a**), EWNT (**b**), EWHT (**c**) phenotype, compared with individuals with NWNT.

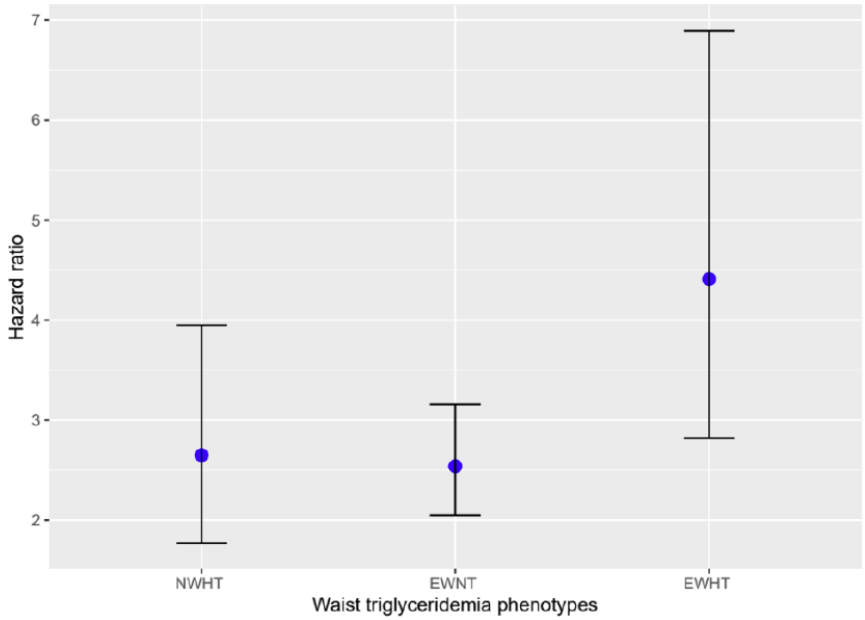

Figure 3: Trend graph about waist triglyceridemia phenotypes.

predominance of works carried out in China, along with studies carried out in Iran and Korea, may reflect cultural, genetic, or lifestyle differences specific to these populations that may influence the results obtained. Indeed, Asians develop diabetes with a lower BMI compared to Caucasians, so the association between abdominal obesity and diabetes may be different [24].

Likewise, it is crucial to consider the variability in the follow-up time of the works, which ranges between 3 and 15 years. The shorter follow-up may not be long enough to optimally evaluate the incidence of diabetes, which usually evolves slowly. Analyses that are too short could underestimate the association between exposure and outcome. On the other hand, the longer follow-up increases the likelihood that patients will experience changes in adiposity measures, medication use, and other covariates that can confuse the relationship. Therefore, research with an intermediate follow-up of 5 to 10 years could provide the most solid evidence.

This disparity in the use of cut-off criteria can be a source of variability in the results of the works. The only one that used the ATP III criteria to define abdominal obesity, based on waist circumference, was that of Janghorbani and Amini Amini [13]. This is the most commonly used set of criteria, so in other works, some participants may have been misclassified. Also, the waist circumference cut-off points varied for females, and ranged from ≥80 cm to ≥85 cm. This variability could be the reason for the differences in the prevalence of abdominal obesity in women between the works and influence the strength of association observed with diabetes. It has been proven that lower cut-off points (≥80 cm) tend to overestimate abdominal obesity in females, compared to the values of ≥88 cm recommended by the ATP III [25]. Conversely, it was encouraging that all works used the same cut-off point to define hypertriglyceridemia (≥1.7 mmol/L). This consistency makes it less likely that differences in the definition of hypertriglyceridemia contribute to heterogeneity between research.

The results of this review highlight a statistically significant association between different phenotypes and the risk of metabolic diseases, compared to the NWHT phenotype. Both participants with the NWHT phenotype and those with the EWNT phenotype had an increase in risk. However, it was the EWHT phenotype that showed a stronger association. These results suggest that abdominal obesity [26,27] and hypertriglyceridemia [28,29] are independently associated with type 2 diabetes, but their coexistence amplifies the risk. The synergy between these two conditions, which together constitute the hypertriglyceridemic waist phenotype, could exacerbate pathophysiological mechanisms, such as insulin resistance (IR), inflammation, and pancreatic beta-cell dysfunction, which cause diabetes.

Interpretation of Results

Central obesity, in particular, is an indicator of visceral adiposity, which is associated with an increase

in the release of free fatty acids, pro-inflammatory cytokines such as interleukin 6 and tumor necrosis factor alpha, and alterations in adiponectin levels, which can interfere with insulin signaling, leading to IR, which in peripheral tissues leads to an increase in hepatic glucose production and a decrease in muscle glucose uptake, which ultimately leads to hyperglycemia, a key feature of T2DM [32].

On the other hand, elevated triglyceride levels are also associated with IR and in turn have direct toxic effects on pancreatic beta cells, causing dysfunction and even cell death, which can also contribute to the development of T2DM [33]. Excess triglycerides could induce lipotoxicity, a phenomenon that affects pancreatic beta cells and interferes with their ability to optimally secrete insulin. Together, central obesity and elevated triglyceride levels, which define the hypertriglyceridemic waist phenotype, could interact to increase the risk of T2DM through the promotion of insulin resistance and pancreatic beta-cell dysfunction. Elevated triglycerides are also associated with an increased production of small, dense very low-density lipoprotein particles that are specifically atherogenic, which increases the risk of cardiovascular disease, a frequent complication of type 2 diabetes [34,35].

Public Health Importance

First, identifying these phenotypes as a significant risk factor for diabetes could contribute to improving early detection and prevention of the disease. Public health strategies could focus on promoting the detection and early management of elevated triglyceride levels and central obesity, which would reduce the risk of diabetes in susceptible patients.

Second, these results underscore the importance of an integrated management strategy for metabolic diseases. Often, these disorders do not occur in isolation and the interaction between different risk factors could enhance the impact on health. Health systems may need to address these risk factors in a multidisciplinary way to effectively manage diabetes and associated ailments.

Study Limitations and Strengths

In general, while the lack of geographical diversity limits the generalization of these findings, the large number of people included and the variation in follow-up duration produce certain strengths. While all the studies included in this systematic review were conducted in Asia, which definitely strengthens their direct relevance to Asian populations, the findings may also be useful to citizens of other continents. Hypertriglyceridemic waist and diabetes are health problems that occur in regions and populations around the world. The accumulated evidence from well-designed studies, even if they have been conducted on a single continent, could provide valuable insight that would apply to a broader context.

Also, the hypertriglyceridemic waist phenotype is based on measures and risk factors that are universally known in the field of metabolic medicine [23], and that, regardless of ethnic or geographic origin, have an impact on the risk of diabetes. Thus, although the extrapolation of findings to other people must be done with caution, due to possible differences in genetic, environmental, and lifestyle factors, this systematic review significantly contributes to the global literature in this field and to inform future strategies for the prevention and management of diabetes in different populations globally.

CONCLUSIONS

This SR and meta-analysis have a clear association between triglyceride waist phenotypes and diabetes. Although central obesity and elevated triglyceride levels are associated with a higher risk of diabetes, their combination confers an even greater risk. This underscores the importance of considering these interactions when assessing the risk of diabetes in the clinical setting.

Given the growing burden of diabetes worldwide, more research is encouraged, specifically in prospective works, in different populations to confirm these results. A more complete understanding of these associations can have important implications for the prevention and treatment of diabetes, and could ultimately help reduce its prevalence and associated complications.

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FINANCIAL DISCLOSURE

This study is self-financed.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

INFORMED CONSENT

Since this study consists of a secondary analysis of public databases that do not contain personally identifiable information, informed consent was not required.

DATA AVAILABILITY

The data supporting the findings of this study can be accessed by the original research paper at the follow link: http://iinei.inei.gob.pe/microdatos/

AUTHOR CONTRIBUTIONS

Conceptualization: Both authors were involved in generating the research idea and formulating the research problem.

Methodology: Joint development and design of the research methods.

Data Analysis: Collaborative processing and statistical analysis of the data.

Validation: Both authors contributed to the verification and confirmation of the results.

Writing – Original Draft: Co-creation of the initial manuscript draft.

Writing – Review & Editing: Both authors participated in the critical revision and editing of the manuscript for intellectually important content.

Supervision: Shared direction and advising on the overall project.

Project Funding Acquisition: Joint efforts in the management and acquisition of project funding.

Administration: Collaborative organization and coordination of the research activities.

SUPPLEMENTARY DATA

The supplementary data can be downloaded from the journal website along with the article.

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