META-ANALYSIS

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Hypertriglyceridemic waist phenotype and abnormal glucose metabolism: a system review and meta-analysis

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Abstract

Objective This study was to perform a meta-analysis to assess the relationship between hypertriglyceridemic-waist (HTW) phenotype and abnormal glucose metabolism.

Methods The data sources were PubMed and EMBASE up to June 2018. Studies providing the relationship between HTW phenotype and abnormal glucose metabolism were included.

Results In total, 48 eligible studies that evaluated 2,42,879 subjects were included in the meta-analysis. In the general population, the pooled odds ratios (ORs) for elevated blood glucose and diabetes related to HTW phenotype was 2.32 (95% confidence interval (CI): 1.98–2.71) and 2.69 (95% CI: 2.40–3.01), respectively. In cohort studies, the pooled OR for diabetes related to HTW phenotype was 2.89 (95% CI: 1.97–4.25) in subjects without diabetes. The levels of homeostasis model assessment of insulin resistance (HOMA-IR) in the HTW population were increased with values of mean differences (MD) 1.12 (95% CI: 0.81–1.43. $P < 0.00001$, $I^2 = 99\%$) in the general population and 0.89 (95% CI: 0.75–1.04, $P < 0.00001$, $I^2 = 67\%$) in subjects without diabetes.

Conclusion HTW phenotype was closely associated with increased risk of abnormal glucose metabolism. There was also a significant correlation between HTW phenotype and insulin resistance.

Keywords Hypertriglyceridemic-waist phenotype · Insulin resistance · Islet cell dysfunction · Diabetes · Diabetic complication

Introduction

Diabetes mellitus is a chronic metabolic disease. Long-term hyperglycemia is the factor that promotes vascular lesions and dysfunction, leading to a variety of complications of diabetes mellitus. The incidence of diabetes is increasing globally. Now, diabetes is a global health burden due to its high prevalence, deaths attributable, and healthcare expenditure [1, 2].

The hypertriglyceridemic-waist (HTW) phenotype is represented by the simultaneous presence of elevated serum triglyceride (TG) and increased waist circumference (WC). Lemieux et al. suggested that the simultaneous measurement and interpretation of WC and fasting TG could be used as inexpensive screening tools to identify men characterized by the atherogenic metabolic triad and at high risk for coronary artery disease [3].

A meta-analysis has shown that HTW phenotype was significantly associated with risk of type 2 diabetes worldwide [4]. However, this meta-analysis only analyzed the relationship between HTW phenotype and diabetes in cross-sectional studies. As we know, the cross-sectional design could not identify the causal relationship. Cohort studies have confirmed the association between HTW phenotype and risk of future diabetes in subjects without diabetes. The predictive power of HTW phenotype was similar to metabolic syndrome. For simpler and fewer components, HTW phenotype might be more practical than metabolic syndrome, and it might be recommended in most clinical practices [5]. Insulin resistance and islet beta cell dysfunction are the main pathogenesis of type 2 diabetes. The comprehensive assessment and management of

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cardiovascular risk factors were also very important in patients with type 2 diabetes. In recent years, the applications of HTW phenotype in the fields of abnormal glucose metabolism have attracted more and more attention, including insulin resistance [6, 7], islet cell dysfunction [8] and cardiometabolic abnormality [9], and diabetic complications [10] in subjects with diabetes. This systematic review aimed to meta-analyze the relationship between hypertriglyceridemic-waist phenotype and each phase of abnormal glucose metabolism.

Methods

Search strategy and eligibility criteria

A systematic review of the published articles was performed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines (http://www.prisma-statement.org/). The predefined inclusion criteria for study selection were as follows: the study must have (1) prospective cohort study, case–control study or cross-sectional study; (2) the exposure was hypertriglyceridemic-waist phenotype; (3) the outcome was abnormal glucose metabolism, including prevalence or incidence of elevated blood glucose and diabetes, insulin resistance, islet cell function. Metabolic abnormality and diabetic complications in diabetic patients were also included. Studies were excluded if (1) the paper were presented without necessary data or other information that allowed calculation of necessary data; (2) letters, reviews, and abstracts from conference proceedings were excluded.

A systematic search was conducted in the bibliographic databases, including PubMed and Embase from inception to June 17, 2018. First, a categorical search using the following keywords was conducted (i) hypertriglyceridemic-waist phenotype or their synonyms (e.g., hypertriglyceridemic waist or HTW); (ii) elevated blood glucose, diabetes, insulin resistance, islet β cell function, metabolic abnormality, and diabetic complications or their synonyms (e.g., impaired fasting glucose or impaired glucose tolerance). Second, categories 'i' to 'ii' were combined using "and", and the duplicates were removed. Also, Reference lists of retrieved articles were manually scanned for all relevant additional studies and review articles. The study selection was limited to English language and studies on humans only.

Study selection and quality assessment

Irrelevant articles were eliminated from the primary search based on the information in the title and abstract. Once the studies were identified by the information in the titles and abstracts, full papers were obtained for all relevant studies.

Two reviewers (C-M.M. and X-L.L.) independently read the full papers obtained from the search for relevance. All studies that did not meet the inclusion criteria or that met the exclusion criteria were removed. Disagreements between the two reviewers regarding study inclusion were resolved through face-to-face discussion of the full-text assessment. Eligible studies were further reviewed.

The methodological quality of case–control studies and cohort studies was assessed using a checklist based on the Newcastle–Ottawa Quality Assessment Scale (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). The methodological quality of cross-sectional studies was assessed using a checklist based on the Agency for Healthcare Research and Quality (https://www.ncbi.nlm.nih.gov/books/NBK35156/). These enabled the reviewers to evaluate the quality of the studies. Disagreements between the reviewers on individual items were resolved through consensus meeting with a third reviewer (F.-Z.Y.).

Data extraction

We extracted the following information about the studies: study characteristics (study name, authors, publication year, journal, study country, study type, follow-up years, and number of participants) and participants' characteristics (mean age or age range, sex).

The diagnostic criteria of HTW phenotype were extracted. There are three grouping methods according to the status of WC and TG. First, four groups: (i) normal WC and normal TG level (NWNT); (ii) normal WC and high TG level (NWHT); (iii) enlarged WC and normal TG level (EWNT); and (iv) enlarged WC and high TG level (HTW phenotype). Second, three groups: (i) NWNT; (ii) sole high TG or enlarged WC (including NWHT and EWNT); (iii) HTW phenotype. Third, two groups: (i) non-HTW phenotype (including NWNT, NWHT, and EWNT); (ii) HTW phenotype. The data were extracted according to original grouping methods and then the data were combined into two groups, non-HW phenotype and HW phenotype.

Disease outcomes include four parts: (i) elevated blood glucose or diabetes: dichotomous data, number of participants and cases were extracted; (ii) insulin resistance and islet cell function: continuous data, mean (standard deviation (SD), standard errors (SE) and 95% confidence interval (CI)), median (interquartile range (IQR)) and geometric mean (95% CI) were extracted. The median or geometric mean was considered equivalent to mean. The 95% CI and SE were converted to SD by the calculator from cochrane (http://training.cochrane.org/sites/training.cochrane.org/files/public/uploads/resources/embedded_resources/online_learning_modules/Analysing_and_Presenting_Data/AD_continuous/files/Finding_SDs.xls). The width of the interquartile range was considered as 1.35 SD. The mean and SD

were combined into two groups by our own calculator; (iii) metabolic abnormality in subjects with diabetes, including fasting plasma glucose (FPG), glycosylated hemoglobin A1c (HbA1c), total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), apolipoprotein B (Apo B), systolic blood pressure (SBP), and diastolic blood pressure (DBP): continuous data, mean (SD) or median (IQR) were extracted. The data was handled as the same way with insulin resistance; (iv) diabetic complications: dichotomous data, number of participants and cases were extracted.

If the information was unavailable or not clear from a published report, we collected relevant data by corresponding with the authors. The data were extracted from primary studies by two reviewers (C.-M.M. and X.-L.L.) independently.

Data synthesis and statistical analysis

We used Review Manager 5.3 for data merging and statistical analysis. For dichotomous data, the statistical model is based on Mantel–Haenszel, the effect index is odds ratio (OR) with 95% CI, and the analysis model is the random-effects model. For continuous data, we used the random-effects model and the inverse variance (IV) method to interpolate the mean differences (MD) of each study. The results are reported with a 95% CI. Heterogeneity across studies was evaluated by the I^2 statistic (ranges from 0 to 100% with lower values representing less heterogeneity). The possibility of publication bias was evaluated using the Egger test and visual inspection of a funnel plot. Moreover, stratified analyses and sensitivity analyses were performed to evaluate the influences of selected study and participant characteristics on the results. Analyses were performed using the STATA version 12.0 software (STATA Corporation, TX, USA).

Results

Figure 1 summarizes the selection process of the studies. In total, 249 references were obtained using PubMed and Embase. Additional six full-text articles were included after scanning the related literature and reference lists of the studies selected for inclusion. Eventually, a total of 48 studies were included in this review [5–52]. In these studies, 33 studies were analysis of elevated blood glucose and/or diabetes [5, 7, 8, 11, 13, 15, 18–20, 22–24, 26, 28–36, 39–42, 46–52], 18 studies were analysis of insulin resistance and/or islet cell function [6–8, 12, 14, 16, 17, 23, 25, 27–29, 36, 38, 41, 45, 46, 49], 5 studies were analysis of metabolic abnormality [9, 10, 21, 37, 43], and 4 studies were for analysis of diabetic complications [10, 21, 44, 48]

(Table 1). Several studies included more than one disease outcome. The quality of the included articles is also summarized in Table 1.

Supplementary Table 1 shows the characteristics of articles about the risk of elevated blood glucose and/or diabetes included in the meta-analysis. Elevated bood glucose include subjects with prediabetes or diabetes at the same time. The definition of elevated blood glucose was FPG ≥ 5.6 mmol/L and/or OGTT 2-h plasma glucose ≥ 7.8 mmol/L and/or HbA1c ≥ 5.7% and/or had been diagnosed with diabetes. The definitions of elevated blood glucose were not the same among each studies. The definitions of elevated blood glucose and diabetes were shown in Supplementary Table 1. The risk of diabetes in the HTW phenotype was increased. The pooled OR for diabetes related to HTW phenotype was 2.69 (95% CI: 2.40–3.01, P < 0.00001, I^2 = 86%) in overall [5, 11, 18, 22–24, 26, 28–31, 33–36, 39–42, 47–52], 2.65 (95% CI: 2.17–3.25, P < 0.00001, I^2 = 72%) for males [23, 29, 31, 33–35, 39–41, 49, 51], and 3.16 (95% CI: 2.51–3.97, P < 0.00001, I^2 = 84%) for females [7, 23, 29, 31, 34, 39–41, 49, 51], respectively (Fig. 2). In these studies, 20 studies were cross-sectional studies [7, 18, 22–24, 26, 29, 31, 33–36, 39–41, 47–50, 52] and 5 studies were cohort studies [5, 28, 30, 41, 51]. Subgroup analyses were done, and the results were similar between two research methods. In cross-sectional studies, the pooled OR for diabetes related to HTW phenotype was 2.66 (95% CI: 2.35–3.01, P < 0.00001, I^2 = 87%). In cohort studies, the pooled OR for diabetes related to HTW phenotype was 2.89 (95% CI: 1.97–4.25, P < 0.00001, I^2 = 83%). In 13 studies [23, 24, 28, 30, 31, 35, 40, 42, 47–51], the samples were devided into four groups, NWNT, NWHT, EWNT, and HTW phenotype. Compared with NWNT, the pooled OR for diabetes was 2.37 (95% CI: 2.04–2.75, P < 0.00001, I^2 = 65%) in NWHT, 2.66 (95% CI: 2.11–3.34, P < 0.00001, I^2 = 91%) in EWNT and 4.66 (95% CI: 3.60–6.03, P < 0.00001, I^2 = 94%) in HTW phenotype. Compared with NWHT and EWNT, the pooled ORs for diabetes related to HTW phenotype was 1.88 (95% CI: 1.57–2.25, P < 0.00001, I^2 = 79%) and 1.76 (95% CI: 1.53–2.02, P < 0.00001, I^2 = 80%), respectively (Fig. 3).

The risk of elevated blood glucose in the HTW phenotype was also increased. The pooled OR for elevated blood glucose related to HTW phenotype was 2.32 (95% CI: 1.98–2.71, P < 0.00001, I^2 = 80%) in overall [8, 11, 13, 15, 18–20, 22–24, 32, 39, 46, 48, 49, 51], 2.35 (95% CI: 1.79–3.09, P < 0.00001, I^2 = 66%) for males [8, 23, 32, 39, 49, 51], and 2.89 (95% CI: 2.25–3.72, P < 0.00001, I^2 = 70%) for females [8, 15, 23, 32, 39, 49, 51], respectively. In these studies, 12 studies were about adults [8, 13, 15, 18, 22–24, 39, 46, 48, 49, 51] and 4 studies were about children [11, 19, 20, 32]. In adults, the pooled OR for
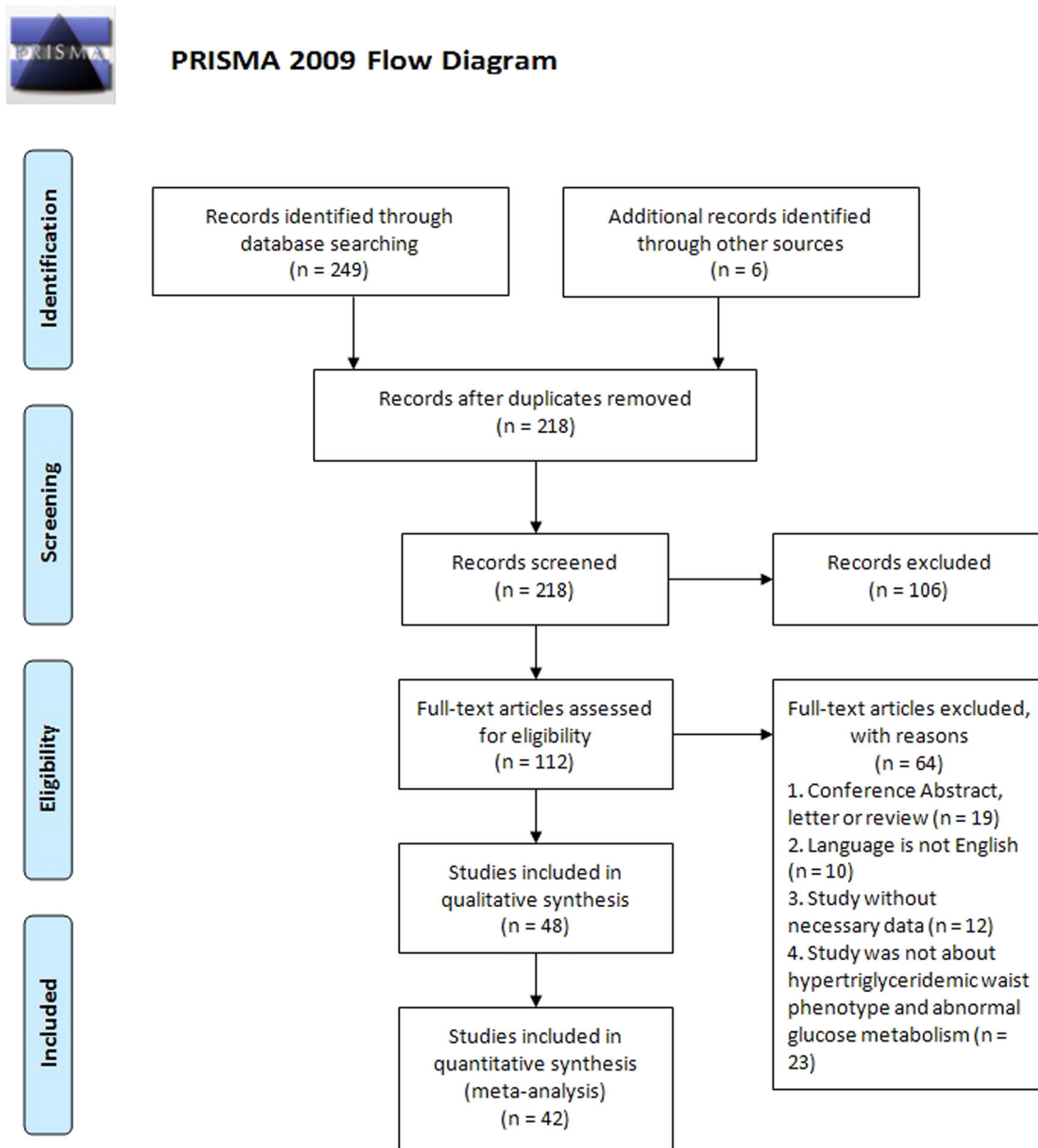
Fig. 1 Flowchart of selection of studies and specific reasons for exclusion from the meta-analysis

elevated blood glucose related to HTW phenotype was 2.45 (95% CI: 2.08–2.88, $P < 0.00001$, $I^2 = 82\%$). In children, the pooled OR for elevated blood glucose related to HTW phenotype was 1.66 (95% CI: 1.02–2.69, $P = 0.04$, $I^2 = 47\%$). In seven studies [13, 23, 24, 46, 48, 49, 51], the samples were devided into four groups, NWNT, NWHT, EWNT, and HTW phenotype. Compared with NWNT, the pooled OR for elevated blood glucose was 2.06 (95% CI: 1.80–2.35, $P < 0.00001$, $I^2 = 36\%$) in NWHT, 2.23 (95% CI: 1.86–2.67, $P < 0.00001$, $I^2 = 79\%$) in EWNT and 3.67 (95% CI: 2.68–5.03, $P < 0.00001$, $I^2 = 91\%$) in HTW phenotype. Compared with NWHT and EWNT, the pooled

ORs for elevated blood glucose related to HTW phenotype was 1.70 (95% CI: 1.41–2.06, $P < 0.00001$, $I^2 = 54\%$) and 1.61 (95% CI: 1.35–1.91, $P < 0.00001$, $I^2 = 68\%$), respectively.

Overall, 18 studies analyzed the relationship between HTW phenotype and insulin resistance (Supplementary Table 2). In these studies, insulin resistance was evaluated by homeostasis model assessment of insulin resistance (HOMA-IR) in 16 studies [6, 7, 12, 14, 16, 23, 25, 27–29, 36, 38, 41, 45, 46, 49], by HOMA2-IR in one study [8] and by euglycaemic–hyperinsulinaemic clamp technique in one study [17]. Due to only one study, the study of

Table 1 Characteristics of studies included in the meta-analysis

Source	Published years	Country	Type of studies	n	Male/female	Age	Mean follow-up years	WC used for HTW detection (cm) Male	WC used for HTW detection (cm) Female	TG used for HTW detection (mmol/L) Male	TG used for HTW detection (mmol/L) Female	Disease outcomes	Score
Abbasi F et al.	2016	South Asians	Cross-sectional study	2998	1842/1156	>18		90	80	1.7	1.7	Insulin resistance	AHRQ 8
Bailey DP et al.	2013	United Kingdom	Cross-sectional study	234	112/122	10–19		Age- and gender-specific 90th percentile	Age- and gender-specific 90th percentile	1.24	1.24	Elevated blood glucose	AHRQ 8
Bardini G et al.	2011	Italy	Cross-sectional study	1344	526/818	About 45		90	85	2	2	Elevated blood glucose; insulin resistance and islet cell function	AHRQ 8
Blackburn P et al.	2003	Canada	Cross-sectional study	66	66/NA	22–67		90	NA	2	NA	Insulin resistance and islet cell function	AHRQ 9
Blackburn P et al.	2012	Canada	Cross-sectional study	254	NA/254	32–82		NA	85	NA	1.5	Diabetes; insulin resistance	AHRQ 8
Brisson D et al.	2010	Canada	Cohort study	144	NA/144	28.3 ± 3.9	From 11–14 weeks to 24–28 weeks of gestation	NA	85	NA	1.7	Elevated blood glucose	NOS 8
Buchan DS et al.	2016	Scottish and Welsh	Cross-sectional study	387	210/177	12–17.5		<17 years: ≥90th percentile for age and sex; ≥17 years: ≥94 cm	<17years: ≥90th percentile for age and sex; ≥17 years: ≥80 cm	1.24	1.24	Insulin resistance	AHRQ 8
Cabral NA et al.	2012	Brazil	Cross-sectional study	218	NA/218	≥31		NA	88	NA	1.7	Elevated blood glucose	AHRQ 11
	2015	Brazil		976		20–59		90	80	1.7	1.7		AHRQ 10

Table 1 (continued)

Source	Published years	Country	Type of studies	n	Male/female	Age	Mean follow-up years	WC used for HTW detection (cm) Male	Female	TG used for HTW detection (mmol/L) Male	Female	Disease outcomes	Score
Cabral Rocha AL et al.			Cross-sectional study		443/533							Insulin resistance	AHRQ 10
Carlsson AC et al.	2014	Sweden	Cross-sectional study	1026	1026/NA	70		90	NA	2	NA	Insulin resistance	AHRQ 9
Chen S et al.	2016	China	Cross-sectional study	11579	5361/6218	≥ 35		90	80	1.7	1.7	Elevated blood glucose and diabetes	AHRQ 11
Conceição-Machado ME et al.	2013	Brasil	Cross-sectional study	1076	427/649	11–17		Age- and gender-specific 90th percentile	Age- and gender-specific 90th percentile	1.13	1.13	Elevated blood glucose	AHRQ 11
Costa PRF et al.	2017	Brasil	Baseline of cohort study	492	205/287	7–15	1	Age- and gender-specific 90th percentile	Age- and gender-specific 90th percentile	1.13	1.13	Elevated blood glucose	NOS 8
de Graaf FR et al.	2010	Netherlands	Cross-sectional study	202	120/82	54 ± 11		102	88	1.7	1.7	Metabolic abnormality; diabetic complication	AHRQ 8
Díaz-Santana MV et al.	2016	Puerto Rico	Cross-sectional study	858	295/563	21–79		91.4	86.3	2	1.5	Elevated blood glucose and diabetes	AHRQ 8
Du T et al.	2014	China	Cross-sectional study	7639	3624/4015	≥ 18		90	80	1.7	1.7	Elevated blood glucose and diabetes; insulin resistance	AHRQ 11
Egeland GM et al.	2011	Canada	Cross-sectional study	1938	739/1199	≥ 18		102	88	1.7	1.7	Elevated blood glucose and diabetes	AHRQ 9
Gazi IF et al.	2008	Greece	Cross-sectional study	228	NA/228	NA		NA	88	NA	1.7	Insulin resistance	AHRQ 7
	2011	Spain		2270	NA	18–80		94	80	1.71	1.71	Diabetes	AHRQ 10

Table 1 (continued)

Source	Published years	Country	Type of studies	n	Male/female	Age	Mean follow-up years	WC used for HTW detection (cm)		TG used for HTW detection (mmol/L)		Disease outcomes	Score
								Male	Female	Male	Female		
Gomez-Huelgas R et al.			Cross-sectional study										
Guattini VL et al.	2015	Brazil	Cross-sectional study	45	25/20	≥40		94	80	1.7	1.7	Insulin resistance	AHRQ 9
Han KJ et al.	2014	Korea	Cohort study	2900	2078/822	44.3±6.5	4	90	85	1.7	1.7	Diabetes; insulin resistance	NOS 7
He S et al.	2013	China	Cohort study	687	399/288	About 50	15	90	80	1.7	1.7	Diabetes	NOS 7
Huang J et al	2015	China	Cross-sectional study	2142	683/1145	18–75		90	80	1.7	1.7	Diabetes; insulin resistance	AHRQ 11
Janghorbani M et al.	2016	Iran	Cohort study	1865	487/1378	30–70	7.3 (range 1–10)	102	88	1.7	1.7	Diabetes	NOS 8
Karagöz A et al.	2017	Turkey	Cross-sectional study	1924	943/981	55±11		95	88	1.7	1.7	Diabetes	AHRQ 9
Kelishadi R et al.	2016	Iran	Cross-sectional study	5625	2824/2801	10–18		Age- and gender-specific 90th percentile	Age- and gender-specific 90th percentile	Age- and gender-specific 95th percentile	Age- and gender-specific 95th percentile	Elevated blood glucose	AHRQ 7
LeBlanc S et al.	2018	Canada	Cross-sectional study	467	467/NA	19.4–77.6		90	NA	2	NA	Diabetes	AHRQ 9
Lee BJ et al.	2016	Korea	Cross-sectional study	11937	4906/7031	31–80		90	85	2	1.5	Diabetes	AHRQ 7
Lemieux I et al.	2002	Canada	Cross-sectional study	907	907/NA	18–74		90	NA	2	NA	Diabetes	AHRQ 9
Li Y et al.	2014	China	Cross-sectional study	1534	568/966	57.21±10.97		90	85	2	2	Diabetes; insulin resistance	AHRQ 11
Ma CM et al.	2017	China	Cross-sectional study	538	287/251	≥18		90	85	1.7	1.7	Metabolic abnormality; diabetic complication	AHRQ 8
Mayer O et al.	2014	Czech Republic	Cross-sectional study	458	366/92	65.5±8.3		90	85	2	2	Metabolic abnormality	AHRQ 10

Table 1 (continued)

Source	Published years	Country	Type of studies	n	Male/female	Age	Mean follow-up years	WC used for HTW detection (cm)		TG used for HTW detection (mmol/L)		Disease outcomes	Score
								Male	Female	Male	Female		
Moon BS et al.	2015	Korea	Cross-sectional study	32186	25823/6363	41.3 ± 7.5		90	85	1.7	1.7	Insulin resistance	AHRQ 10
Pollex RL et al.	2006	Canada	Cross-sectional study	522	223/299	≥ 18		90	90	2	2	Elevated blood glucose and diabetes	AHRQ 11
Radenković SP et al.	2011	Serbia	Cross-sectional study	300	155/145	About 60		90	85	2	2	Metabolic abnormality	AHRQ 9
Ramezankhani A et al.	2017	Iran	Cross-sectional study	12012	5265/6747	20–88		90	85	2	2	Diabetes	AHRQ 11
Ren Y et al.	2016	China	Case–control study	8826	3872/4954	20–85		90	80	1.7	1.7	Diabetes	NOS 8
Ren Y et al.	2017	China	Cohort study	12086	4498/7588	18–92	6.0 (range 0.06–7.10)	90	80	1.7	1.7	Diabetes; insulin resistance and islet cell function	NOS 8
Sam S et al.	2009	United States	Cross-sectional study	375	230/145	About 60		90	85	2	2	Metabolic abnormality	AHRQ 9
St-Pierre J et al.	2007	Canada	Cross-sectional study	592	NA	About 50		90	85	2	2	Diabetic complication	AHRQ 8
Vaverková H et al.	2015	Czech Republic	Cross-sectional study	607	295/312	About 40		90	85	2	1.5	Insulin resistance	AHRQ 8
von Bibra H et al.	2017	German	Cross-sectional study	1848	808/1040	> 20		90	85	2	1.5	Elevated blood glucose; insulin resistance	AHRQ 9
Wang A et al.	2014	China	Cross-sectional study	95015	75605/19410	18–98		90	85	2	1.5	Diabetes	AHRQ 10
Wang W et al.	2018	China	Cohort study	4081	1657/2424	35–75	5.16	90	85	2	1.5	Elevated blood glucose and diabetes; diabetic complication	NOS 7
Yu Z et al.	2012	China	Cross-sectional study	3289	1458/1831	50–70		90	80	1.7	1.7	Elevated blood	AHRQ 8

Table 1 (continued)

Source	Published years	Country	Type of studies	n	Male/female	Age	Mean follow-up years	WC used for HTW detection (cm) Male	WC used for HTW detection (cm) Female	TG used for HTW detection (mmol/L) Male	TG used for HTW detection (mmol/L) Female	Disease outcomes	Score
Zeng J et al.	2016	China	Cross-sectional study	2102	848/1254	60–95		90	80	1.7	1.7	glucose and diabetes; insulin resistance	AHRQ 9
Zhang M et al.	2012	China	Cohort study	2908	1957/951	≥20	3	90	80	1.7	1.7	Elevated blood glucose and diabetes	NOS 8
Zhou C et al.	2018	China	Cross-sectional study	1172	391/781	About 50		90	85	2	2	Diabetes	AHRQ 8

WC waist circumference, *TG* triglyceride, *HTW* hypertriglyceridemic-waist phenotype, *AHRQ* Agency for Healthcare Research and Quality, *NOS* Newcastle–Ottawa Scale, *NA* not available

HOMA2-IR and euglycaemic–hyperinsulinaemic clamp technique was not involved in the quantitative synthesis. The results were statistically different from non-HTW phenotype to HTW phenotype with values of MD 1.12 (95% CI: 0.81–1.43, $P < 0.00001$, $I^2 = 99\%$) (Fig. 4a). The levels of HOMA-IR in the HTW population were increased for both men and women. The results were statistically different from non-HTW phenotype to HTW phenotype with values of MD 1.18 (95% CI: 0.91–1.44, $P < 0.00001$, $I^2 = 77\%$) for males [12, 23, 29, 41, 45] and MD 1.01 (95% CI: 0.82–1.21, $P < 0.00001$, $I^2 = 75\%$) for females [7, 23, 25, 29, 41, 45], respectively. In these 16 studies, the data were described as mean (SD, 95% CI, or SE) and geometric mean (95% CI) in 11 studies [6, 7, 12, 14, 16, 25, 27, 28, 38, 45, 49] and median (interquartile range) in 6 studies [23, 29, 36, 41, 46, 49]. Subgroup analyses were done, and the results were similar between two description methods. HTW phenotype was also worse insulin resistance than non-HTW phenotype in five studies without diabetes patients with an MD 0.89 (95% CI: 0.75–1.04, $P < 0.00001$, $I^2 = 67\%$) [25, 28, 41, 46, 49]. In five studies [23, 28, 38, 46, 49], the samples were devided into four groups, NWNT, NWHT, EWNT, and HTW phenotypes. The results were statistically different from NWNT to NWHT (MD 0.57, 95% CI: 0.44–0.70, $P < 0.00001$, $I^2 = 86\%$), EWNT (MD 0.76, 95% CI: 0.57–0.94, $P < 0.00001$, $I^2 = 96\%$), and HTW phenotype (MD 1.49, 95% CI: 1.24–1.73, $P < 0.00001$, $I^2 = 95\%$), respectively. The results were also statistically different from NWHT to HTW phenotype (MD 0.87, 95% CI: 0.72–1.02, $P < 0.00001$, $I^2 = 76\%$) and EWNT to HTW phenotype (MD 0.73, 95% CI: 0.60–0.85, $P < 0.00001$, $I^2 = 74\%$), respectively (Fig. 5). Three studies analyzed the relationship between HTW phenotype and islet β cell function. In these studies, islet β cell function was evaluated by homeostasis model assessment of β cell function (HOMA-β) in two studies [12, 41], by HOMA2-β in one study [8]. In two studies of HOMA-β, the results were not statistically different from non-HTW phenotype to HTW phenotype with values of MD 33.88 (95% CI: −13.37 −81.13. $P = 0.16$, $I^2 = 91\%$) (Fig. 4b).

Five studies analyzed the metabolic abnormality (Supplementary Table 3). Overall, the results were statistically different from non-HTW phenotype to HTW phenotype with values of MD 1.18 (95% CI: 0.24–2.12, $P = 0.01$, $I^2 = 84\%$) for FPG [9, 10, 37], MD 0.47 (95% CI: 0.30–0.64, $P < 0.00001$, $I^2 = 25\%$) for HbA1c [9, 10, 21, 37, 43], MD 0.98 (95% CI: 0.73–1.23, $P < 0.00001$, $I^2 = 0\%$) for TC [9, 21], MD 0.36 (95% CI: 0.19–0.52, $P < 0.0001$, $I^2 = 0\%$) for LDL [9, 21, 43], MD −0.18 (95% CI: −0.27 to −0.08, $P = 0.0003$, $I^2 = 73\%$) for HDL [9, 10, 21, 43], MD 20.27 (95% CI: 14.78–25.75, $P < 0.00001$, $I^2 = 0\%$) for Apo B [21, 43], MD 6.33 (95% CI: 1.52–11.15, $P = 0.010$,
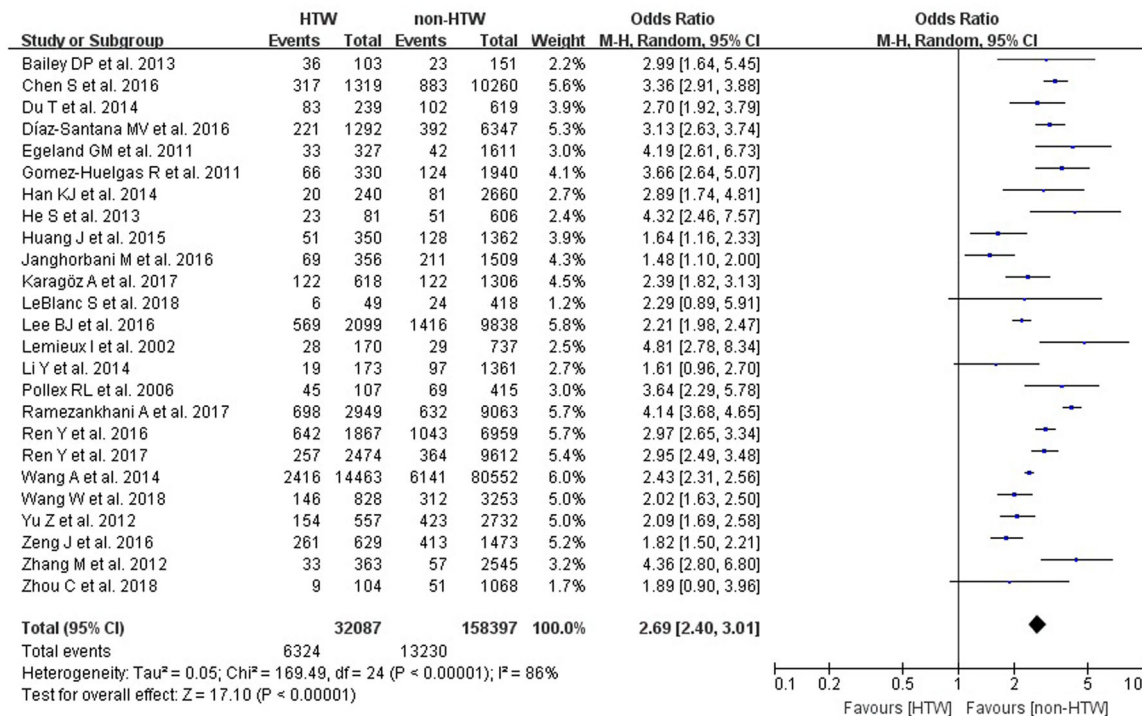
Fig. 2 Risk of diabetes in the hypertriglyceridemic-waist (HTW) phenotype

$I^2 = 71\%$) for SBP [9, 10, 21], and MD 5.30 (95% CI: 1.70–8.90, $P = 0.004$, $I^2 = 84\%$) for DBP [9, 10, 21], respectively. Diabetic complications were analyzed in four studies, one about ischemic stroke [48], two about coronary artery disease [21, 44], and one about early diabetic nephropathy [10]. Due to a limited number of studies, the results of these studies were only shown in Supplementary Table 4.

We performed a sensitivity analysis by omitting one study at a time to estimate the pooled ORs of elevated blood glucose and diabetes, and MD of HOMA-IR. No individual study affected the ultimate conclusion. Visual inspection of the funnel plot revealed symmetry for elevated blood glucose and diabetes, and the Egger's test was not significant (elevated blood glucose $P = 0.883$, diabetes $P = 0.605$). Visual inspection of the funnel plot revealed asymmetry for HOMA-IR (Supplementary Figs. 1–3).

Discussion

Our study is the first systematic review with meta-analysis to evaluate the application value of HTW phenotype in each phase of abnormal glucose metabolism. A previous study focused on diabetes [4]. HTW phenotype had an association with abnormal glucose metabolism regardless of gender, age, and the definition of abnormal glucose metabolism.

This study provides evidence that subjects with HTW phenotype were 2.32-fold and 2.69-fold as likely to have elevated blood glucose and diabetes as those with non-HTW phenotype. The results were similar between genders. Unlike adult researches, the results of children were not uniform [11, 19, 20, 32]. Pooled analysis shown that HTW phenotype also correlated with abnormal glucose metabolism in children.

A lot of researches have shown that abdominal obesity and hypertriglyceridemia are independent risk factors for abnormal glucose metabolism [53–56]. Compared with NWNT subjects, NWHT and EWNT have higher risk of abnormal glucose metabolism and the risk further increased in subjects with HTW phenotype. These results highlight the importance of the simultaneous analysis of WC and TG in clinical screening of individuals at risk for abnormal glucose metabolism.

The results from cross-sectional studies and cohort studies were consistent. Whether in cross-sectional studies or in cohort studies, HTW phenotype is all related to diabetes. The results suggest that the prevalence of diabetes was higher in subjects with HTW phenotype. Subjects with HTW phenotype have already existed abnormal glucose metabolism. Even in HTW subjects without diabetes, the incidence of diabetes was higher in the future. Subjects with HTW phenotype, all should screen diabetes in the baseline and in the future. HTW phenotype is an important cause of
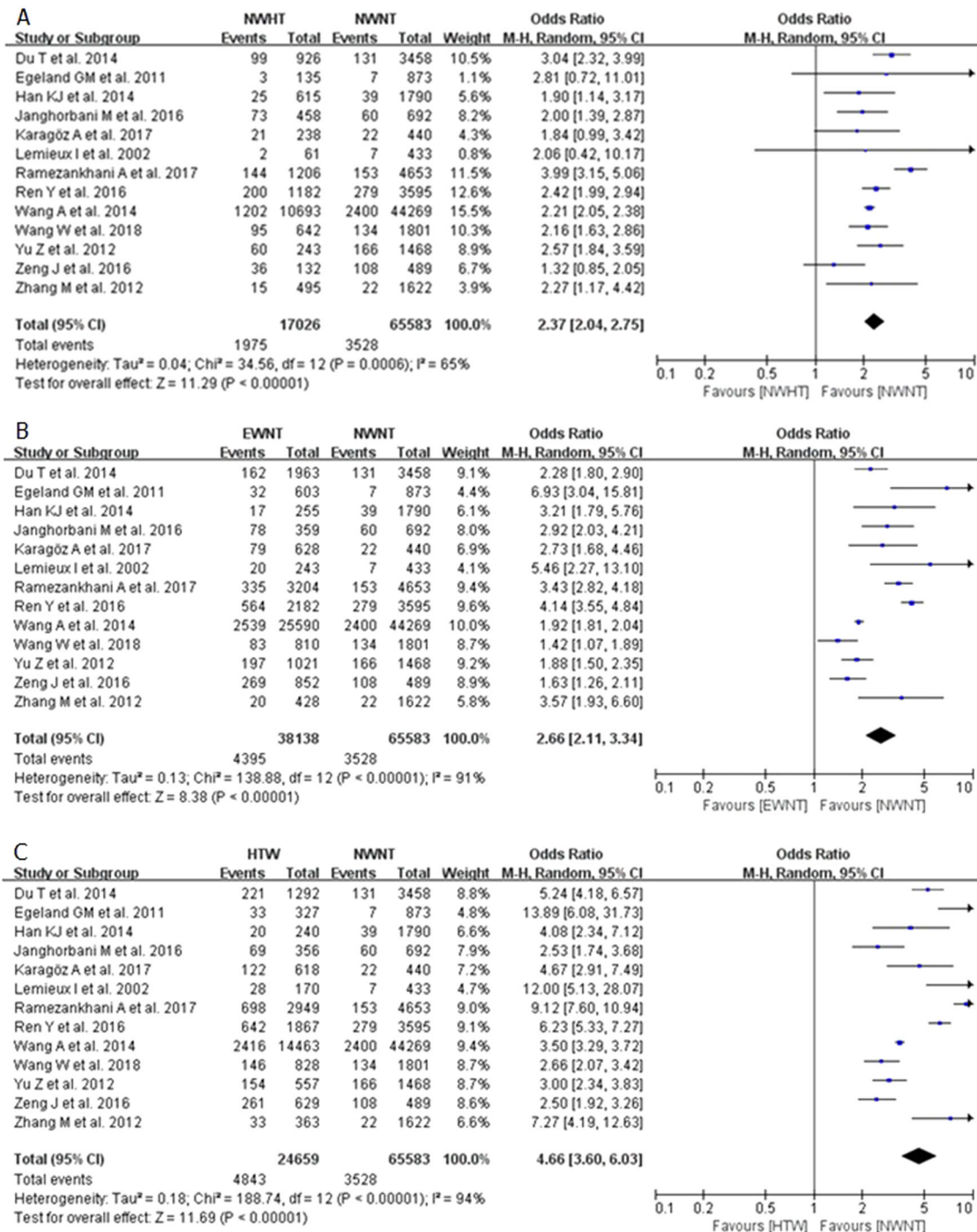
Fig. 3 Risk of diabetes according to the status of waist circumference and triglyceride. NWNT normal WC and normal TG level, NWHT normal WC and high TG level, EWNT enlarged WC and normal TG level, HTW enlarged WC and high TG level, WC waist circumference, TG triglyceride. **a** NWNT vs. NWHT, **b** NWNT vs. EWNT, **c** NWNT vs. HTW, **d** NWHT vs. HTW, **e** EWNT vs. HTW

diabetes. Insulin resistance and islet β cell dysfunction may be the biological mechanism linking HTW phenotype and abnormal glucose metabolism.

Insulin plays a critical role in balancing glucose metabolism in the body. Glucose metabolism is normally regulated by a feedback loop, including islet β cells and insulin-sensitive tissues. If insulin resistance is present, β cells maintain normal glucose tolerance by increasing insulin output. Only when β cells cannot release sufficient insulin in the presence of insulin resistance do glucose concentrations rise [57]. HTW phenotype was closely related to insulin resistance, even in subjects without diabetes. Compared
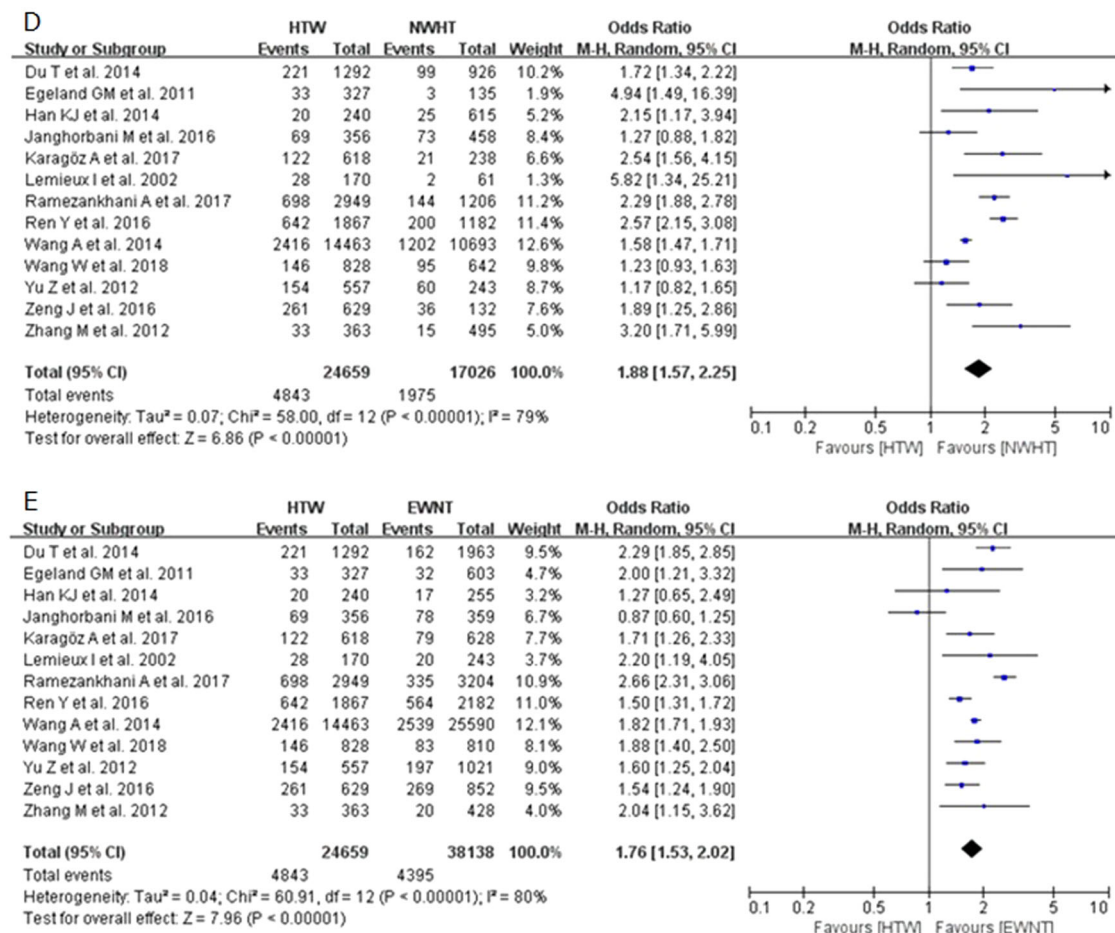
D

Study or Subgroup	HTW Events	HTW Total	NWHT Events	NWHT Total	Weight	Odds Ratio M-H, Random, 95% CI
Du T et al. 2014	221	1292	99	926	10.2%	1.72 [1.34, 2.22]
Egeland GM et al. 2011	33	327	3	135	1.9%	4.94 [1.49, 16.39]
Han KJ et al. 2014	20	240	25	615	5.2%	2.15 [1.17, 3.94]
Janghorbani M et al. 2016	69	356	73	458	8.4%	1.27 [0.88, 1.82]
Karagöz A et al. 2017	122	618	21	238	6.6%	2.54 [1.56, 4.15]
Lemieux I et al. 2002	28	170	2	61	1.3%	5.82 [1.34, 25.21]
Ramezankhani A et al. 2017	698	2949	144	1206	11.2%	2.29 [1.88, 2.78]
Ren Y et al. 2016	642	1867	200	1182	11.4%	2.57 [2.15, 3.08]
Wang A et al. 2014	2416	14463	1202	10693	12.6%	1.58 [1.47, 1.71]
Wang W et al. 2018	146	828	95	642	9.8%	1.23 [0.93, 1.63]
Yu Z et al. 2012	154	557	60	243	8.7%	1.17 [0.82, 1.65]
Zeng J et al. 2016	261	629	36	132	7.6%	1.89 [1.25, 2.86]
Zhang M et al. 2012	33	363	15	495	5.0%	3.20 [1.71, 5.99]
Total (95% CI)		24659		17026	100.0%	1.88 [1.57, 2.25]
Total events	4843		1975			

Heterogeneity: Tau² = 0.07; Chi² = 58.00, df = 12 (P < 0.00001); I² = 79%
Test for overall effect: Z = 6.86 (P < 0.00001)

Favours [HTW] Favours [NWHT]

E

Study or Subgroup	HTW Events	HTW Total	EWNT Events	EWNT Total	Weight	Odds Ratio M-H, Random, 95% CI
Du T et al. 2014	221	1292	162	1963	9.5%	2.29 [1.85, 2.85]
Egeland GM et al. 2011	33	327	32	603	4.7%	2.00 [1.21, 3.32]
Han KJ et al. 2014	20	240	17	255	3.2%	1.27 [0.65, 2.49]
Janghorbani M et al. 2016	69	356	78	359	6.7%	0.87 [0.60, 1.25]
Karagöz A et al. 2017	122	618	79	628	7.7%	1.71 [1.26, 2.33]
Lemieux I et al. 2002	28	170	20	243	3.7%	2.20 [1.19, 4.05]
Ramezankhani A et al. 2017	698	2949	335	3204	10.9%	2.66 [2.31, 3.06]
Ren Y et al. 2016	642	1867	564	2182	11.0%	1.50 [1.31, 1.72]
Wang A et al. 2014	2416	14463	2539	25590	12.1%	1.82 [1.71, 1.93]
Wang W et al. 2018	146	828	83	810	8.1%	1.88 [1.40, 2.50]
Yu Z et al. 2012	154	557	197	1021	9.0%	1.60 [1.25, 2.04]
Zeng J et al. 2016	261	629	269	852	9.5%	1.54 [1.24, 1.90]
Zhang M et al. 2012	33	363	20	428	4.0%	2.04 [1.15, 3.62]
Total (95% CI)		24659		38138	100.0%	1.76 [1.53, 2.02]
Total events	4843		4395			

Heterogeneity: Tau² = 0.04; Chi² = 60.91, df = 12 (P < 0.00001); I² = 80%
Test for overall effect: Z = 7.96 (P < 0.00001)

Favours [HTW] Favours [EWNT]

Fig. 3 (Continued)

with sole high TG or enlarged WC, HTW phenotype has more serious insulin resistance. Our study shown overstimulation of β-cell function in subjects without diabetes, although there is no significant statistical difference. This may be due to insulin secretion increases to maintain normal glucose levels in the face of insulin resistance resulting from abdominal obesity and hypertriglyceridemia. Bardini et al. found that β-cell function declined in impaired glucose tolerance (IGT) subjects with HTW phenotype [8]. With the progress of abnormal glucose metabolism, β-cell function declined earlier in HTW phenotype than non-HTW phenotype.

The UK Prospective Diabetes Study (UKPDS) has demonstrated that blood glucose control decreases the risk of microvascular complications in patients with type 2 diabetes [58]. Diabetic patients often accompany with cardiovascular risk factors, such as elevated blood pressure, dyslipidemia, etc., and higher incidence of cardiovascular diseases [59, 60]. Multiple risk-factor control may lower the increased risks for mortality and cardiovascular events in people with diabetes [61]. Our study shows that subjects with HTW phenotype have inappropriate blood glucose control and worse cardiovascular risk factor in diabetic patients.

The burden of diabetes is associated primarily with increased risks of macrovascular and microvascular diseases. HTW phenotype was associated with an increased risk for coronary artery disease and chronic kidney disease [36, 62]. The study about diabetic complications is fewer. The existing researches have found that HTW phenotype was associated with coronary artery disease and early diabetic nephropathy in type 2 diabetes [10, 21]. Interestingly, HTW phenotype is also associated with an increased risk of ischemic stroke in subjects with normal glucose levels, but not in subjects with impaired fasting glucose and diabetes [48]. When HTW phenotype is used to screening diabetic complications, further work will be necessary to confirm the performance of HTW phenotype.

There are some strengths in our meta-analysis. First, the systematic search was conducted from inception to February 2014 in previous meta-analysis [4]. In our studies, a systematic search was conducted from inception to June 17,
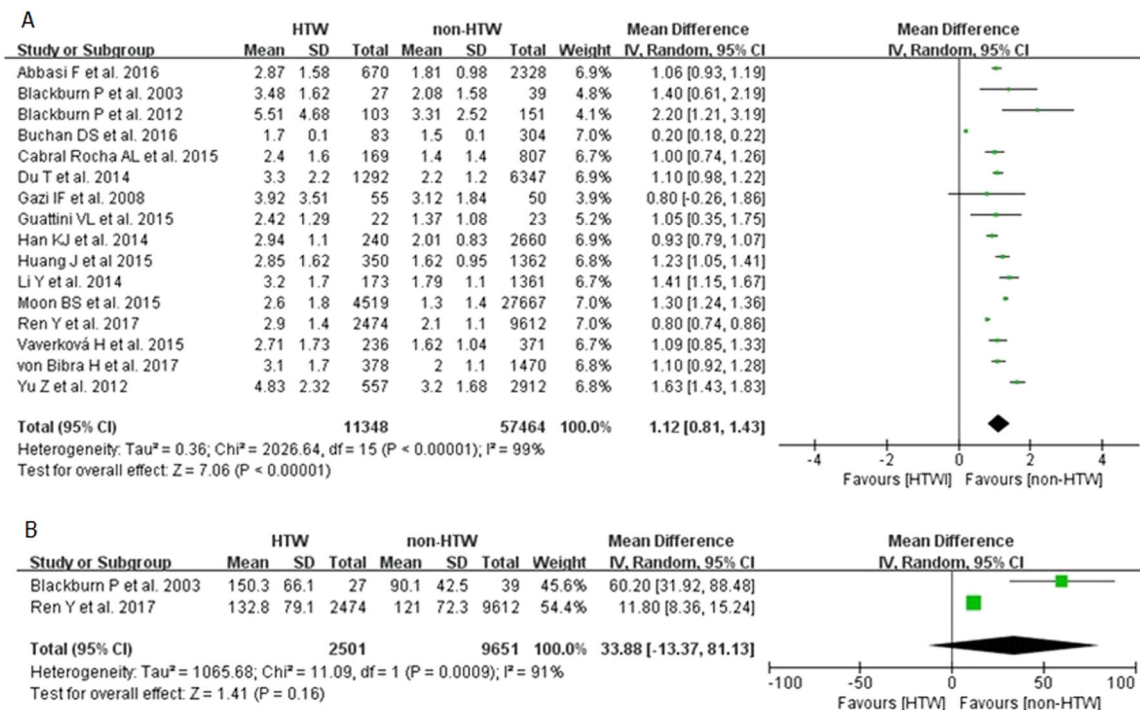
Fig. 4 The levels of insulin resistance and islet β cell function in the hypertriglyceridemic-waist (HTW) phenotype. HTW hypertriglyceridemic-waist phenotype, HOMA-IR homeostasis model assessment of insulin resistance, HOMA-β homeostasis model assessment of β cell function. **a** HOMA-IR and **b** HOMA-β

2018. Therefore, many new studies were included in our study. A total of 48 studies were included in our review, and 23 (47.9%) of them were published from 2015 to 2018. Second, the prevention of diabetes is of paramount importance. HTW phenotype can be used for screening high-risk groups for future diabetes in subjects without diabetes. Third, to our knowledge, this is the first meta-analysis to evaluate the relationship between HTW phenotype and insulin resistance. Subjects with HTW phenotype have more serious insulin resistance, even among subjects without diabetes. Fourth, our meta-analysis found that HTW phenotype can be used for evaluating the cardiovascular risk factors in type 2 diabetes. Fifth, HTW phenotype was proposed because HTW phenotype has more serious atherogenic metabolic abnormalities compared with NWHT and EWNT [3]. In our meta-analysis, some data were analyzed according to four groups: NWNT, NWHT, EWNT, and HTW phenotypes. HTW phenotype has higher risk of abnormal glucose metabolism compared with subjects with NWNT, NWHT, and EWNT.

There are some limitations in our meta-analysis. First, we found heterogeneity in the meta-analyses, and the heterogeneity still remained in many subgroup analysis. Second, the definition of HTW phenotype varied across studies. It is well known that WC was different in different races. Population- and country-specific definition of WC was recommended [63]. Third, abnormal glucose metabolism in most studies were evaluated by FPG only, not OGTT. Fourth, median (IQR) was transformed to mean (SD) in the studies of HOMA indexes. The distribution of HOMA indexes are skewed in these studies. This conversion might not be appropriate. So subgroup analyses were done, and the results were similar between two description methods, median (IQR) and mean (SD).

Prospect

The studies about HTW phenotype and abnormal glucose metabolism were observational study. As compared with the consistent HTW phenotype, the risk of developing type 2 diabetes was greatly reduced in subjects recovering to normal TG level and/or normal WC [41]. The intervention study should be done in HTW phenotype to prove whether appropriate intervention can improve insulin resistance or prevent future diabetes and diabetic complications.

Conclusion

HTW phenotype was closely associated with increased risk of abnormal glucose metabolism in the general population. There was also a significant correlation between HTW
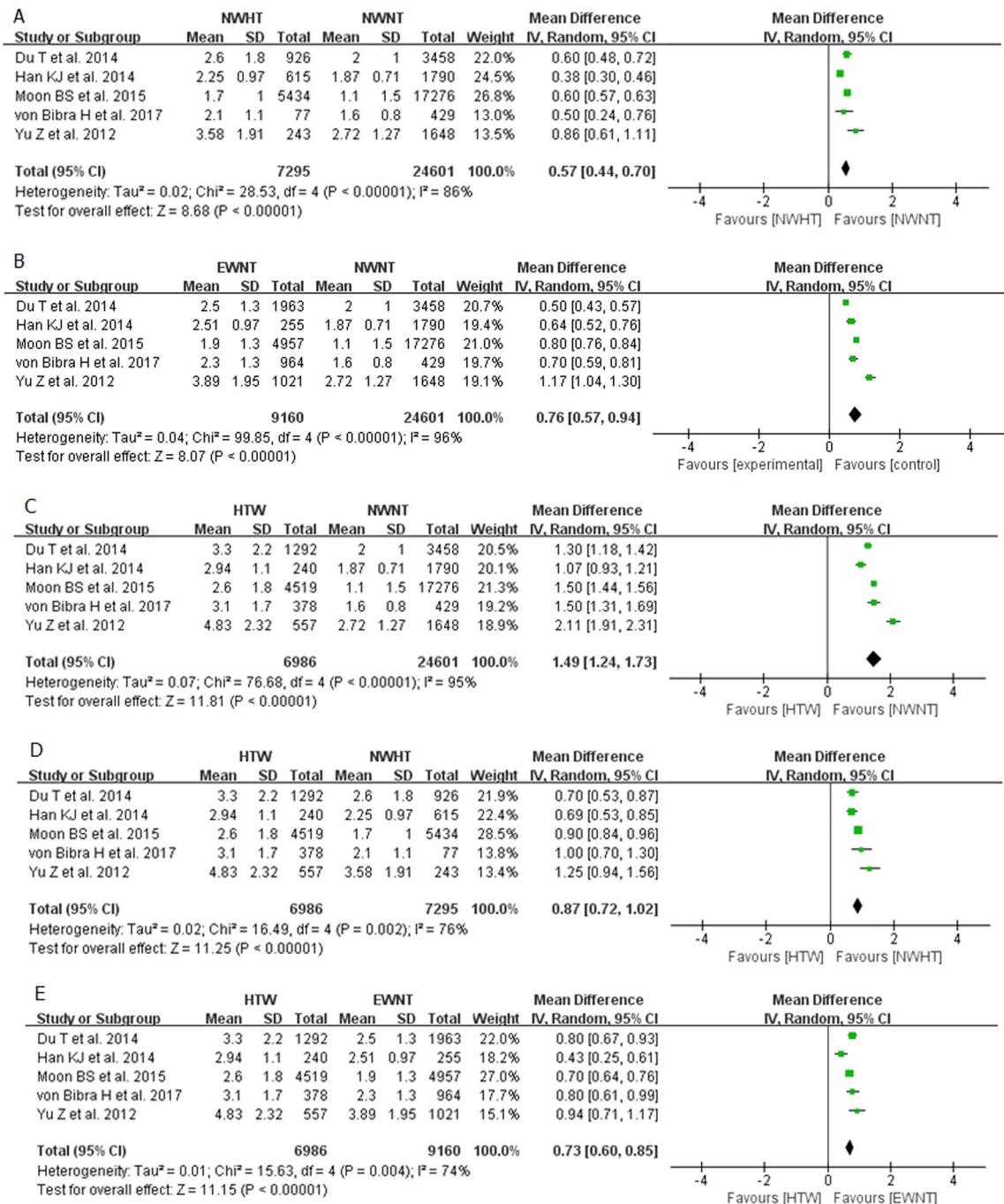
Fig. 5 The levels of insulin resistance according to the status of waist circumference and triglyceride. NWNT normal WC and normal TG level, NWHT normal WC and high TG level, EWNT enlarged WC and normal TG level, HTW enlarged WC and high TG level, WC

waist circumference, TG triglyceride. **a** NWNT vs. NWHT, **b** NWNT vs. EWNT, **c** NWNT vs. HTW, **d** NWHT vs. HTW, **e** EWNT vs. HTW

phenotype and insulin resistance. With the progress of abnormal glucose metabolism, β-cell function declines earlier in HTW phenotype. HTW phenotype has inappropriate blood glucose control and worse cardiovascular risk factor. The relationship between HTW phenotype and diabetic complications should be further confirmed.

Study Highlights

What is already known about this subject?

- Diabetes is a global health burden due to its high prevalence, deaths attributable and healthcare expenditure.

- HTW phenotype was significantly associated with risk of type 2 diabetes.

What does this study add?

- HTW phenotype can predict future diabetes in subjects without diabetes.
- Subjects with HTW phenotype have more serious insulin resistance, even among subjects without diabetes.
- HTW phenotype has inappropriate blood glucose control and worse cardiovascular risk factor in type 2 diabetes.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent This paper is a system review and meta-analysis. No informed consent was obtained.

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