# Association between visceral adiposity index and risk of prediabetes: A meta-analysis of observational studies

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## Keywords

Meta-analysis, Prediabetes, Visceral adipose index

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## **ABSTRACT**

**Background and Objective:** Epidemiological studies suggested that the association between the visceral adiposity index (VAI) and the risk of prediabetes is inconsistent. Whether VAI is a useful predictor of prediabetes remains unclear. Up until April 2021, there had been no systematic review on this topic. In this meta-analysis, the available observational epidemiological evidence was synthesized to identify the association between VAI and prediabetes risk.

**Methods:** PubMed, EMBASE, and Cochrane databases in any language were searched systematically from the earliest available online indexing year to April 2021 for relevant observational studies published on the association between VAI and the risk of prediabetes. A random effects model was used to combine quantitatively the odds ratios (ORs) and 95% confidence intervals (CIs).

**Results:** Ten relevant studies (2 cohort study, 2 case-control studies, and 6 cross-sectional studies) involving 112,603 participants were identified. Compared with the highest VAI, the lowest level of VAI was associated with an increased risk of prediabetes. The pooled OR of VAI for prediabetes was 1.68 (95% CI: 1.44–1.96), with significant heterogeneity across the included studies (P = 0.000, P = 91.4%). Exclusion of any single study did not materially alter the combined risk estimate.

**Conclusions:** Integrated epidemiological evidence supports the hypothesis that VAI is a lipid combined anthropometric index and may be a risk factor for prediabetes. VAI may be related to a high risk of prediabetes. However, it should be noted that the included studies have a publication bias and there was significant heterogeneity between our pooled estimate.

## **INTRODUCTION**

Type 2 diabetes is a progressive metabolic disease sweeping the world, which could be prevented if high-risk individuals could be identified<sup>1</sup>. In recent years, many studies have confirmed that prediabetes is the early reversible stage of type 2 diabetes. Prediabetes means an impaired blood glucose regulation with the blood glucose level above the normal range and below the recommended diabetes range. At the present time, prediabetes is a term increasingly used for people with impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG)<sup>2</sup>. Long-term follow-up studies in the UK and the USA show that

about 5–10% of prediabetic people progress to diabetes every year<sup>3,4</sup>, with a final incidence rate of about 70%<sup>5</sup>. A cross-sectional survey of 170,287 participants in mainland China in 2013 revealed that the prevalence of prediabetes was 35.7%, and the prevalence of prediabetes in Tibetans and Muslim Chinese individuals was lower than that of Han individuals<sup>6</sup>. These findings are different from another study, which estimated that the prevalence of prediabetes was 50.1%<sup>7</sup>. This difference is considered to be due to the unstandardized detection of glycosylated hemoglobin. Although the conversion rate varies with population characteristics, the definition of prediabetes is also different. Previous studies and reports suggest that the rate of prediabetes is increasing year by year<sup>6,7</sup>. In addition, studies

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have shown that prediabetes predicts an increased risk of cumulative cardiovascular events, vascular diseases, microvascular diseases, kidney disease, tumors, and dementia<sup>8–11</sup>.

In previous studies, obesity, especially visceral adiposity, is closely related to a variety of metabolic-related diseases, such as abnormal glucose metabolism, hyperlipidemia, hypertension, and cardiovascular disease<sup>12–14</sup>. The waist circumference (WC) is more representative than the body mass index (BMI) of central obesity to predict obesity-related metabolic abnormalities. However, the WC cannot distinguish between subcutaneous and visceral fat<sup>15</sup>. An elevated fasting triglycerides (TG) level reflects those individuals who are unable to manage and store additional energy in the subcutaneous fat depot<sup>16</sup>. Therefore, the waist phenotype of hypertriglyceridemia is related to various metabolic abnormalities and reflects visceral fat. In addition to being a better marker for identifying diabetes or cardiovascular disease than BMI or WC, it has been suggested as an alternative method to replace hyperlipidemia 17-19. The visceral adiposity index (VAI) is a validated gender-specified model, which consists of basic anthropometrics including BMI and WC, lipid parameters including high-density lipoprotein cholesterol (HDL), and triglycerides (TG). The VAI is an important indicator reflecting the 'visceral fat function' and insulin sensitivity, which is negatively correlated with insulin sensitivity<sup>20</sup>.

Previous studies of VAI and prediabetes risk prediction and correlation may be related to age, gender, race, and other factors. However, the correlation between the visceral adiposity index and the risk of prediabetes is inconsistent. Whether VAI is a predictor of prediabetes remains unclear. Furthermore, there is no meta-analysis to evaluate VAI and prediabetes risk. Therefore, we conducted this systematic review and meta-analysis to investigate the relationship between the visceral adiposity index and the risk of prediabetes.

## **METHODS**

This study was reported according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE)<sup>21</sup>.

#### Search strategy

PubMed, EMBASE, Cochrane, and Web of Science databases were searched for observational studies published in any language from the earliest available online indexing year to 5 August 2021. A combined MeSH heading and text search strategy with the following terms was used: 'prediabetes', 'prediabetic state', 'prediabetes mellitus', 'blood glucose', 'impaired fasting glucose', 'impaired glucose intolerance', 'hyperglycaemia', 'high risk of diabetes', 'borderline diabetes', 'earlystage diabetes' and 'visceral adiposity index', 'visceral fat indexes', 'visceral adipose index', 'VAI', 'VFI'. The detailed search strategies are shown in Appendix S1. Additionally, to identify potentially eligible publications, we also searched the reference lists of relevant reviews and retrieved original articles.

#### Study selection

Titles and abstracts were screened in duplicate by authors (D.W. and R.F.) for eligibility. Author (Y.Y.) resolved disagreements. The inclusion criteria were (1) Only human observational studies were considered and the study design was cohort, cross-sectional, or case-control; (2) All diagnostic criteria for prediabetes among studies were considered, including, but not limited to, impaired glucose tolerance (140-199 mg/dL), impaired fasting glucose (WHO: 110-126 mg/dL; ADA: 100-126 mg/dL), or raised glycated hemoglobin (5.7-6.4%); (3)The indicators reported on included studies evaluating the correlation between the visceral adiposity index and prediabetes including odds ratio (OR) or relative risk (RR) with corresponding 95% confidence intervals (CI). Studies providing data on the relationship between VAI and the change of prediabetes but not reporting the association of VAI with the risk of impaired glucose regulation were excluded. If there were multiple reports in the same study, we only included the latest published data for our analysis.

#### Data extraction and quality assessment

Data extraction was conducted by one author (D.W.) and double-checked by a second author (R.F.). From each of the included studies, the following information was extracted: last name of the first author, publication year, country (state), study design, gender, age, sample size, diagnostic criteria of prediabetes, type of prediabetes, adjusted odds ratios (ORs), or relative risks (RRs) with 95% CI. Differences in data extraction were resolved by discussion with a third author (Y.Y.).

Assessment involving 11 items recommended by the Agency for Healthcare Research and Quality (AHRQ) was used to evaluate the qualities of cross-sectional studies<sup>22</sup>, in which a study is scored '1' if it was clearly considered and '0' otherwise. For cohort studies and case-control studies, the Newcastle-Ottawa Scale (NOS)<sup>23</sup> was used. All the included studies were classified as being of high quality (scores of 7–9), moderate quality (4–6), or low quality (0–3), respectively.

Studies scoring 0–3 points (AHRQ assessment and NOS), 4–7 points (AHRQ assessment), or 4–6 points (NOS), and 8–11 points (AHRQ assessment) or 7–9 points (NOS) were categorized as low, moderate, and high quality studies, respectively.

Each study was rated independently by two authors (D.W. and R.F.). Discrepancies were resolved by consultation with a third investigator (Y.Y.).

# Statistical analysis

In our meta-analyses, the relationship between VAI and the risk of prediabetes, the multivariable-adjusted effect estimate OR with 95% CI was used as a common measure. The reported RR was considered approximately as OR. The highest vs lowest VAI were used to assess the relationship between VAI and prediabetes risk. In forest plots, OR > 1 represented a risk effect, while OR < 1 represented a protective effect. Statistical heterogeneity between the studies was assessed with the Cochran Q and  $I^2$  statistics. When P < 0.1 and  $I^2 > 50\%$ ,

heterogeneity was considered statistically significant and substantial. We explored potential sources of heterogeneity in the meta-regression and group analysis, such as study design, country, diagnostic criteria of prediabetes, and type of prediabetes. The fixed effect model was used when there was no literature heterogeneity. Otherwise, a random effect model was used. Publication bias was assessed by visual inspection of funnel plots. Begg's test and Egger's tests were used to assess the symmetry of a funnel plot, with a significance level of P < 0.05 to indicate significant asymmetry. All analyses were calculated by using STATA 13.0 software (Stata Corporation, College Station, TX, USA). The level of statistical significance was defined as P < 0.05.

## **RESULTS**

## Literature search results

The search strategy identified 2697 potentially relevant records, of which 244 duplicate records were excluded. The title and abstract of the resulting 2,453 manuscripts were screened. In addition, 2,389 publications, including reviews, letters or conference summaries, and unrelated manuscripts were removed. Therefore, 64 articles were eligible for full-text review and data assessment. 46 articles were excluded for the following reasons: 13 studies were based on the new Chinese visceral adiposity index (CVAI) developed on the Chinese population; 16 studies were based on MRI or CT examination of visceral fat; 12 articles only analyzed the relationship between VAI and diabetes;

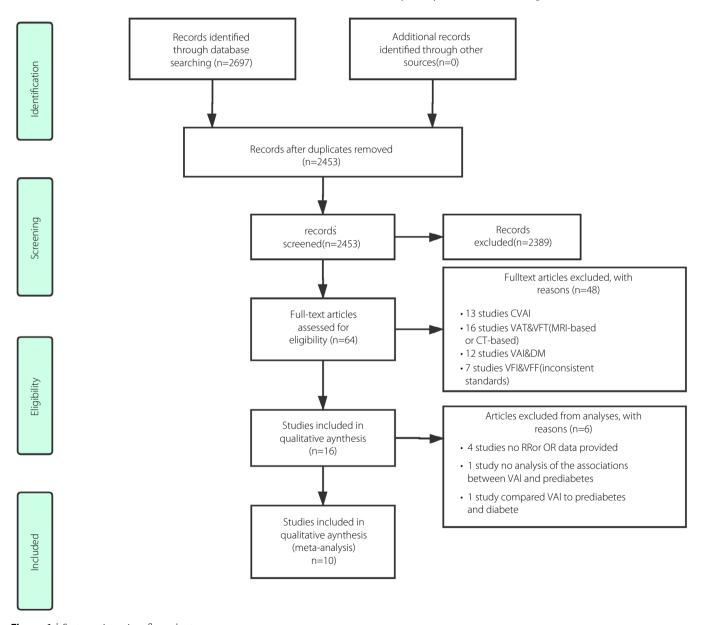


Figure 1 | Systematic review flow chart.

**Table 1** | Main characteristics of studies

Study	Country (State)	Study design	Sample size	Sample No. of valid size participants	Male (%)	Age (years)	Diagnostic criteria of prediabetes	Type of prediabetes	Study quality
Zheng 2016	China (East Asia)	cohort	1,544	423	174 (41.1%)	52.0 (44.0, 58.0)§	FPG:6.1-6.9 mmol/L(WHO)	IFG\IGT\\FG+IGT	High quality
Yang2015	China (East Asia)	cross-sectional	824	179	75 (41.9%)	43.5 ± 13.3 <sup>†</sup>	FPG:6.1—6.9 mmol/L and/or	IFG\\GT\\FG+\GT	High quality
							2hPG:7.8-11.1 mmol/l (WHO)		
Gu2017	China (East Asia)	cross-sectional	5,457	783	357 (45.6%)	NR	FPG:5.6-6.9 mmol/L (ADA)	IFG	High quality
Nusrianto 2019	India (South Asia)	cohort	3,283	652	130 (19.9%)	NR	FPG:5.6–6.9 mmol/L and/or	IFG\IGT\\FG+IGT	High quality
							2hPG:7.8-11.1 mmol/l (ADA)		
Ramdas	India (South Asia)	case-control	83	83	43 (51.8%)	46.04 ± 7.71 <sup>†</sup>	FPG:5.6–6.9 mmol/L and/or	IFG\IGT\\FG+IGT	High quality
Nayak2019						(male); 46.9 ± 6.99 <sup>†</sup>	2hPG:7.8-11.1 mmol/l and/or		
						(female)	HbA1C:5.7%-6.4%(ADA)		
Liu2016	China (East Asia)	cross-sectional	2,754	275	173 (62.9%)	NR	FPG:5.6-6.9 mmol/L (ADA)	IFG	High quality
Elizalde-	Mexica	case-control	280	110	51 (35.4%)	$49.94 \pm 10.05^{\dagger}$	FPG:5.6-6.9 mmol/L (ADA)	IFG	moderate
Barrera2019	(Northern America)								quality
Wang2020	China (East Asia)	cross-sectional 24,871	24,871	24,871	7,014 (28.2%)	56.93 ± 8.84 <sup>†</sup>	FPG:6.1–6.9 mmol/L and/or	IFG\IGT\\FG+IGT	High quality
							2hPG:7.8-11.1 mmol/l (WHO)		
Ramírez-	Colombia	cross-sectional	3,307	839	N.	70.2(7.7)*	FPG:5.6-6.9 mmol/L (ADA)	PG	High quality
Vélez2019	(South America)								
Li2019	China (East Asia)	cross-sectional 70,200	70,200	27,842 (ADA)& 9117 (WHO)	13,253 (47.6%) (ADA) & 4,385	42.1 ± 12.22 <sup>‡</sup> (ADA)&	FPG:5.6-6.9 mmol/L (ADA) & FPG:6.1-6.9 mmol/L (WHO)	IFG	High quality
				•	(48.1%) (WHO)	42.1 ± 12.22*			

2hPG7.8–11.1 mmol/L; ADA, FPG:5. 6-6.9 mmol/L and or2hPG:7. 8-11.1 mmol/L and orHbA1C:5.7%-6.4%; IFG, impaired fasting glucose; IGT, impaired glucose tolerance. \*Statistical description of age was presented as median(inter quartile range). \*Statistical description of age was presented as NR, no report; ADA, American Diabetes Association; FBG, fasting plasma glucose; 2hPG, 2 h post-load blood glucose; HbA1c, glycosylated hemoglobin; WHO, FPG.6. 1-6.9 mmol/L and or mean (range). the definition of visceral fat index in seven articles was different from ours. Finally, 16 studies were assessed for inclusion in the meta-analyses performed, of which six were excluded for the following reasons: four reference studies did not provide OR or RR data; one study did not provide regression analysis of the associations between VAI and risk of prediabetes; one study that calculated VAI demonstrated a significant correlation with glucose metabolism (including diabetes and prediabetes) abnormalities. A detailed overview of the study review process is presented in Figure 1<sup>24–33</sup>.

# Study characteristics and quality assessment

The characteristics of the included studies<sup>24–33</sup> are summarised in Table 1. These studies were published between 2015 and 2020, and involved 112,603 participants. Six studies were from China<sup>24–26,29,31,33</sup>, two studies were from India<sup>27,28</sup>, two studies were from Mexico and Colombia<sup>30,32</sup>. Seven studies had fewer males than females<sup>24–27,30,31,33</sup>, two studies had more males than females<sup>28,29</sup>, one study was excluded with no data on gender<sup>32</sup>, with the proportion of males ranging from 19.9% to 62.9%. Six studies only tested fasting blood glucose (FPG)<sup>26,28–30,32,33</sup>, three studies tested FPG and 2 h postprandial blood glucose (2hPG)<sup>25,27,31</sup>, only one study not only tested FPG and 2hPG, but also tested glycosylated hemoglobin (HbA1c)<sup>24</sup>. For

prediabetes diagnostic criteria, six studies were based on the definition of the American Diabetes Association  $(ADA)^{26-30,32}$ , three were based on the WHO<sup>24,25,31</sup>, and one study compared the standards of ADA and WHO<sup>33</sup>.

There were two prospective cohort studies<sup>24,27</sup>, six cross-sectional studies<sup>25,26,29,31–33</sup>, and two case-control studies<sup>28,30</sup>. The risk of bias within cross-sectional studies assessed using AHRQ assessment, cohort and case-control studies assessed using NOS. The quality assessments of the included studies are shown in TableS 1 and TableS 2. Most of the included studies were of high quality, only one study was of moderate quality. None of the studies was considered to have a high risk of bias. Therefore, all ten studies were included in the meta-analysis.

#### Association between VAI and risk of prediabetes

The ORs for prediabetes in relation to VAI, and the results from the random effects model were combined as shown in Figure 2. A total of 10 studies investigated the relationship between VAI and the risk of prediabetes. Compared with the highest VAI, there seems to be a correlation between the lowest VAI and an increased risk of prediabetes. The pooled OR of prediabetes for VAI was 1.52 (95%CI: 1.16–2.00), which showed significant heterogeneity across the included studies  $(P = 0.000, I^2 = 95.4\%)$ .

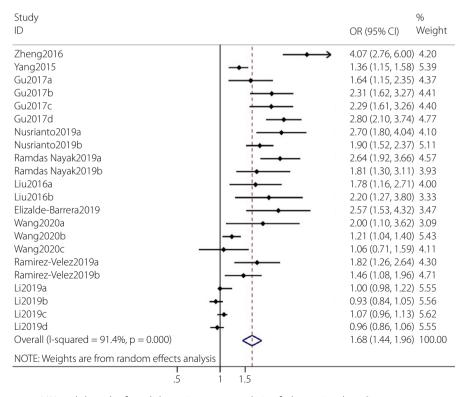


Figure 2 | Association between VAI and the risk of prediabetes in a meta-analysis of observational studies.

**Table 2** | Results of group discussion analyses about VAI and the risk of prediabetes

Group	Number of Studies	OR/RR	95%Confidence intervals	Ζ	Р	l² (%)	P for heterogeneity
Study design							
Cross-sectional	6	1.44	1.24-1.66	4.93	0.000	88.5	0.000
Cohort	2	2.70	1.69-4.30	4.18	0.000	82.8	0.003
Case-control	2	2.36	1.87–2.98	7.25	0.000	0.0	0.000
Gender							
Female	6	1.64	1.21–2.21	3.29	0.001	87.9	0.000
Male	6	1.70	1.31–2.20	4.04	0.000	91.3	0.000
Female+male	4	1.75	1.26-2.45	3.29	0.001	93.6	0.000
Country							
China	6	1.52	1.29–1.80	4.94	0.000	91.4	0.000
India	2	2.19	1.79-2.68	7.58	0.000	34.0	0.208
Mexica	1	2.57	1.53-4.32	3.56	0.000	-	-
Colombia	1	1.59	1.26–2.01	3.93	0.000	0.0	0.363
Diagnostic criteria of prediabetes							
WHO	5	1.64	1.32–2.05	4.45	0.000	92.4	0.000
ADA	6	1.73	1.35–2.23	4.29	0.000	91.1	0.000
Type of prediabetes							
IFG\IGT\IFG+IGT	5	1.87	1.42-2.46	4.46	0.000	88.7	0.000
IFG	6	1.56	1.31–1.86	4.99	0.000	90.3	0.000

OR, odds ratio; RR, relative risk.

## **Group discussion**

Table 2 reports the results of group discussion and metaregression analyses. The groups were analyzed according to the study design, gender, country, diagnostic criteria of prediabetes, type of prediabetes. In general, the group analyses showed no statistically significant difference in the results. The positive and statistically significant relationship between VAI and the risk of prediabetes was reflected by every single pooled result of the group. Variations were not consistently explained by group analysis of the characteristics of the studies.

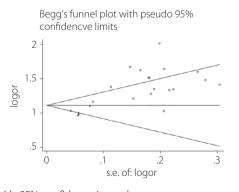
#### **Publication bias**

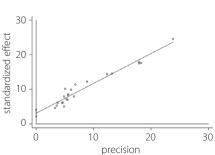
Visual inspection of the funnel plot indicated a significant publication bias (Figure 3). Two statistical methods were used to test the symmetry of the funnel plot, the result of visual

inspection was confirmed by Egger's test and Begg's test (Begg's test, P = 0.045 < 0.05, Egger's test, P = 0.000 < 0.05).

## **DISCUSSION**

In our meta-analysis, VAI may be a risk factor for prediabetes, which is related to a high risk of prediabetes in various populations. Previous studies, consistent with our research, have shown that VAI is closely related to fasting insulin and insulin sensitivity<sup>34–39</sup>. Furthermore, many studies revealed that VAI was superior to easily measurable anthropometric indicators such as BMI, WC, and WHtR<sup>34–37</sup>. While Janghorbani *et al.* concluded just the opposite<sup>38</sup>. This divergence may be related to their different research design and study population. Data from Wu *et al.* demonstrated that the CVAI is a better predictor of prediabetes than the VAI<sup>39</sup>. It may be because their VAI calculation formula





Egger's publication bias plot

Figure 3 | Funnel plot with 95% confidence interval.

takes into account differences of race or region. In addition, Kumpatla *et al.* confirmed that 2.3 is the cut-off value of VAI, with 62.1% sensitivity and 59.7% specificity for detecting glucose intolerance<sup>40</sup>. Juncheol *et al.* that reported the cut-off values were as follows: VAI: men 1.65, women 1.65<sup>41</sup>. As a lipid combined anthropometric indices, VAI can be obtained in the routine medical examination center.

The distribution of visceral adiposity can be accurately assessed by computed tomography (CT) and magnetic resonance imaging (MRI) which are considered to be the gold standard<sup>37,42</sup>. VAI is a convenient, routinely applicable, and affordable indicator of visceral fat distribution and dysfunction<sup>15</sup>. It has been noted that economically developed countries such as the United States, France, and Germany are more inclined to define the visceral adiposity by MRI or CT for a superior measurement<sup>43–46</sup>. Our research data come from developing countries, six from China, two from India, two from Mexico and Colombia. According to the International Diabetes Federation (IDF), the top ten countries with the numbers of people aged 20 to 79 with impaired glucose tolerance in 2019 are China (No. 1), India (No. 4), and Mexico (No. 6)<sup>47</sup>. These results seem to suggest that visceral adiposity and prediabetes are classified as public health issues involving social and economic aspects, regardless of the economic level of the country. High-income countries pay more attention to accurate predictors, such as MRI-based or CT-based visceral adiposity tissue (VAT). However, the low-income countries pay more attention to affordable indicators such as VAI.

Previous studies have shown that VAI is negatively correlated with the insulinogenic index ( $\Delta I30/\Delta G30$ ) and with the homeostasis model assessment of the beta cell function index (Homa-β)<sup>15</sup>. Increased visceral adipose is associated with an increased risk of insulin resistance and β-cell dysfunction<sup>48</sup>. In obese patients, increased circulating levels of macrophagederived factors lead to chronic low-grade inflammation, which is associated with the development of insulin resistance and diabetes. Insulin resistance may lead to endothelial cell dysfunction and changes of insulin signaling pathways<sup>49</sup>. It is reported that one of the key effects of adiponectin is its regulation of glucose and lipid metabolism<sup>50</sup>. An epidemiological study has provided evidence that insulin, GH/IGF-1, and adiponectin signaling are molecular pathways that interconnect and link obesity with the risk of metabolic diseases<sup>51</sup>. Compared with participants with normal VAI, participants with high VAI have higher GH and IGF-1 values, and lower insulin sensitivity and adiponectin concentration, indicating a proneness to metabolic syndrome<sup>52</sup>. Accordingly, we speculate that the mechanism by which VAI affects the outcome of prediabetes may be achieved by affecting insulin resistance, pancreatic beta cell function, and adiponectin levels. The current knowledge strongly encourages further research into novel mechanisms.

This is the first systematic review and meta-analysis to provide an overview of the associations between VAI and the risk of prediabetes. We used robust and standard methods, and conducted a comprehensive search using standard methods. Additionally, we evaluated the quality of the literature based on the category of the literature and assessed the risk of bias of each included study. There are several limitations that should be mentioned. First, most of the included studies are of cross-sectional design, which limited our findings. Although the correlation between VAI and prediabetes was confirmed, the causal relationship between VAI and prediabetes was still unclear. Thus, the relationship between VAI and prediabetes should be further explored in follow-up studies. Second, all participants were from Asia (China and India) and America (Mexico and Columbia), so there may be some selective bias. More studies including other ethnic populations are needed to confirm this relationship. Although we did not exclude any particular group of participants other than those diagnosed with prediabetes, some types of groups may be underrepresented or excluded. Therefore, we caution against generalizing the results of the study to suggest that the relationship is the same in all possible groups. Finally, heterogeneity across the included studies. We explored the source of the heterogeneity by grouping analysis. The results showed that there was no meaningful heterogeneity, which could provide a reference for clinical practice and future research.

In conclusion, this meta-analysis of ten studies with 112,603 participants showed the pooled OR of VAI for prediabetes is 1.68 (95% CI: 1.44–1.96). Recent research has shown that VAI is a lipid combined anthropometric index, which may be a risk factor for prediabetes. It was the publication bias and significant heterogeneity of our pooled estimate that limit the reliability of our conclusions. More robust evidence is necessary to improve our research in the future. If confirmed, actively using VAI to screen for prediabetes could be reasonable and worthy of promotion. These findings could help the rapidly growing number of subjects with prediabetes to obtain health care and could contribute to the public health management of chronic diseases.

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#### **DISCLOSURE**

Authors declare no conflict of interest.

Approval of the research protocol: The protocol for this research project has been approved by a suitably constituted Ethics Committee of the institution and it conforms to the provisions of the Declaration of Helsinki. Scientific Research Ethics Committee of Hangzhou Normal University.

Informed consent: N/A.

Approval date of Registry and the Registration No. of the study/trial: The approval date is July 15, 2021 and Approval No. is 2021-1308.

Animal studies: N/A.

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## **SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Appendix S1** | Search Terms.

Table S1 | Quality assessment of individual studies using Agency for Healthcare Research and Quality.

Table S2 | Quality assessment of individual studies using Newcastle-Ottawa Scale.