

# Meta-Analysis of the Relationship between Abdominal Obesity and Diabetic Kidney Disease in Type 2 Diabetic Patients

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## Keywords

Abdominal obesity · Diabetic kidney disease · Type 2 diabetes · Meta-analysis

## Abstract

**Background and Objectives:** The meta-analysis aimed to investigate the association of visceral fat area (VFA), waist circumference (WC), waist-hip ratio (WHR) and waist-height ratio (WHtR) with diabetic kidney disease (DKD) in type 2 diabetic patients. **Methods:** Included studies were searched from Pubmed, Embase, and the Cochrane Library before July 2020. We synthesized the pooled results of the above relationships by meta-analysis. **Results:** Fourteen cross-sectional studies were enrolled. The pooled results indicated there was a significant difference in continuous VFA, WC and WHR/WHtR between patients with DKD and those without DKD (standard mean difference, SMD, 0.24, 95% confidence interval, CI, 0.13–0.36,  $p = 0.000$ ). For VFA, patients with DKD had higher VFA levels than those without DKD (SMD 0.27, 95% CI 0.03–0.50). In the WC subgroup, patients with DKD had higher WC levels than those without DKD (SMD 0.17, 95% CI 0.10–0.24); similarly, abdominal obesity (dichotomized WC) was significantly associated with an increase in the odds of DKD (expected shortfall, ES, 1.57, 95% CI 1.32–1.86). However, the association of continuous WHR/WHtR with DKD was not sta-

tistically significant (SMD 0.43, 95% CI –0.12 to 0.97), while we found this relationship was statistically significant when analyzed categorically (ES 1.58, 95% CI 1.22–2.06). **Conclusion:** In this meta-analysis, we found abdominal obesity parameters (continuous VFA, WC) were associated with increased odds of DKD, and type 2 diabetic patients with DKD were more likely to have abdominal obesity (categorized using WC or WHR/WHtR).

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## Introduction

Diabetic kidney disease (DKD), a serious microvascular complication of diabetes, is defined as a decrease in estimated glomerular filtration rate (eGFR) or the occurrence of albuminuria. It is well known that DKD already becomes the major cause of end-stage renal disease in the world [1], which even aggravates the occurrence and development of cardiovascular disease and mortality [2]. Therefore, it is important to identify the related risk factors of DKD.

Obesity is a critical risk factor for type 2 diabetes mellitus (T2DM) and hypertension [3, 4], which is closely related to the development of DKD [5]. General and abdominal obesity are the major subtypes of obesity. Some

studies reported that, compared with general obesity, abdominal obesity had been shown to be superior to contribute to the risk of DKD in T2DM [6–10], while Man et al. [11] found that individuals with abdominal obesity had no association with DKD in T2DM. Kanakamani et al. [12] also observed that waist circumference (WC) was not associated with microalbuminuria in 670 patients attending the endocrine outpatient clinic. It is necessary to further ascertain the relationship between abdominal obesity and DKD in type 2 diabetic patients.

In this meta-analysis, we aimed to investigate the association of visceral fat area (VFA), WC and waist-hip ratio (WHR)/waist-height ratio (WHtR) with DKD in type 2 diabetic patients through existing research.

## Methods

### *Assessment of Abdominal Obesity and DKD*

VFA, WC, WHR and WHtR were common markers to evaluate abdominal obesity. Abdominal obesity was defined as WC >90 cm for males or 80 cm for females [13], or WC >102 cm for males and 88 cm for females [14], or VFA  $\geq 100$  cm<sup>2</sup> [15]. DKD was defined as eGFR <60 mL/min/1.73 m<sup>2</sup> [16], or urinary albumin excretion rate >30 mg/24 h (20 mg/min) [17], or microalbuminuria (urinary albumin creatinine ratio within 30–300 mg/g creatine), or macroalbuminuria (urinary albumin creatinine ratio >300 mg/g creatine) [1].

### *Study Selection*

We searched Pubmed, Embase and Cochrane databases before July 2020, using the following terms: visceral fat, waist, abdominal obesity, visceral obesity, central obesity, diabetic nephropathy, diabetic kidney disease, glomerular filtration rate, eGFR, albuminuria and diabetic patients. Eligible studies met the following criteria: (1) DKD and controls were included and defined; (2) the associations of VFA, WC, WHR and WHtR with DKD were evaluated; (3) reported the standard mean difference (SMD) or odds ratio (OR) and its 95% confidence interval (CI). In these studies, we excluded duplicated studies, literature reviews, unavailable studies, animal experiments and case reports.

### *Data Extraction*

Two independent reviewers conducted a literature search, study selection, data extraction and quality assessment. The author's name, publication year, study design, type of diabetes, marker of abdominal obesity, definition of DKD, the number of patients, the mean  $\pm$  SD of marker, adjusted OR and 95% CI were included in each study. And the disagreement was resolved by consensus with a third reviewer.

### *Statistical Analysis and Quality Assessment*

The meta-analysis was performed using the Stata 16.0 (Stata Corp., College Station, TX, USA). For continuous variables, which were presented as mean  $\pm$  SD, SMD with 95% CI were calculated. While OR and 95% CI were calculated on pooled effects for categorized variables. Heterogeneity among studies was examined by the  $I^2$  statistic [18, 19].  $I^2$  values of 25–50%, 50–75% and 75% were

considered indicative of low, moderate and high heterogeneity, respectively [19]. If  $I^2 > 50\%$ , a random-effect model was performed to synthesize study effects; otherwise, a fixed-effect model was used. In addition, sensitivity analyses were attempted to identify potential sources of the heterogeneity. Egger's test [20] was used to evaluate publication bias, and  $p < 0.05$  was statistically significant. Quality assessment was evaluated using the Healthcare Research and Quality [21]. Finally, this meta-analysis complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (shown in online suppl. Table 1; for all online suppl. material, see [www.karger.com/doi/10.1159/000516391](http://www.karger.com/doi/10.1159/000516391)).

## Results

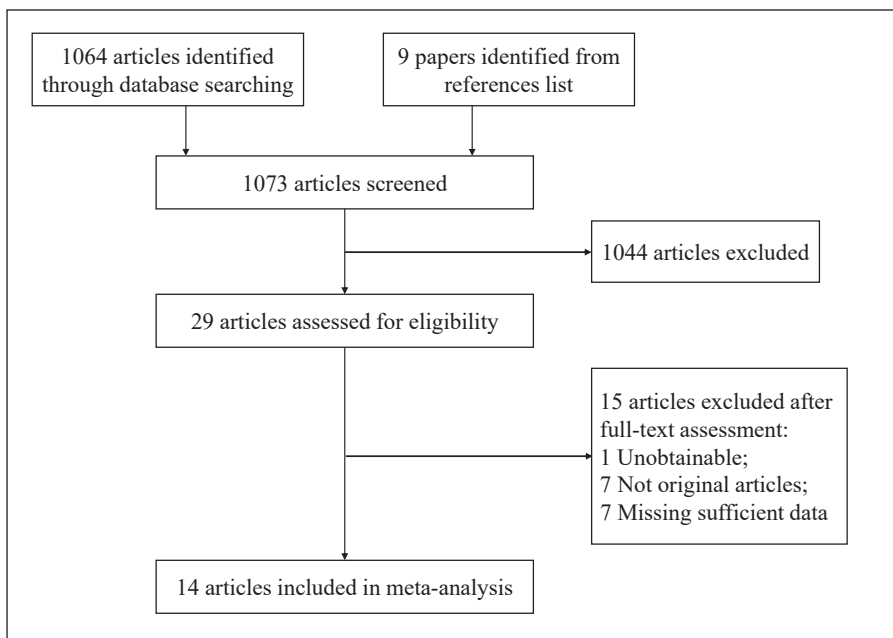
We initially retrieved 1,064 publications from databases and 9 citations from reference lists; of these, 29 articles were included after reading the title and abstract. After full-text review, 14 studies [9–12, 17, 22–30] involving 13,743 patients were identified and enrolled in this meta-analysis (Fig. 1). Detailed information of another 15 excluded articles is accessible in Figure 1. The baseline characteristics of these enrolled studies are shown in Table 1.

### *DKD and All Abdominal Obesity Parameters*

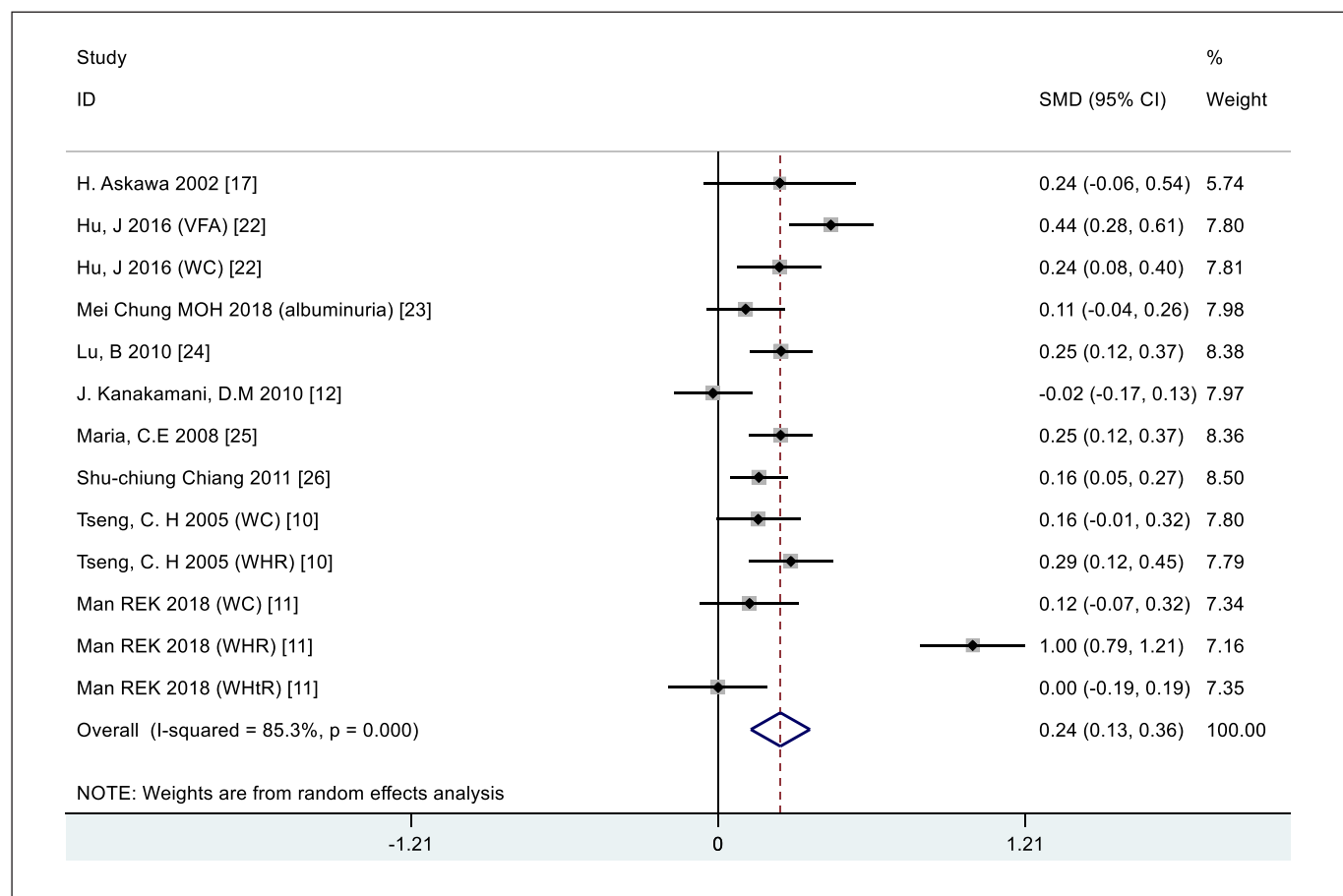
A total of 14 articles were included in this meta-analysis of all abdominal obesity parameters including VFA [17, 22, 23], WC [10–12, 22, 24–26] and WHR/WHtR [10, 11] with DKD (Fig. 2). The  $p$  value of heterogeneity between these studies was significant ( $I^2$  85.3%), so we used the random-effect model indicating that there was a statistically significant difference between patients with DKD and those without DKD (SMD 0.24, 95% CI 0.13–0.36,  $p = 0.000$ ). No publication bias was found by Egger's test ( $p = 0.449$ ; shown in online suppl. Fig. S1A). We used sensitivity analysis and subgroup analysis to explore the resources of heterogeneity. The sensitivity analysis was performed to recalculate the pooled risk estimates for the remaining studies by excluding one study at a time, which resulted in little change in the observed risk estimates from 0.19 (95% CI 0.15–0.23) to 0.25 (95% CI 0.20–0.29; online suppl. Fig. S2A). In addition, the results of subgroup analysis by VFA, WC or WHR/WHtR were summarized as follows.

### *DKD and VFA*

In the VFA subgroup [17, 22, 23], we found a significant association between increased VFA and likelihood of DKD (SMD 0.27, 95% CI 0.03–0.50,  $p = 0.014$ ; Fig. 3). High heterogeneity was observed ( $I^2$  76.5%). No publication bias was found by Egger's test ( $p = 0.948$ ; online



**Fig. 1.** Flow chart of literature search and study selection.

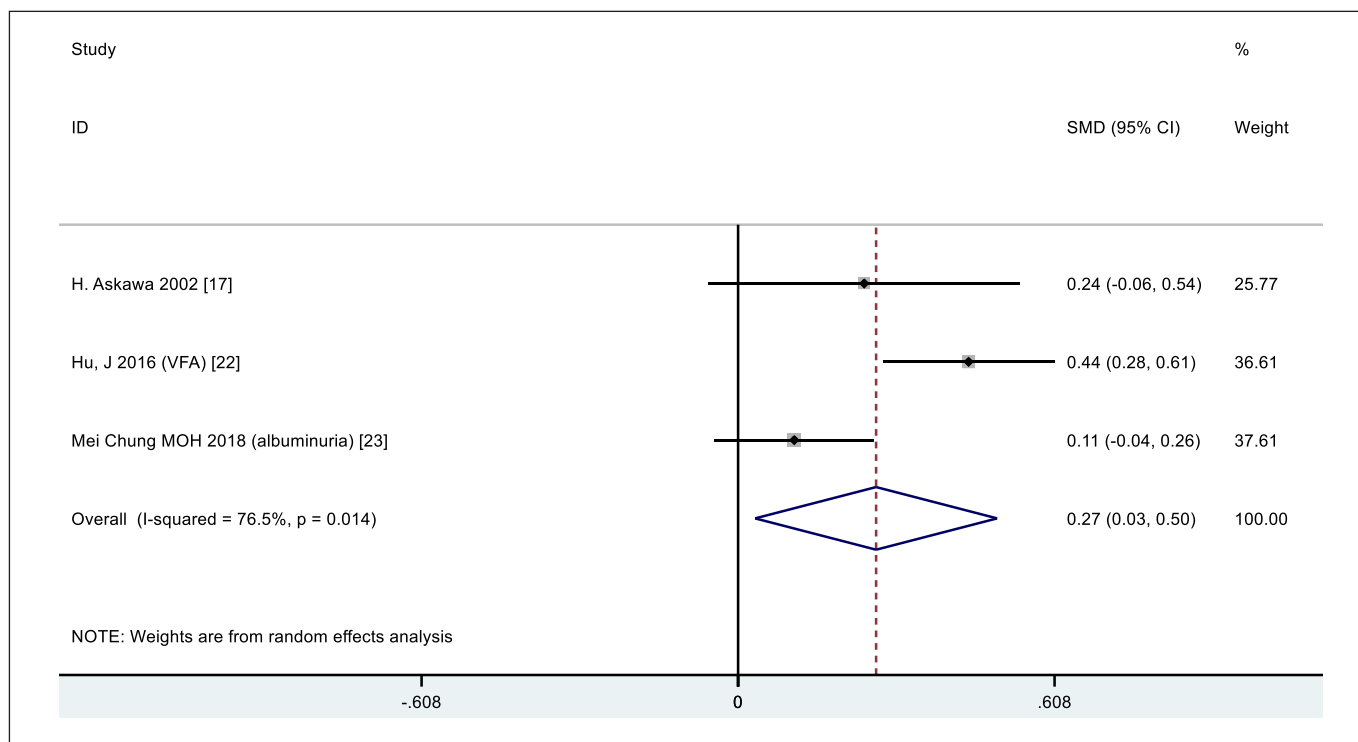


**Fig. 2.** Forest plot of the association of continuous waist circumference, visceral fat area and waist-hip ratio/waist-height ratio with diabetic kidney disease.

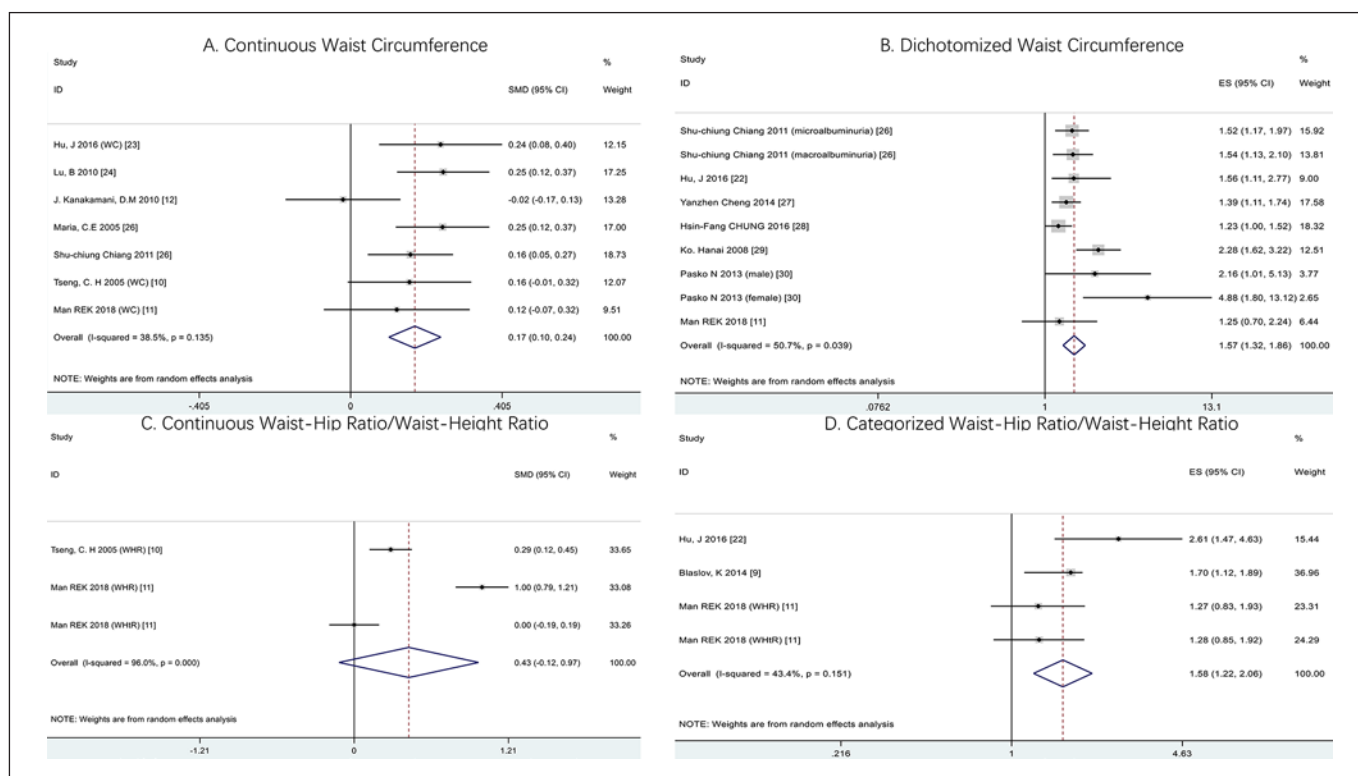
**Table 1.** Characteristics of included studies

Study	Study design	Type of diabetes	Marker of abdominal obesity	Patients with DKD		Patients without DKD		Adjusted OR (95% CI)		
				n	mean	SD	n		mean	SD
Asakawa et al. [17], 2002	Cross-sectional	T2DM	VFA (cm <sup>2</sup> )	79	86.6	47.7	96	75.4	45	NR
Hu et al. [22], 2016	Cross-sectional	T2DM	VFA (cm <sup>2</sup> )	172	133.3	45	844	114	43.3	NR
			WC (cm)	172	95.5	8.9	844	93.3	9.2	NR
			WC (categorized)	172	NR	NR	844	NR	NR	1.56 (1.11–2.77)
			WHR (categorized)	172	NR	NR	844	NR	NR	2.61 (1.47–4.63)
Chung et al. [23], 2018 (albuminuria)	Cross-sectional	T2DM	VFA (cm <sup>2</sup> )	207	138.7	43.4	807	134.1	42.4	NR
Lu et al. [24], 2007	Cross-sectional	T2DM	WC (cm)	504	85.8	9.4	514	83.5	9.2	NR
Kanakamani et al. [12], 2010	Cross-sectional	T2DM	WC (cm)	279	93.3	10.7	391	93.5	9.1	NR
Rossi et al. [25], 2008	Cross-sectional	T2DM	WC (cm)	308	103.5	12.3	1,249	100.4	12.7	NR
Chiang et al. [26], 2011	Cross-sectional	T2DM	WC (cm)	372	89.3	11.2	1,455	87.6	10.5	NR
			WC >90 cm (men), 80 cm (women)	372	NR	NR	1,455	NR	NR	1.52 (1.17–1.97)
				372	NR	NR	1,455	NR	NR	1.54 (1.13–2.10)
Yanzhen et al. [27], 2014	Cross-sectional	T2DM	WC >90 cm (men), 80 cm (women)	632	NR	NR	2,225	NR	NR	1.39 (1.11–1.74)
Chung et al. [28], 2016	Cross-sectional	T2DM	WC >90 cm (men), 80 cm (women)	64	NR	NR	1,123	NR	NR	1.23 (1.00–1.52)
Hanai et al. [8], 2010	Cross-sectional	T2DM	WC >90 cm (men), 80 cm (women)	300	NR	NR	703	NR	NR	2.28 (1.62–3.22)
Pasko et al. [30], 2013	Cross-sectional	T2DM	WC >102 cm (men), 88 cm (women)	131	NR	NR	190	NR	NR	Males 2.156 (1.012–5.125)
				131	NR	NR	190	NR	NR	Females 4.875 (1.802–13.115)
Tseng [10], 2005	Cross-sectional	T2DM	WC (cm)	302	89.7	9.4	266	88.2	9.7	NR
			WHR	302	0.96	0.07	266	0.94	0.07	NR
Blaslov et al. [9], 2014	Cross-sectional	T2DM	WHR (categorized)	36	NR	NR	89	NR	NR	1.70 (1.12–1.89)
Man et al. [11], 2018	Cross-sectional	T2DM	WC (cm)	203	94	10.4	202	92.7	10.7	NR
			WC >90 cm (men), 80 cm (women)	203	NR	NR	202	NR	NR	1.25 (0.70–2.24)
			WHR	203	1	0.1	202	0.9	0.1	NR
			WHR (categorized)	203	NR	NR	202	NR	NR	1.27 (0.83–1.93)
			WHR	203	0.6	0.1	202	0.6	0.1	NR
			WHR (categorized)	203	NR	NR	202	NR	NR	1.28 (0.85–1.92)

T2DM, type 2 diabetes mellitus; DKD, diabetic kidney disease; WC, waist circumference; VFA, visceral fat area; WHR, waist-hip ratio; WHtR, waist-height ratio; NR, not reported; SD, standard deviation; OR, odds ratio; 95% CI, 95% confidence interval.



**Fig. 3.** Forest plot of the association of continuous visceral fat area with diabetic kidney disease.



**Fig. 4.** Forest plot of the association of different parameters of abdominal obesity with diabetic kidney disease.

suppl. Fig. S1B). Sensitivity analysis demonstrated that the observed risk estimate was not robust, which changed from 0.14 (95% CI -0.00 to 0.27) to 0.40 (95% CI 0.25–0.54; online suppl. Fig. S2B).

#### *DKD and WC*

In the WC subgroup, there were 7 and 7 studies included in the meta-analysis of the effects of continuous WC [10–12, 22, 24–26] and abdominal obesity (dichotomized WC) [11, 26–30]. Patients with DKD had higher WC levels than those without DKD (SMD 0.17, 95% CI 0.10–0.24,  $I^2$  38.5%,  $p = 0.135$ ; Fig. 4a). Egger's test showed that no publication bias existed in the meta-analysis ( $p = 0.439$ ; online suppl. Fig. S3A). The sensitivity analysis presented a robust result that was not influenced by individual studies (shown in online suppl. Fig. S4A). Similarly, abdominal obesity (dichotomized WC) was significantly associated with an increase in the odds of DKD (ES 1.57, 95% CI 1.32–1.86,  $I^2$  50.7%,  $p = 0.039$ ; Fig. 4b). No publication bias existed in the subgroup analysis ( $p = 0.061$ ; online suppl. Fig. S3B). The sensitivity analysis also presented a robust result that was not influenced by individual studies (online suppl. Fig. S4B).

#### *DKD and WHR/WHtR*

In the WHR/WHtR subgroup, 3 studies were included in the meta-analysis of the effects of continuous [10, 11] and categorized WHR/WHtR [9, 11]. The association of continuous WHR/WHtR with DKD was not statistically significant (SMD 0.43, 95% CI -0.12 to 0.97,  $I^2$  96.0%,  $p = 0.000$ ; Fig. 4c). No publication bias was found by Egger's test ( $p = 0.686$ ; online suppl. Fig. S3C), but sensitivity analysis demonstrated that the observed risk estimate was not robust, which changed from 0.17 (95% CI 0.04–0.29) to 0.57 (95% CI 0.44–0.69; online suppl. Fig. S4C).

However, we found this association was statistically significant when analyzed categorically (ES 1.58, 95% CI 1.22–2.06,  $I^2$  43.4%; Fig. 4d). No publication bias existed in the meta-analysis ( $p = 0.871$ ; online suppl. Fig. S3D). The sensitivity analysis also presented a robust result that was not influenced by individual studies (online suppl. Fig. S4D).

## Discussion

This meta-analysis included 2,205 participants from 3 cross-sectional studies with VFA measurements, 12,429 participants from 11 cross-sectional studies with WC measurements, and 2,114 participants from 4 cross-sectional

studies, which demonstrated that WC, VFA and WHR/WHtR were associated with greater odds of DKD in type 2 diabetic patients. The results further supported abdominal obesity might play an important role in the pathophysiology of DKD in type 2 diabetic patients.

The relationship between abdominal obesity and DKD was reported by previous studies. In a cross-sectional research of 1,016 individuals with T2DM, patients with DKD had significantly higher VFA or WC levels than those without DKD [22]. Rossi et al. [25] found abdominal obesity, defined with WC, substantially increased the risk of microalbuminuria. However, some researchers reached the opposite conclusion. Man et al. [11] found that individuals with abdominal obesity had no association with DKD in T2DM (male: OR 1.45, 95% CI 0.88–2.37; female: OR 1.69, 95% CI 0.56–5.11). Kanakamani et al. [12] reported that WC was negatively associated with macroalbuminuria (OR 0.41, 95% CI 0.22–0.57) but not with microalbuminuria (OR 1.43, 95% CI 0.83–2.47). Therefore, the results concerning this association should be investigated. In our study, we found that abdominal obesity parameters were significantly associated with increased odds of having DKD. However, high heterogeneity ( $I^2$  85.3%) was detected in our meta-analysis, which might be due to the difference in the definition of abdominal obesity. For instance, Asakawa et al. [17] defined abdominal obesity as VFA  $\geq 100$  cm<sup>2</sup>, Lu et al. [24] and Rossi et al. [25] identified abdominal obesity as WC  $\geq 90$  cm for men or 80 cm for women, while Tseng [10] defined abdominal obesity with WHR/WHtR. Hence, we assessed the relationship between different parameters of abdominal obesity and DKD in subgroup analysis.

In the WC subgroup analysis, patients with DKD had higher WC levels than those without DKD (SMD 0.17, 95% CI 0.10–0.24), and this association became enhanced when we analyzed the dichotomized WC (ES 1.57, 95% CI 1.32–1.86,  $p = 0.039$ ). In the VFA subgroup, a tight association of continuous VFA with DKD in type 2 diabetic patients had been reported (SMD 0.27, 95% CI 0.03–0.50,  $p = 0.014$ ). Additionally, in the WHR/WHtR subgroup, the categorized WHR/WHtR was significantly associated with an increase in the odds of DKD (ES 1.58, 95% CI 1.22–2.06), while this association became attenuated when we analyzed the continuous WHR/WHtR (SMD 0.43, 95% CI -0.12 to 0.97). In our meta-analysis, a positive correlation between abdominal obesity parameters (continuous VFA or WC) and DKD was confirmed, and type 2 diabetic patients with DKD were more likely to have abdominal obesity (categorized using WC or WHR/WHtR).

Although the mechanisms about the relationship between abdominal obesity and DKD are still unclear, several hypotheses may be proposed. First, visceral fat can cause an increase in adipocytokines, such as free fatty acids, tumor necrosis factor- $\alpha$  and interleukin-6, which result in insulin resistance, mitochondrial dysfunction, oxidative stress and eventual renal damage [31, 32]. Second, adipose tissue activates the renin-angiotensin system or the sympathetic nervous system, which allows for the changes in renal hemodynamics and sodium retention, leading to renal damage [33, 34]. In addition, other manifestations of metabolic syndrome such as dyslipidemia, insulin resistance and hypertension also play an important role in the occurrence and development of DKD [35]. For instance, dyslipidemia can induce a series of pathophysiological changes such as endothelial dysfunction and oxidative stress, stimulate glomerular sclerosis, interstitial fibrosis and eventual renal dysfunction [36].

Our meta-analysis had some strengths. First, we used different parameters of abdominal obesity, including VFA, WC and WHR/WHtR, to evaluate the association of abdominal obesity with DKD, with more comprehensiveness and rationality. Second, the meta-analysis could avoid some potential errors through the subgroup analysis. The significant limitation in our meta-analysis is that all included studies were based on cross-sectional design, which could not confirm the causal association between abdominal obesity and DKD. Therefore, large prospective cohorts were needed to confirm the association of abdominal obesity with DKD in the future. For another, the adjustments for potential confounders differed in each study, and the influence of possible confounders on the meta-analysis could not be entirely excluded.

## Conclusion

In summary, this meta-analysis demonstrated that abdominal obesity parameters (continuous VFA or WC) were associated with increased odds of DKD, and type 2 diabetic patients with DKD were more likely to have abdominal obesity (categorized using WC or WHR/WHtR). Large prospective cohort studies should be carried out to confirm the significant association or causality between abdominal obesity and DKD in the future.

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## Statement of Ethics

This study is a meta-analysis, and all analyses are based on previous published studies; thus, no ethical approval and patient consent are required.

## Conflict of Interest Statement

The authors have no conflicts of interest in this work.

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## Author Contributions

The first draft of the manuscript was written by Q.Z.; Q.Z., X.Y. and Z.W. designed the study, oversaw the data collection and performed data analysis. Z.W. contributed to the critical revisions of the article for important intellectual content. All authors took part in revising this meta-analysis, gave final approval of the version to be published and agree to be accountable for all aspects of the work.

## Data Availability Statement

Full data sets can be obtained from the corresponding author at towzh713@126.com.

The authors confirm that the manuscript is an honest, accurate and transparent research; important aspects of the research have not been omitted; all discrepancies with the planned and registered research have been explained.

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