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Impact of body mass index on adverse kidney events in diabetes mellitus patients: A systematic-review and meta-analysis

Jing-Fang Wan, Yan Chen, Tian-Hua Yao, Ya-Zhou Wu, Huan-Zi Dai

Abstract

BACKGROUND

The incidence of chronic kidney disease (CKD) among patients with diabetes mellitus (DM) remains a global concern. Long-term obesity is known to possibly influence the development of type 2 DM (T2DM). However, no previous meta-analysis has assessed the effects of body mass index (BMI) on adverse kidney events in patients with DM.

AIM

To determine the impact of BMI on adverse kidney events in patients with DM.

METHODS

A systematic literature search was performed on the PubMed, ISI Web of Science, Scopus, Ovid, Google Scholar, EMBASE, and BMJ databases. We included trials with the following characteristics: (1) type of study: prospective, retrospective, randomized, and non-randomized in design; (2) participants: restricted to patients with DM aged ≥ 18 years; (3) intervention: no intervention; (4) kidney adverse events: onset of diabetic kidney disease (DKD) (estimated glomerular filtration rate [eGFR] of < 60 mL/min/1.73 m² and/or microalbuminuria value of ≥ 30 mg/g Cr), serum creatinine increase of more than double the baseline or ESRD (eGFR < 15 mL/min/1.73 m² or dialysis), or death.

RESULTS

Overall, 11 studies involving 8,01 patients with DM were included. High BMI (≥ 25 kg/m²) was significantly associated with higher blood pressure (BP; systolic BP [SBP] by 0.20, 95% confidence interval [CI]: 0.15–0.25, P < 0.00001; diastolic BP [DBP] by 0.21 mmHg, 95%CI: 0.04–0.37, P = 0.010), serum albumin, triglycerides (TG; standard mean difference [SMD] = 0.35, 95%CI: 0.29–0.41, P < 0.00001), low-density lipoprotein (LDL; SMD = 0.12, 95%CI: 0.04–0.20, P = 0.030), and lower high-density lipoprotein (HDL; SMD = –0.36, 95%CI: –0.51 to –0.21, P < 0.00001) in patients with DM compared with those with low BMIs (< 25 kg/m²). Our analysis showed that high BMI was associated with a higher risk ratio (RR) of adverse kidney events than low BMI (RR: 1.22, 95%CI: 1.01–1.43, *P* = 0.036).

CONCLUSION

The present analysis suggested that high BMI was a risk factor for adverse kidney events in patients with DM.

INTRODUCTION

According to the 2020 Hemodialysis Annual Report[1], approximately 700,000 patients with end-stage renal disease (ESRD) require maintenance hemodialysis. The incidence of chronic kidney disease (CKD) among patients with diabetes mellitus (DM) was noted to be as high as 64.0 cases per 1000 person-years (95% confidence interval [CI], 62.2–65.9)[2].

Patients with DM and CKD have a substantially increased risk of all-cause mortality, cardiovascular mortality, and ESRD[3]. Obesity is a major contributor to the development of diabetes [4]. A historical cohort study[5] showed that a higher baseline body mass index (BMI) was an independent predictor of ESRD when compared to individuals with normal weight in the normal range (BMI: 18.5–24.9 kg/m²), and the

adjusted relative risk of ESRD was 1.87 (95%CI, 1.64–2.14) for those who were overweight (BMI: 25–29.9 kg/m^2). Long-term obesity has the potential to influence the development of type 2 DM (T2DM) and has significant effects on the kidneys that can include changes to intraglomerular hemodynamics, increased sympathetic activity, hypertension, systemic inflammation, endothelial dysfunction, expression of growth factors, and compression associated with visceral adiposity[6-8].

Some studies have found that obesity and DM exert a synergic effect on decreases in estimated glomerular filtration rate (eGFR)[5, 9-11]. However, the influence of BMI on adverse kidney events in patients with DM remains unclear, and some studies have shown that BMI is positively correlated with DKD[12-14]. Obesity has also been associated with an increased risk of decreased renal function in patients with DM[15-17]. Other studies have suggested that BMI is a protective factor against renal function deterioration[18-21] or that declines in renal parameters are not influenced by BMI[22, 23]. To the best of our knowledge, no previous meta-analysis has evaluated the effects of BMI on adverse kidney events in patients with DM. Therefore, this study aimed to evaluate the effects of BMI on adverse kidney events in patients with DM.

MATERIALS AND METHODS

Literature search

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines[24]. Two reviewers independently identified relevant studies in the PubMed, ISI Web of Science, Scopus, Ovid, Google Scholar, EMBASE, and BMJ databases from their respective inceptions until December 2022. We restricted the included studies to those published in English. The following terms were used in our search: diabetes mellitus, diabetic kidney disease, diabetic nephropathy, DM, BMI, obesity, excessive body weight, overweight, and underweight.

Study selection

We included trials with the following characteristics: (1) type of study: prospective, retrospective, randomized, and non-randomized in design; (2) participants: restricted to patients with DM aged ≥ 18 years; (3) intervention: no intervention; and (4) kidney adverse events: onset of diabetic kidney disease (DKD; eGFR of < 60 mL/min/1.73 m² and/or microalbuminuria value of ≥ 30 mg/g. Cr), serum creatinine increase of more than double from baseline levels, end-stage renal disease (ESRD; eGFR < 15 mL/min/1.73 m², or need for dialysis), or death. Studies were excluded if: (1) they involved particular niche-group populations, such as pregnant or lactating women; (2) they were meta-analyses, case studies, duplicates, repetitive results, or reviews; or (3) they were preclinical studies that used animal models. The following data were extracted: the study characteristics, baseline data, clinical comorbidities, and clinical outcomes.

BMI classifications

Various BMI classifications were observed in the selected studies. According to the World Health Organization (WHO), BMI values of > 30, 25–30, and < 25 kg/m² have been defined in the Western population as obesity, overweight, and normal, respectively. In the Asian population, the recommended cut-off values of BMI corresponding to these three categories are > 25, 23–25, and < 23 kg/m². Because of the variations in BMI classifications used in the studies we included, we simplified these classifications to ≥ 25 kg/m² or < 25 kg/m² to define high and low BMI, respectively.

Study quality assessment

We evaluated the quality of the cohort studies using the Newcastle–Ottawa Scale (NOS)[25]. The NOS evaluates the quality of articles using three levels, with eight items. The three major aspects include the selection of study groups, the comparability of the groups, and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies. A star rating system was used to

assess the quality of the literature through a semi-quantitative principle, with the highest score being nine stars.

The reliability of the eligible studies was assessed using the quality assessment forms recommended by the US Agency for Healthcare Research and Quality (AHRQ)[26]. This checklist comprises 11 items. Each item was coded with a "yes/no/unclear": "no" or "unclear" was scored "0," and "yes" was scored "1." Quality scoring was performed out of 11, with scores of 8-11, 4-7, and < 3 indicating high, medium, and low quality, respectively.

Quality assessments demonstrated moderate to high quality for all included studies (Appendix Table-1 and Appendix Table-2).

Statistical analysis

Between-study heterogeneity was estimated using Cochran's Chi-squared (c^2)-based Q statistical test and the I-squared (I^2) statistic. Values of 25%, 50%, and 75% corresponded to the cut-off points for low, moderate, and high degrees of heterogeneity, respectively. Once high heterogeneity was confirmed, a random-effects model was adopted, or a subgroup analysis was conducted; otherwise, a fixed-effects model was used. A pooled analysis of categorical data was performed using the Mantel–Haenszel model, and odds ratios (ORs) with 95%CIs were reported. Our pooled analysis of continuous data was performed using the inverse variance (I-V) model and was reported as the weighted mean difference (WMD) or standardized mean difference (SMD) at the 95%CI. ORs were converted to risk ratios (RRs)[27], which were presumed to be equivalent to hazard ratios (HRs). Statistical significance was set at two-tailed P values of < 0.05. As there were < 10 meta-analyses for each result in this study, Egger's test was used to assess the possibility of publication bias. To exclude the possibility that one particular study exerted an excessive influence on the heterogeneity of the overall results, we conducted a sensitivity analysis by omitting one study at a time and reanalyzing the data to assess the corresponding change in effect size. All analyses were conducted

using STATA (version 17, Stata Corporation, LLC, TX) and RevMan Review Manager (version 5.4.1, The Cochrane Collaboration, Oxford, UK) softwares.

RESULTS

Flowchart of article selection and quality assessments

A flowchart of the article selection process is shown in Fig 1. We identified 889 articles through a literature search. After excluding systematic reviews and duplicate publications, as well as after reviewing the titles and abstracts, 18 studies remained. We further examined the full texts of these 18 studies and excluded incomplete data or data that could not be obtained through calculations. Ultimately, 11 studies[12, 13, 15-23] were included in our meta-analysis.

Study characteristics

The included studies are summarized in Table 1. They were published between 1999 and 2022; of the 11 single-center studies, 5 were prospective, and 6 were retrospective. Data from 8011 patients were included, and the sample size varied from 49 (in the study by Kanauchi et al.[21]) to 3224 (in the study by Zhang et al.[13]). Three studies reported renal outcomes [19, 22, 23], one study evaluated mortality rates and renal endpoints[18], six studies included Asian Pacific populations (Chinese [n = 3][13, 18, 19], Japanese [n = 2][12, 21], and Korean [n = 1][17]), whereas five included Afro-European populations (African [n = 1][22], Dutch [n = 1][20], German [n = 1][14], British [n = 1][23], and French [n = 1][16]).

Meta-analysis of baseline characteristics

The results of our pooled analysis revealed a significant positive association between high BMI and the incidence of hypertension (OR: 1.640, 95%CI: 1.17–2.29, P = 0.004; I^2 = 68%; Appendix Figure 1a)[13, 17, 18], without publication bias (P = 0.378, Egger). High-BMI patients with DM were also associated with a low prevalence of Renin-angiotensin system blockers (RAS) (OR: 0.690, 95%CI: 0.57–0.84, P = 0.0002; I^2 = 0%; Appendix Figure 1b)[13, 18, 22], without publication bias (P = 0.178, Egger). Using the random-effects

model, we found a higher proportion of males in the high BMI group (OR: 1.33, 95%CI: 1.10–1. 61, $P < 0.003$), without publication bias ($P = 0.087$, Egger), but with higher heterogeneity ($P = 0.0003$, $I^2 = 70\%$; Appendix Figure 1c). The study by Haupt et al.[14] contributed to most of the heterogeneity. Compared to patients with low BMIs, high-BMI patients showed significantly higher systolic blood pressure (SBP) levels, by 0.20 mmHg (SMD: 0.20, 95%CI: 0.15–0.25, $P < 0.00001$; $I^2 = 0\%$; $P = 0.895$, Egger; Appendix Figure 1d) and diastolic blood pressure (DBP), by 0.21 mmHg (SMD: 0.21, 95%CI: 0.04–0.37, $P = 0.010$; $I^2 = 85\%$; $P = 0.858$, Egger; Appendix Figure 1e)[12, 13, 16, 21-23]. When we excluded the study by Zhang et al[13], the heterogeneity decreased significantly (rate of hypertension I^2: from 68% to 0%, DBP I^2: from 84% to 55%). We observed significantly higher serum albumin and lower serum uric acid levels in high-BMI patients with DM [13, 19], although the data for this came from just two studies. The results revealed no significant differences in terms of hemoglobin A1C (HbA1c; SMD: 0.06, 95%CI: -0.11–0.23, $P = 0.46$; $I^2 = 92\%$)[12-14, 16-23], hemoglobin (HB)[18, 22]and age (SMD: -0.15, 95%CI: -0.33–0.04, $P = 0.12$; $I^2 = 93\%$)[12-14, 16-23] between the two groups, without publication bias (HbA1c: $P = 0.689$, Egger; age: $P = 0.492$, Egger). The meta-analysis was performed using a random-effects model.

Our meta-analysis showed no significant increases in cholesterol levels in the high BMI group (SMD = 0.07, 95%CI: -0.13–0.26, $P = 0.500$; $I^2 = 89\%$[12, 14, 16-18, 22, 23]; Appendix Figure 2a), without publication bias ($P = 0.658$, Egger). Lower heterogeneity values ($I^2 = 69\%$, $P = 0.007$) were found when the study by Kim et al[17] was excluded. We found significantly higher levels of triglycerides (TGs; SMD = 0.35, 95%CI: 0.29–0.41, $P < 0.00001$; $I^2 = 42\%$;[12, 14, 16-18, 22] Appendix Figure 2b) and low-density lipoprotein (LDL; SMD = 0.12, 95%CI: 0.04–0.20, $P = 0.030$; $I^2 = 43\%$[14, 16-18, 22]; Appendix Figure 2c) in the high BMI group. Publication bias in terms of TG levels was not detected by Egger's test ($P = 0.337$), although publication bias was observed ($P = 0.001$, Egger) for LDL, suggesting that the sample sizes of the included studies were not well balanced and that the varying BMI grouping methods used may have been the most responsible for the publication bias. High BMI was associated with lower baseline levels of high-density

lipoprotein (HDL; SMD = -0.36, 95%CI: -0.51--0.21, P < 0.00001; Appendix Figure 2d), with high heterogeneity (I² = 79%, P = 0.0002)[12, 14, 16-18, 22]. The study by Kim *et al* contributed to most of the heterogeneity[17], but we found no noticeable publication bias (P = 0.920, Egger).

Meta-analysis of baseline renal characteristics

The association between BMI and urine protein level was reported in four studies. Two assessed 24-h proteinuria[18, 19], and two measured 24-h urinary albumin [14, 21]. No significant increase in urine protein levels was found in the high BMI group *via* random effects analyses. There was also no significant difference in baseline serum creatinine levels (SMD: 0.07, 95%CI -0.06–0.20, P = 0.310; I² = 70%; Figure 2a)[13, 14, 16, 18-21], without publication bias (P = 0.141, Egger). Our subgroup analysis showed that the serum creatinine levels in the high BMI group were significantly higher compared to those of the low BMI group in the European population for those aged > 60 (sample size > 500; Table 2). When the study by Chen *et al*[19] was excluded, heterogeneity decreased significantly (I² = 6%, P = 0.380).

No significant difference was found in baseline eGFR between the two groups (SMD = -0.03, 95%CI: -0.23–0.18, P = 0.800; I² = 89%; Figure 2b)[13, 16-19, 21, 22], with no significant publication bias (P = 0.085, Egger). The study by Chen *et al* contributed the greatest source of heterogeneity[19]; when this article was removed, the heterogeneity decreased significantly (I² = 68%, P = 0.009). Our results showed a significant decrease in eGFR in our subgroup analysis based on age > 60 and study sample size > 500 in the high BMI group (Table 2).

Meta-analysis of follow-up kidney adverse events

Six of the included studies reported adverse kidney events, but each reported different endpoints, and the definitions of these endpoints were inconsistent[12, 17-19, 22, 23]. These endpoints were combined to perform a meta-analysis. The random-effects model was used owing to the obvious heterogeneity (I² = 64%, P = 0.02). No significant difference

was found between the two groups in terms of adverse kidney events (OR: 0.86, 95%CI: 0.70–1.05, P = 0.132; Fig. 3a)[19, 22, 23], without publication bias (P = 0.389, Egger). The study by Chen et al was found to be the most significant source of heterogeneity[19], and six of the studies[12, 13, 16, 17, 19, 23] evaluated the risk of adverse kidney events. Various statistical indicators were pooled in this meta-analysis. The ORs and RRs were combined, which resulted in our meta-analysis suggesting that high BMI was associated with a higher RR than lower BMI (RR: 1.22, 95%CI: 1.01–1.43, P = 0.036; Figure 3b), without publication bias (P = 0.389, Egger).

DISCUSSION

Main findings

To the best of our knowledge, this is the first meta-analysis to assess the role that BMI plays in the renal prognoses of patients with DM. Our analysis showed that the Serum creatinine of the high BMI group was significantly higher in the older European population. Compared with patients with low BMIs, those with high BMIs showed significantly higher levels of BP, serum albumin, TG, LDL, and significantly lower levels of HDL. High BMI was also associated with higher RR in adverse kidney events. These results have important clinical implications for intervention and risk stratification.

Mechanisms behind BMI leading to adverse kidney events

Obesity is a global issue. According to an international epidemiologic study[28], the global prevalence of obesity will reach 18% in men and surpass 21% in women by 2025. Obesity is regarded as an overnutrition-induced state, with hypertension and diabetes representing its three most common comorbidities. We found higher levels of serum albumin and blood pressure (BP) and rate of male sex in patients with DM with higher BMIs. These findings are consistent with those of other studies[29, 30].

Obesity and DM lead to elevated serum uric acid levels [31], and we observed lower serum uric acid levels in patients with DM with higher BMIs; however, the data supporting this notion were provided by only two studies. Thus, more well-designed studies with larger sample sizes are warranted to confirm the relationship between BMI and serum uric acid levels in patients with DM. High BMI in patients with DM was associated with a low rate of RAS use; however, only three articles provided limited data on this matter. Therefore, more evidence is necessary to draw a clear relationship between RAS, BMI, and adverse kidney events in patients with DM.

Owing to factors such as ethnic differences and dietary habits, the median BMI is higher in the European population than in Asian ones[13, 23, 32]. For example, the rate of high BMI (≥ 25 kg/m^2) varies from 34.7% in Japan[21]to 71.21% in the Netherlands[20]. BMI is associated with new-onset CKD, CKD progression, and end-stage renal failure[33]. Kidney complications are highly prevalent in patients with DM[36]. The results of our study were similar to those of previous ones, with the scores of the high-BMI group being significantly higher in the European population aged > 60 years (sample size > 500). Obesity is the main cause of the worldwide DM epidemic[34]. Studies have found that both DM and obesity may play key roles in the pathophysiology of CKD [32, [35]. However, other studies have suggested that BMI is a renal protective factor in patients with DM[18-21]. Our study has answered this question by demonstrating that high BMI is associated with a higher RR of adverse kidney events than lower BMI (RR: 1.22, 95% CI: 1.01–1.43, P = 0.036).

Hypertension was found to be the most common comorbidity associated with obesity in patients with DM. Our study showed that high BMI was associated with significantly higher levels of BP (SBP by 0.20, 95% CI: 0.15–0.25, P < 0.00001; DBP by 0.21 mmHg, 95% CI: 0.04–0.37, P = 0.01). Tightening of the afferent arterioles in patients with hypertension may cause partial ischemia of the glomerulus with varying degrees of capillary collapse and tuft retraction; however, the ischemic glomerulosclerosis and nephron loss that occur over time are usually not sufficient to result in ESRD[36].

Patients with hypertension progress to ESRD at a faster speed if their conditions are further complicated by obesity and DM[37].

Obesity and DM are also the most common causes of dyslipidemia[38-40], and our findings support this notion as well. Abnormal lipid homeostasis (biosynthesis, lipid transport, and degradation) was observed at a higher prevalence in patients with both obesity and DM[41], likely because these conditions produce local inflammation and oxidative stress that promote atherogenicity and the progression of kidney damage[42].

Relationship between BMI and adverse kidney events in diabetic and non-diabetic nephropathy.

Two articles reported on adverse kidney events in patients with diabetic nephropathy (DN), but their results regarding the role of BMI were conflicting. Chen et al.[19] reported that the lean phenotype (BMI < 25 kg/m^2) was associated with the development of ESRD, particularly in the later stages, while Bentata et al.[22] claimed that eGFR declines observed in patients with DN are not directly influenced by BMI. Thus, we did not examine the relationship between BMI and the development of CKD in this study owing to a lack of sufficient usable data.

Limitations

Our study has a few limitations worth noting. First, varying classifications of BMI were observed among the selected studies. Therefore, we divided the participants into high- and low-BMI groups according to a cut-off value of 25 kg/m^2. Second, we did not account for changes in BMI values during follow-ups, which may have influenced occurrences of adverse kidney events. Third, the use of varying eGFR calculation formulas means that final eGFR results may not always reflect actual renal status. Drion et al.[20] found that all equations used to predict renal function (including the Modification of Diet in Renal Disease formula and the Chronic Kidney Disease Epidemiology Collaboration equation) are biased when used in populations with DM

who are overweight or obese but have preserved renal function. In these cases, the Cockcroft-Gault equation provides the best estimate of kidney function. Fourth, most of the included studies did not report renal endpoint events or mortality; therefore, we could not exclude the potential effects of survival bias and competing risks. Finally, high-quality and rigorously controlled observational studies were lacking from our pool of studies; currently, evidence to conclusively evaluate the effects of BMI on the long-term outcomes of patients with DM is insufficient.

CONCLUSION

Patients with DM and higher BMIs had higher BP and serum albumin levels, as well as worse lipid profiles. We demonstrated that high BMI was a risk factor that contributed to the development of adverse kidney events in patients with DM. Further studies that focus on the optimal weight range for patients with DM would be beneficial to this field of study.

ARTICLE HIGHLIGHTS

Research background

Obesity and diabetes are global public health concerns. Poor control of weight or blood sugar may lead to damage to multiple organs, including the kidneys.

Research motivation

The effect of obesity on adverse renal effects in patients with diabetes remains unclear.

Research objectives

This study aimed to explore the impact of body mass index (BMI) on adverse kidney events in patients with diabetes mellitus (DM).

Research methods

A systematic literature search was performed of the PubMed, ISI Web of Science, Scopus, Ovid, Google Scholar, EMBASE, and BMJ databases. We included trials with the following characteristics: (1) type of study: prospective, retrospective, randomized, and non-randomized in design; (2) participants: restricted to patients with DM aged ≥ 18 years; (3) intervention: no intervention; (4) kidney adverse events: onset of diabetic kidney disease (DKD) (estimated glomerular filtration rate [eGFR] of < 60 mL/min/1.73 m^2 and/or microalbuminuria value of ≥ 30 mg/g Cr), serum creatinine increase of more than double the baseline or end stage renal disease (ESRD) (eGFR < 15 mL/min/1.73 m^2 or dialysis), or death.

Research results

High BMI (≥ 25 kg/m^2) was significantly associated with higher blood pressure (BP), serum albumin, triglycerides (TG), low-density lipoprotein cholesterol (LDL), and lower high-density lipoprotein cholesterol (HDL) levels in patients with DM than in those with low BMIs (< 25 kg/m^2). Our analysis showed that a high BMI was associated with a higher risk ratio (RR) of adverse kidney events than a low BMI.

Research conclusions

High BMI was identified as a risk factor contributing to adverse kidney events in patients with DM.
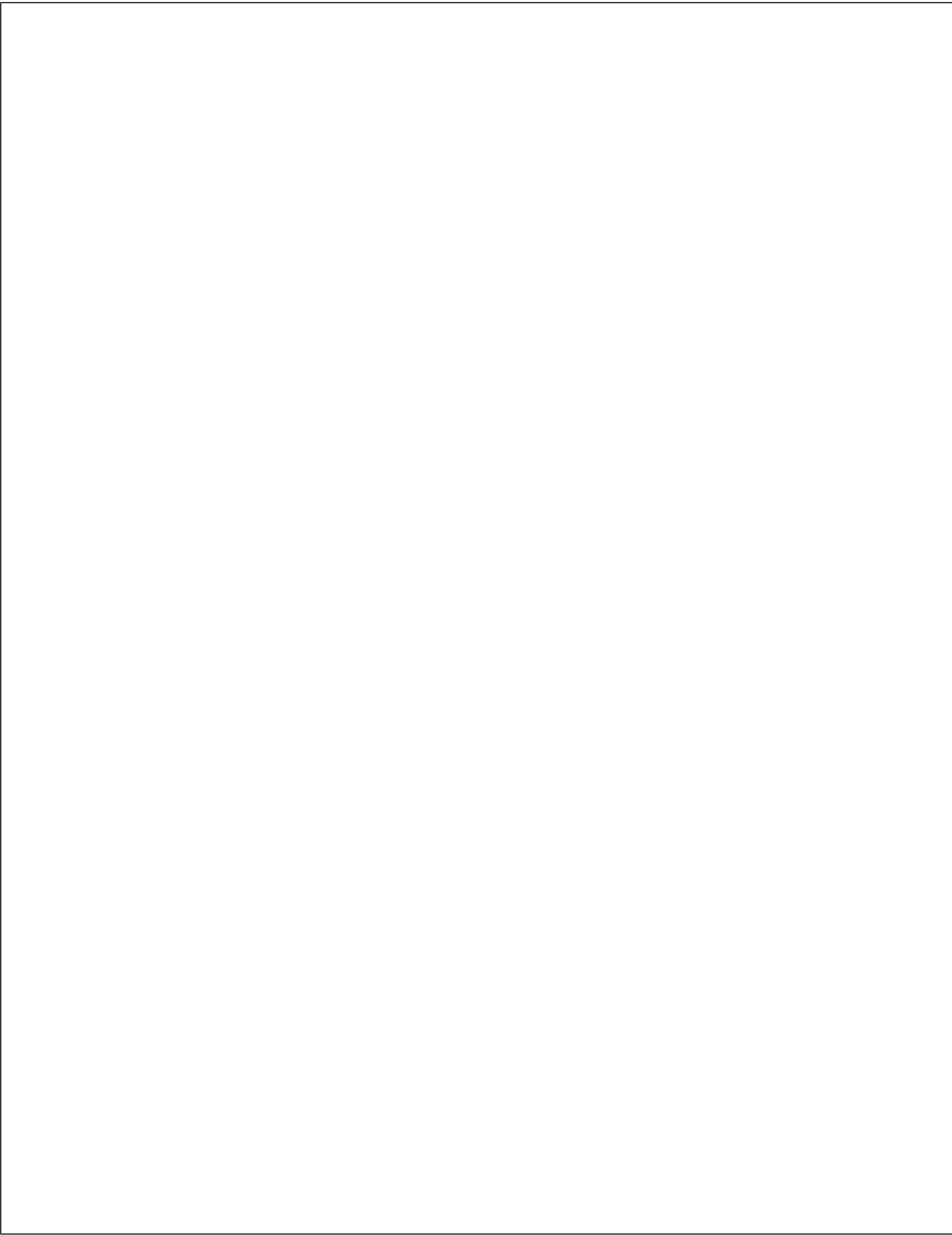
Research perspectives

A larger sample size and higher quality studies are warranted to corroborate the findings of this meta-analysis, and future studies focusing on the optimal weight range for patients with DM would also be beneficial.

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