Effect of obstructive sleep apnoea on diabetic retinopathy and maculopathy

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The association between obstructive sleep apnea on diabetic kidney disease:

a systematic review and meta-analysis

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Abstract

Study Objective: This systematic review aims to summarise the association between obstructive sleep apnea (OSA) and diabetic kidney disease (DKD).

Design: MeSH terms and free text searches were performed on MEDLINE, EMBASE and Cochrane Database of Systematic Reviews from inception to April 2015. Zetoc and OpenGrey databases were queried for grey literature and lastly, hand searches were carried out. Study selection and quality assessment were conducted by two authors. One author carried out data extraction, which was checked by other authors. The relationships between apnea-hypopnea index (AHI), oxygen desaturation index (ODI), time spent under 90% oxygen saturation (%TST<90), minimum and mean oxygen saturation (O_2) on DKD were examined.

Measurement and Results: Two longitudinal and ten cross-sectional studies were included for our narrative synthesis, and seven studies for meta-analysis. Studies that performed multi-variable analysis demonstrated significant associations between OSA (assessed using either apnea-hypopnea index or ODI) and DKD in type 2 diabetes mellitus (T2DM). This was confirmed by meta-analysis (pooled OR 1.73, 95% CI: 1.13-2.64). There was some evidence to suggest that %TST<90 may have an association with DKD. There was insufficient evidence to conclude on the relationship between minimum and mean oxygen saturation on DKD. There was no evidence available on the associations between OSA and other respiratory parameters in type 1 diabetes mellitus populations.

Conclusion: There is moderate evidence that OSA is associated with DKD in patients with T2DM. Large prospective studies with long-term follow up are needed to assess the possible bi-directional mechanisms between OSA and DKD.

Introduction

Obstructive sleep apnea (OSA) is a chronic sleep disorder characterized by episodic complete or partial upper airway obstruction causing intermittent hypoxemia (IH) and sleep fragmentation. The prevalence of OSA amongst patients with diabetes mellitus (DM) is high[1] and OSA has been shown to influence glycemic control[2] and blood pressure[3], two common factors contributing to vascular complications in DM. Apart from an impact on glycemic control[4] and hypertension[3], OSA and accompanying IH can trigger shared pathophysiological pathways mediating DM vascular complications including activation of oxidative and inflammatory pathways and greater production of advanced glycation end products (AGEs)[5]. Thus, identifying and addressing factors such as OSA may contribute to the prevention, delay, and amelioration of the serious DM vascular complications that significantly impinge on quality of life and increase mortality[6]. The evidence regarding the relationships between OSA and DM complications, however, is inconsistent and has not been systematically reviewed.

In the context of diabetic kidney disease (DKD), a common and serious DM complication, one study found no significant correlation between urinary albumin creatinine ratio (ACR) and OSA[7] while another study found that chronic IH was associated with a three-fold increase in odds for macro-albuminuria and a two-fold increase for micro-albuminuria[8]. Our previous work showed that the measure of OSA, the apnea-hypopnea index (AHI), defined as the average number of complete and partial airway obstruction events per hour of sleep during the night, had an inverse relationship with estimated glomerular filtration rate (eGFR) in DM patients with extreme obesity[9]. We also reported that the duration of nocturnal hypoxemia was related to a lower eGFR.

Due to the incongruity of the existing literature, the primary aim of this systematic review was to summarise the evidence on the association between OSA or chronic nocturnal hypoxemia with DKD. As nocturnal hypoxemia can be assessed differently according to different parameter definitions, we also examined the associations between oxygen desaturation index (ODI), minimum oxygen saturation, mean oxygen saturation and time spent below 90% oxygen saturation (%TST<90) on DKD to gain further insight into pathophysiological mechanisms.

Methods

The systematic review followed the recommendations by the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement[10] as well as the Meta-analysis of Observational Studies in Epidemiology (MOOSE) statement[11]. The protocol was registered in Prospero database (registration number CRD42014008757).

Eligibility criteria

A summary of the eligibility criteria is presented in the supplementary materials. We had no language restrictions and the following inclusion criteria were used:

Participants: Adults with either Type 1 diabetes mellitus (T1DM) or Type 2 diabetes mellitus (T2DM) were included.

Exposure: T1DM and T2DM participants with a diagnosis of OSA. It was not necessary for the diagnosis of OSA to follow the American Academy of Sleep

Medicine (AASM) guidelines[12] using AHI obtained from polysomnography (PSG). Thus, studies using oxygen desaturation index (ODI) as a criterion for OSA were also included. However, we excluded studies which used screening questionnaires only as diagnostic criteria for OSA (such as the Berlin questionnaire or Epworth Sleepiness Score).

Comparator: Participants without OSA were the comparator.

Outcomes: The primary outcome was the risk of DKD assessed using either estimated glomerular filtration rate (eGFR) ($<60ml/min/1.73m^2$) or albuminuria, which included both micro- and macro-albuminuria ($>30mg/day$) or urinary albumin creatinine ratio ($>3.4mg/mmol$).

Study design: We included observational studies (cross-sectional, cohort or case-control studies). We also included prevalence studiesthat include data on DKD.

Search Strategy

Index terms such as medical subject headings (MeSH) and free text were utilised to capture wide aspect of the literature. The search terms are described in supplementary materials. No restrictions were applied when searches were performed. The following electronic databases were searched from inception to January 2014: MEDLINE, Excerpta Medica DataBase (EMBASE) and Cochrane Database of Systematic Reviews. We also searched OpenGrey and Zetoc databases for grey literature such as conference abstracts. Free text "obstructive sleep apnoea" and "obstructive sleep apnea" were used for OpenGrey. For Zetoc, the following free text was used: "obstructive sleep apnoea/apnea and diabetes" and "apnoea/apnea and diabetes". Citations of the included papers were also hand

searched for additional studies. An updated search on MEDLINE, EMBASE, OpenGrey and Zetoc was carried out from January 2014 to April 2015.

Study Selection

Titles and abstracts were independently reviewed by two authors to select eligible studies. Following that, full texts of the eligible studies were retrieved and studies were excluded if the inclusion criteria were not met. Again, two authors reviewed the full texts independently. Any disagreements were resolved through discussion and a third author was available to arbitrate when no consensus was reached. When duplicate or 'kin' studies were obtained, results from the most recent study or most comprehensive results were used for data synthesis and analysis.

Data Extraction

A pilot data extraction form was designed based on the Strengthening and Reporting of Observational studies in Epidemiology (STROBE) statement[13]. The form was piloted on a sample of 5 studies and further improvements made prior to formal use for the systematic review. One author performed data extraction, checked by other authors. For any missing data or when additional information was required, study authors were contacted.

Assessment of study quality

We designed a revised quality assessment form based on the Newcastle Ottawa Scale[14] for non-randomised studies in the meta-analysis. Study quality was assessed on five components: selection bias, study methods, blinding of the

assessor carrying out sleep recording analysis, respiratory measurement and finally the overall analysis (supplementary materials). Each component consisted of a set of criteria and each criterion was rated as 'yes', 'no' or 'unclear'. Following that, a judgment of either 'weak', 'moderate' or 'strong' were given to each component. Finally, an overall judgment of 'weak', 'moderate' or 'strong' was made. We utilised a rating system as per the Cochrane Collaboration recommendation[15]. Two authors carried out quality assessments independently. The form was piloted on studies and improvements were made prior to formal use.

Data synthesis and analysis

Narrative description was used to summarise our findings. Statistical analysis was carried out using Stata 13 (StatCorp LP, College Station, Texas). We performed a meta-analysis on the studies that reported unadjusted OR on the association between OSA (defined using AHI) and DKD. We also meta-analysed studies that only reported adjusted OR and 95% CI (relationships between ODI and AHI on DKD) because these results minimises the influence of potential confounders. All meta-analyses were performed using random effects model analysis.

Meta-analysis was not performed on the association between mean and minimum oxygen saturation or the percentage of time spent below 90% oxygen saturation (%TST<90) and DKD. Publication bias was assessed visually using funnel plot for meta-analyses which contained >5 studies. We also carried out kappa (κ) statistics to assess the agreement between the two authors for study selection (87%, κ statistic = 0.71, p<0.001) and quality assessment (89%, κ statistic = 0.80, p<0.0004).

Results

The initial searches identified a total of 1163 studies (1129 from databases and 34 from grey literature). An updated search in April 2015 identified 447 studies (350 from databases and 97 from grey literature). After excluding duplicates, there were 1509 studies and 1474 were subsequently removed after title and abstract screening. Thirty-five full text articles were retrieved. We excluded 23 articles: 10 studies did not include DM populations, 9 were duplicate studies, 2 did not include participants with OSA, 1 study did not have DKD as an outcome and 1 study was a review article. A total of 12 studies were included in our narrative synthesis. Figure 1 showed the PRISMA flow chart for study selection.

Study characteristics

The majority of the studies had a cross-sectional study design except two[16, 17] which included a follow-up component. Most studies (n=7) were from Europe[7, 9, 16-20], two studies were from Japan[8, 21], two from China[22, 23] and one from the USA[24]. There were a total of 4344 DM participants (4286 T2DM) across all studies. The mean age of participants ranged from 51 to 62 years and the proportion of females ranged from 32% to 73%[7-9, 16-24]. The mean HbA_{1c} and DM duration were between 6.5 and 9.2% and 7.5 and 15.0 years[7-9, 16-24] respectively. One study[9] only included extremely obese individuals with a mean BMI of 46.8Kg/m^2. For the remainder of the studies[7, 8, 16-24], mean BMI ranged from 25.2 to 37.0Kg/m^2.

The characteristics of the studies are summarized in Table 1. Most of the studies used an ambulatory sleep device with 3 channels (oximetry, air-flow, and respiratory effort) to assess OSA[9, 16, 22, 24] while one performed full polysomnography (PSG)[7]. Others used a two-channeled device[18, 19], mixed methods[20] or pulse oximetry for sleep assessment[8, 21]. One study used a single-channel recording device, unfortunately, the authors did not specify which channel[23]. One study did not report on the device used for overnight respiratory assessment[17].

A small degree of heterogeneity was present for the definition of apneas and hypopneas as well as OSA diagnosis (please see supplementary materials for details). As expected, there were variations in the diagnoses of DKD. Six studies reported on albuminuria results[7, 8, 18, 20, 22, 24]. One UK study reported on both urinary ACR and eGFR[16]. The eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) equation. Another UK study[9] only used eGFR, calculated using the MDRD and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formulae. Additionally, a Japanese study[21] utilized serum creatinine levels (mg/dl).

Narrative review of OSA (defined by AHI) and DKD

Ten studies (n=2927) out of a total 12 studies examined the association between OSA (using apnea-hypopnea index) and DKD[7, 9, 16-20, 22-24]. Seven studies (n=1729) performed unadjusted analysis,[7, 18-20, 22, 24]; only one study demonstrated significant association[18]. Univariate and multivariate analyses were carried out by two UK-based studies and one Chinese study (n=1198)[9, 16, 23]. The Chinese study demonstrated significant associations after adjusting for age and gender[23]. Leong et

al. demonstrated a linear association between AHI and MDRD eGFR[9]. However, this was not confirmed using the CKD-EPI formula. Table 1 list the covariates used for adjustment. The longitudinal study by Tahrani and colleagues reported that OSA was an independent predictor for DKD after adjusting for a range of confounders at baseline[16]. Additionally, 196 participants were followed-up for 2.5±0.7 years and OSA was associated with a lower study-end MDRD eGFR result (p=0.04) after adjusting for confounders. Substituting OSA with AHI revealed similar results (p=0.02).

Meta-analysis of OSA (defined by AHI) and DKD

A meta-analysis was carried out for seven studies which reported unadjusted ORs on the relation between OSA and DKD[7, 9, 16, 18-20, 22]. The pooled estimates showed a small, but significant association, with higher risk of DKD in those who have OSA (pooled OR 1.59, 95%CI: 1.16-2.18, I^2=26.8%; see supplementary materials). The funnel plot of these studies[7, 9, 16, 18-20, 22] suggest an imbalance of small studies with positive results (see supplementary materials). In summary, pooling of studies using crude ORs suggests that there is a significant association between OSA and DKD. Our narrative review on studies[9, 16, 23] that undertake multivariate analysis also support this hypothesis. Additionally, the one study[16] which followed up patients longitudinally, showed that patients with DM who have OSA had a higher risk of DKD.

Narrative review of DKD and oxygen desaturation index

Two studies (n=1317) from Japan used drop in oxygen levels during sleep (3%ODI ≥5events/hr) as the diagnostic criterion for OSA[8, 21]. Both reported a significant association between ODI and DKD.

Meta-analysis of DKD and oxygen desaturation

A meta-analysis was carried out on these two studies[8, 21] resulting in a pooled OR 2.00, 95%CI:1.36 to 2.94 (I^2=0.0%; supplementary materials). Combining the studies by Tahrani[16] and Zhang 2014[23] which used AHI criterion for OSA diagnosis into the model showed similar results (pooled OR 1.73, 95% CI: 1.13 to 2.64 I^2=69.3%) as shown in Figure 2. However, substantial heterogeneity[25] is present therefore the pooled results should be interpreted with caution. Publication bias cannot be ruled out. In summary, our narrative synthesis outlined a likely association between sleep apnoea as measured by ODI on DKD in patients with T2DM, and this was confirmed by our meta-analysis.

Narrative review of DKD and other respiratory parameters

Three studies (n=491) examined the relation between minimum oxygen saturation and DKD[9, 16, 24], with only one reporting a significant association[24]. Two studies examined the association between mean oxygen saturation (n=158) and DKD[9, 17], in which only one study showed a significant association[17]. The association between the percentage of time spent under 90% oxygen saturation (%TST<90) and DKD

was also assessed by two studies (n=158) and both reported significant associations[9, 17].

In summary, there was insufficient evidence to conclude on the <mark>relationship between the level of hypoxemia and mean oxygen saturation and DKD</mark>. Our narrative review suggests that %TST<90 may <mark>have an association with the risk of DKD.</mark>

Quality assessment

The quality of the studies is summarised in Table 2. Overall, the studies were of poor-to-moderate quality (n=10)[7, 8, 17-24]. Only 2 studies were rated as high quality[9, 16]. The majority of studies were at risk of selection bias (n=8)[7, 8, 17, 19, 20, 22-24]. In addition, only one study reported respiratory scoring with an assessor blinded of the participants' clinical characteristics[9]. Several studies were rated at least moderate for methods of sleep assessment (n=9)[7-9, 16, 18-22]. The majority of studies scored reasonably well for study methods (n=6)[9, 16, 18-20, 24] with several studies only carrying out univariate analyses (n=7)[7, 17-20, 22, 24].

Discussion

Our narrative synthesis demonstrated moderate evidence for a possible association between OSA (diagnosed using AHI) and DKD. This was confirmed by a meta-analysis on the studies that carried out univariate analysis. Nevertheless, crude ORs are subjected to multiple confounders such as age, gender and BMI which may lead to an overestimation of the results. Studies which performed multivariate analysis

adjusted for important confounders such as BMI, gender and DM duration, also demonstrated a significant association between OSA and DKD[9, 16, 23]. Additionally, the only longitudinal study with medium-term follow up also showed a significant decline of eGFR in individuals with T2DM and OSA[16]. In that study, 47 participants were offered continuous positive airway pressure (CPAP) treatment with 16 being CPAP adherent. The eGFR decline was slower in the CPAP-adherent group (-7.7%, 95%CI:-15.9% to -1.8% compared to non-compliant group (-10.0%, 95%CI:-17.2%-2.3%). Although the CPAP results were not adjusted for important confounders and has no control group for comparison, it suggests that reversing sleep apnea using CPAP may contribute to decelerating the decline in renal function.

One of the excluded studies, the Nutritional Health And Nutrition Examination Survey (NHANES) study, was published as a conference abstract[26]. The study was excluded because only 9.5% of the participants were diabetic and it was unclear whether the self-reported sleep apnea was central or OSA. Multivariate regression analysis demonstrated that when DM and sleep apnea coexist, the risk of micro-albuminuria was three-fold higher (OR 3.4, 95%CI:1.80-6.39) and risk of macro-albuminuria was 11-times greater (OR 11.39, 95%CI:4.60-28.42) after adjusting for confounders. Assuming the diagnosis of sleep apnea was obstructive in nature in the majority of the participants, this strengthens the evidence of the association between OSA and DKD in T2DM. Our narrative review also suggests that %TST<90 may have an association with DKD. Currently, there is a dearth of information on the relationship between OSA, as well as the other respiratory parameters, and DKD in T1DM population.

A small degree of heterogeneity was identified in the methods and the criteria used for OSA diagnosis. The majority of studies utilised either level III or level IV portable devices because they are less costly and less labor intensive. A recent meta-analysis that compared portable devices to the gold standard in-hospital full PSG reported a good diagnostic performance with areas under curve of between 0.85 and 0.99 according to OSA severity[27]. Differences also occurred with DKD diagnosis. Some studies used albuminuria whilst others used either eGFR or creatinine levels. Nonetheless, several studies demonstrated a significant association with assessment of either albuminuria or eGFR[8, 9, 21] suggesting that the relationship between OSA and DKD might be much larger and the effect size likely to be underestimated. Almost all the studies were cross-sectional in design therefore unable to demonstrate causality. However, the cohort study[16] reported significant deterioration of eGFR after 2.5 years of follow-up. Measures of nocturnal hypoxemia, however, were not associated with eGFR decline in the final analysis.

OSA is likely to impact on both the development and progression of DKD through several mechanisms. IH caused by OSA has been documented to cause greater levels of oxidative stress, and activation of inflammatory pathways, leading to endothelial dysfunction[28, 29]. Additionally, the intermittent intra-renal hemodynamic changes from recurrent sympathetic overdrive secondary to sleep fragmentations can cause ischemia with intra-renal reperfusion injury leading to intrinsic renal injury[30]. Case reports on participants with OSA have shown secondary focal glomerulosclerosis[31, 32] and in one case, complete resolution of proteinuria after bi-level positive airway pressure treatment[32].

In addition, studies have shown a dose-response relationship between the severity of OSA and glycaemia[2]. This is likely to involve several mechanisms including excess sympathetic activity, activation of the hypothalamic-pituitary-adrenal axis, direct insult to beta-cell function, and activation of deleterious inflammatory molecular pathways adversely affecting insulin sensitivity[6]. Collectively, these mechanisms result in greater insulin resistance among DM participants and greater insulin resistance amongst those with T2DM that has been shown to be a predictor of the development of micro-albuminuria irrespective of other metabolic profiles[33]. Furthermore, OSA is a known cause of resistant hypertension[34], and hypertension is a major risk factor for renal damage[35].

It is also plausible that diabetic microvascular complications cause or exacerbate OSA. It is well known that diabetes-related microvascular complications often co-exist. Consequently, those with DKD might also have diabetic neuropathy. Diabetic autonomic neuropathy can affect muscular control of the pharynx increasing the risk of airway collapsibility. In a case series, OSA was found to correlate highly with hereditary motor and sensory neuropathy disease (Charcot-Marie-Tooth disease)[36]. Likewise, patients with diabetic autonomic neuropathy have been reported to have a greater risk of OSA compared with those without[37, 38]. Therefore, there is likely to be a two-way association between OSA and DKD[39].

This systematic review has several limitations. The majority of the studies were cross-sectional which may be subject to selection bias[40]. Most of the studies did not blind the DKD outcome from the assessor who scored the sleep recording reflecting possible measurement bias. A few studies were in the form of conference abstracts

with very limited detail and our quality assessment might not have comprehensively assessed the rigour of these studies. The issue of residual confounders remained as several studies carried out unadjusted analyses. This may represent an overestimation of the effect sizes. Although the majority of the studies were from the European counties with two studies from Japan, two from China and one from the US, the underlying mechanistic effects between OSA and DKD should not differ in other populations therefore our results should be generalisable to all T2DM populations.

Conclusion

Our systematic review demonstrated that OSA, defined as using AHI or ODI, was associated with DKD in T2DM. There is a dearth of information on the relationship between OSA and DKD amongst T1DM. In light of the plausible bi-directional mechanisms between OSA and DKD, there is a need for large prospective studies with long-term follow-up to determine the impact of OSA parameters on both albuminuria and eGFR in both T1DM and T2DM populations.

Word count: 3216

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Table 1: Characteristics of included studies

Study ID (country)	Study design	Participants	Demographics	Diabetes parameters	OSA assessment and diagnosis	Results
Buyukaydin 2012 (Turkey)[7]	CS	52 T2DM	Setting = Diabetes clinic Mean age = 56 years Females = 73% Mean BMI = 32.4 Kg/m^2	Mean HbA$_{1c}$ = 7.9% Mean DM Duration = 12.8 years	Inpatient PSG (Compumedics E 3142) OSA = AHI ≥5 events/hr	*Univariate analysis* - No difference in albuminuria between OSA (21.9%) and non-OSA (29.4%) groups. - No difference in AHI between micro-albuminuria 9.0±14.6 vs. no micro-albuminuria 10.5±10.0events/hr (p>0.05)
Furukawa 2013 (Japan)[8]	CS	513 T2DM	Setting = Multi-center diabetes clinics Mean age = 62 years Females = 43% Mean BMI = 25.2 Kg/m^2	Mean HbA$_{1c}$ = 7.3% Mean DM Duration = 11.7 years	Oximetry (PULSOX-3Si) [#] 3% ODI ≥5 events/hr	*Multivariate analysis* - **Association between ODI and micro-albuminuria (OR 1.84, 95% CI: 1.16 to 2.96)** - **Association between ODI and macro-albuminuria (OR 2.97, 95% CI: 1.36 to 6.90)** Adjusted for age, sex, BMI, hypertension, hyperlipidemia, smoking, alcohol, medications for stroke and IHD, duration of DM and HbA$_{1c}$.
Kosseifi 2010[‖] (US)[24]	CS	98 T2DM	Setting = Sleep clinic Mean age = 61 years Females = NA$^\$$ Mean BMI = 33.7 Kg/m^2	Mean HbA$_{1c}$ = 6.5% Mean DM Duration = NA	Level III sleep test (NovaSom QSG) OSA = NA	*Univariate analysis* - No difference in AHI between micro-albuminuria 33.5 vs. no micro-albuminuria 28.0events/hr (p>0.05) - **Significant difference in oxygen saturation in micro-albuminuria 73.0% vs. no micro-albuminuria 77.4% (p<0.01)**
Laaban 2009[‖]	CS	303 T2DM	Setting = Hospital inpatient (DM)	Mean HbA$_{1c}$ = 9.2%	Level IV sleep test (CID 102) [‡~]	*Univariate analysis* - No difference in albuminuria between

(France)[18]			Mean age = 61 years Females = 49% Mean BMI = 32.0 Kg/m^2	Mean DM Duration = 14.5 years	OSA = AHI ≥5 events/hr	groups: non-OSA (25%), mild OSA (34%), moderate OSA (38%) or severe OSA (39%). - **Association between OSA and albuminuria (unadjusted OR 1.90, 95% CI: 1.10 to 3.31).**
Langrand C 2014 [a] (France)[17]	Cohort	68 T2DM	Setting: NA Mean age = 62 years Females = 43% Mean BMI = 37 Kg/m^2	Mean HbA$_{1c}$ = 8.1% Mean DM Duration = 15.0 years	Sleep test = NA OSA = NA	*Univariate analysis* - **Significant association between diabetic kidney disease and mean nocturnal oxygen saturation (OR 0.814, 95% CI: 0.671 to 0.9880)** - **Significant association between %TST<90 and diabetic kidney disease (OR 1.026, 95% CI: 1.001 to 1.051)** - No association between AHI and diabetic kidney disease
Leong 2014 (UK)[9]	CS	90 T2DM	Setting = Specialist weight management clinic Mean age = 51 years Females = 57% Mean BMI = 46.8 Kg/m^2	Mean HbA$_{1c}$ = 8.3% Mean DM Duration = 7.5 years	Level III sleep test (Embletta) [#] ~ OSA = AHI ≥5 events/hr	*Multivariate analysis (linear regression)* - **Association between AHI and MDRD eGFR (β=-0.17, 95% CI: -0.32 to 0.02).** - **Association between %TST<90 and MDRD eGFR (β=-0.22 to 95% CI: -0.41 to 0.02).** - No association between mean O$_2$ and MDRD eGFR (β=1.91, 95% CI: -0.04 to 2.42). - No association between minimum O$_2$ and MDRD eGFR (β=0.05, 95% CI: -0.39 to 0.50) - No association between AHI and CKD-EPI eGFR (β=-0.19, 95% CI: -0.39 to 0.01) Adjusted for age, gender, BMI,

hypertension, IHD, DM duration, insulin treatment, RAS treatment.

- Association between %TST<90 and CKD-EPI eGFR (β=-0.30, 95% CI: -0.56 to 0.03)
- No association between minimum O_2 and CKD-EPI (β=0.16, 95% CI: -0.44 to 0.76)
- No association between mean O_2 and CKD-EPI (β=1.50, 95% CI: -0.21 to 3.22)
Adjusted for age, gender, BMI, hypertension, IHD, DM duration, insulin treatment, RAS treatment.

Schober 2011[II] (Germany)[19]	CS	58 T1DM & 498 T2DM	Setting = 14 primary care centers Mean age = 60 years Females = 48% Mean BMI = 31.9 Kg/m²	Mean HbA₁c = 7.6% Mean DM Duration = 9.3 years	Level IV sleep test (ApneaLink) [‡]~ OSA = AHI ≥15 events/hr	*Univariate analysis* **- Significant difference between groups: AHI<5/hr 13 patients, AHI 5-14/hr 46 patients, AHI≥15/hr 42 patients (p=0.001).** - No association between OSA (AHI ≥15/hr) and nephropathy (unadjusted OR 1.24, 95% CI: 0.80 to 1.92).
Storgaard 2014[II] (Denmark)[20]	CS	180 T2DM	Setting = Diabetes clinic Mean age = 59 years* Females = 42% Mean BMI = 32.2 Kg/m²*	Mean HbA₁c = 7.4%* Mean DM Duration = 8.2 years*	Berlin Q and ApneaLink +/- level III sleep test (Embletta) [#] OSA = AHI ≥5 events/hr	*Univariate analysis* - No association between OSA and albuminuria (OR 1.38, 95% CI: 0.76 to 2.53).
Tahrani 2013 (UK)[16]	Cohort	224 T2DM	Setting = 2 diabetes clinics Mean age = 57 years* Females = 42%	Mean HbA₁c = 8.2%* Mean DM	Level III sleep test (Alice PDX) [#]~ OSA = AHI ≥5	*Multivariate analysis* **- Association between OSA and nephropathy (OR 2.64, 95% CI: 1.13 to 6.16)**

			Mean BMI = 33.5 Kg/m^2*	Duration = 10.0 years*	events/hr	- No association between minimum O_2 and nephropathy (OR 0.96, 95% CI: 0.93 to 1.00). Adjusted for age, sex, ethnicity, DM duration, BMI, mean arterial pressure, HbA_{1c}, triglycerides, insulin, GLP-1, anti-hypertensives, total cholesterol, high-density-lipoprotein cholesterol, lipid-lowering treatment, anti-platelets, oral DM agents, alcohol and smoking - After 2.5 years follow-up: **linear regression showed OSA predicted study end MDRD eGFR (β=-3.8, p=0.04) and AHI associated with study end MDRD eGFR (β=-4.6, p=0.02).** Adjusted for age, DM duration, ethnicity, sex, BMI, mean arterial pressure, anti-hypertensive agents, HbA_{1c}, insulin, oral DM agents, total cholesterol, lipid lowering treatments, antiplatelet agents and smoking. - No association between minimum O_2 and study end eGFR (effect size not reported)
Tanaka 2009[a][‖] (Japan)[21]	CS	904 T2DM	Setting = Multicenter diabetes clinics Mean age = 62 years* Females = 33% Mean BMI = 25.3 Kg/m^2	Mean HbA_{1c} = 6.9% Mean DM Duration = 10.3 years*	Oximetry 3% ODI ≥ 5 events/hr	*Multivariate analysis* - **Association between OSA and creatinine (OR 2.37, 95% CI: 1.21 to 4.65)** Adjusted for age, gender, BMI, heart rate and hypertension.
Zhang R 2014[a][‖]	CS	884 T2DM	Setting = Multicenter Mean age = NA	Mean HbA_{1c} = NA	Single channel recording device	*Multivariate analysis* - **Association between OSA severity**

(China)[23]			Females = NA Mean BMI = NA	Mean DM Duration = NA	OSA = AHI >5 events/hr	**and stages of diabetic kidney disease (OR 1.18, 95% CI: 1.03 to 1.34)** **- Linear association between AHI and serum creatinine (b=3.49, p=0.024)** **- Linear association between AHI and microalbuminuria (b=3.49, p=0.024)** Adjusted for age and gender
Zhang R 2015[‖] (China)[22]	CS	472 T2DM	Setting = Multicenter inpatient Mean age = 55 years Females = 32% Mean BMI = 26.5 Kg/m^2	Mean HbA1c = 9.1% Mean DM Duration = 7.0 years	Level III sleep test (ApneaLink)~ OSA = AHI ≥ 5 events/hr	*Univariate analysis* - No association between albuminuria and OSA (OR 1.56, 95% CI: 0.80 to 3.03)

NA=information not available, HbA$_{1c}$=glycosylated haemoglobin A$_{1c}$, DM=Diabetes mellitus, BMI=body mass index, CS = cross-sectional study, T1DM=Type 1 diabetes mellitus, T2DM=Type 2 diabetes mellitus, OSA=obstructive sleep apnea, PSG=polysomnography, ODI=oxygen desaturation index, AHI=apnea-hypopnea index, O$_2$=oxygen saturation, eGFR=estimated glomerular filtration rate, MDRD=modification of Diet in Renal Disease, CKD-EPI=chronic kidney disease Epidemiology Collaboration, IHD=ischemic heart disease, RAS=renin-angiotensin system, GLP-1=glucagon-like peptide-1.

[‡]PSG data did not have data on effort; [#]Minimum 4 hours recording; [$]Veteran study with low female participants; [*]Average values from 2 groups;

[a] Conference abstracts; [‖] Prevalence studies; ~Portable home sleep study. Bolded texts represent significant results.

Table 2: Quality assessment of included studies

| Study	Selection bias	Methods and measurement	Blinding	Study design	Analysis	Overall
			Components			
Buyukaydin 2012[7]	Weak	Strong	Weak	Weak	Weak	Weak
Furukawa 2013[8]	Weak	Moderate	Weak	Weak	Strong	Weak
Kosseifi 2010[24]	Weak	Weak	Weak	Moderate	Weak	Weak
Laaban 2009[18]	Moderate	Strong	Weak	Moderate	Weak	Moderate
Langand 2014[17]	Weak	Weak	Weak	Weak	Weak	Weak
Leong 2014[9]	Strong	Strong	Strong	Moderate	Strong	Strong
Schober 2011[19]	Weak	Moderate	Weak	Strong	Weak	Weak
Storgaard 2014[20]	Weak	Moderate	Weak	Strong	Weak	Weak
Tahrani 2013[16]	Weak	Strong	Weak	Strong	Strong	Strong
Tanaka 2009[21]	Moderate	Moderate	Weak	Weak	Strong	Moderate
Zhang 2014[23]	Weak	Weak	Weak	Weak	Moderate	Weak
Zhang 2015[22]	Weak	Moderate	Weak	Weak	Weak	Weak
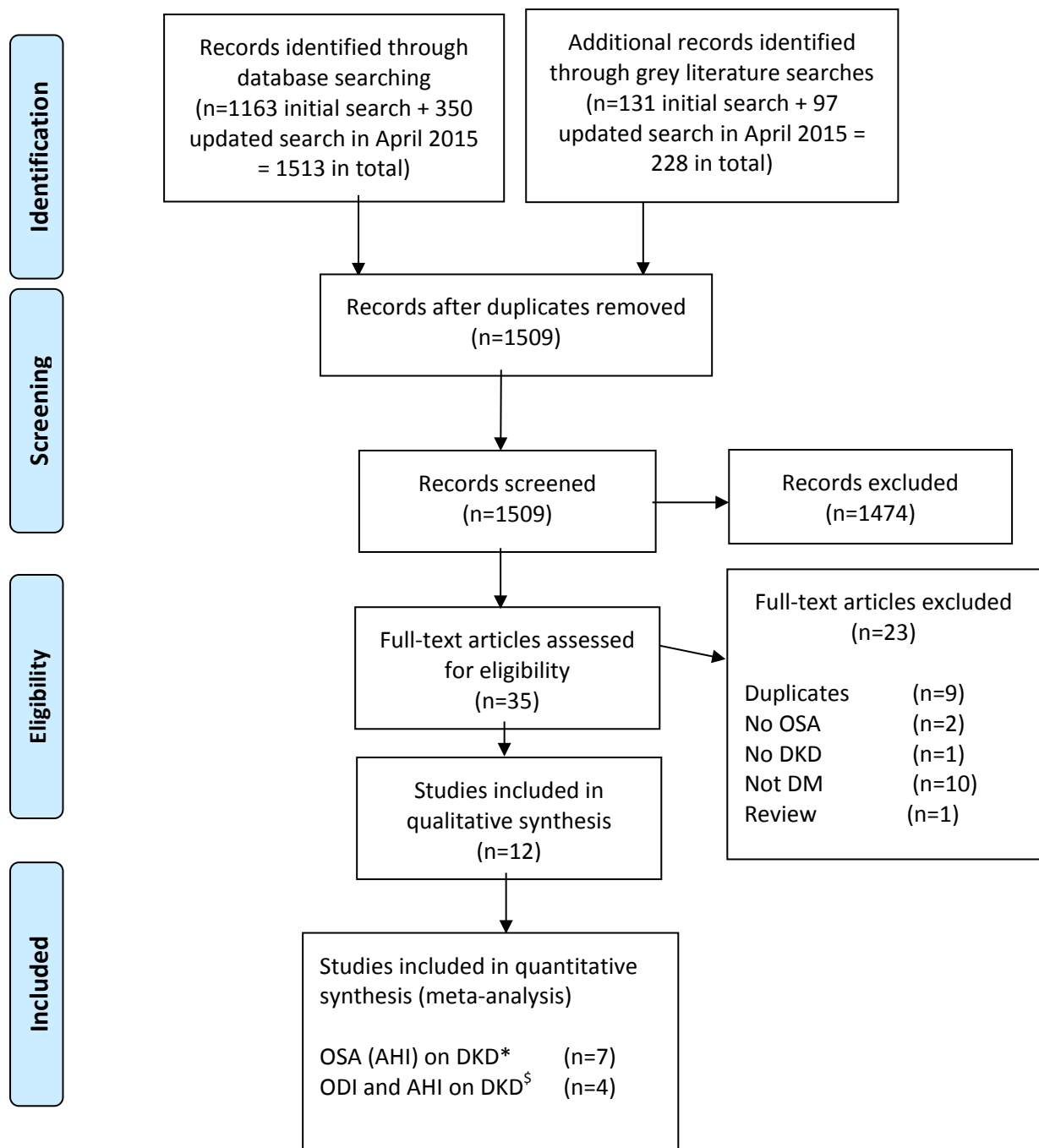
Figure 1: PRISMA flow chart on study selection

OSA = obstructive sleep apnea; DKD = diabetes kidney disease; DM = diabetes mellitus

*Meta-analysis carried out in 7 studies which reported on unadjusted odds ratios

$Meta-analysis carried on 4 studies which reported on adjusted odds ratios
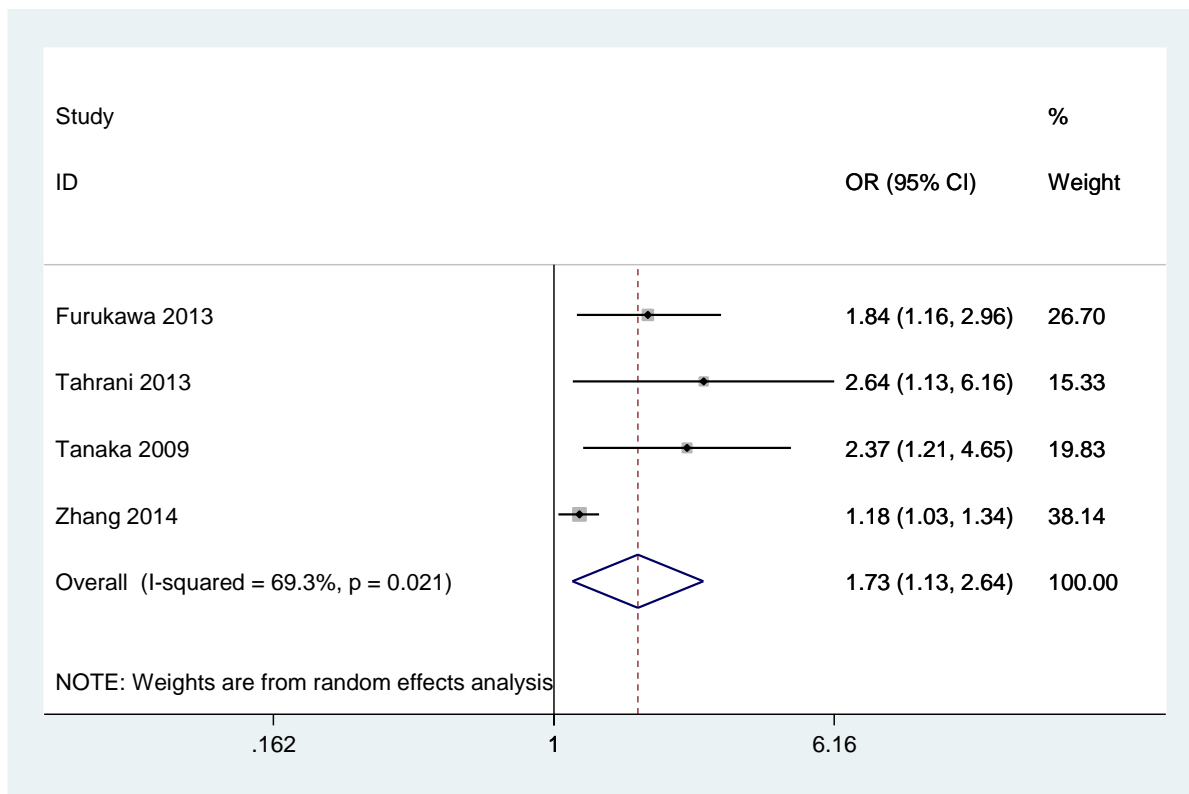
Figure 2: Forest plot of the ==association between obstructive sleep apnea (OSA)== and diabetic kidney disease using results from studies which reported adjusted odd ratios and 95% confidence intervals. Note: Furukawa 2013[8] and Tanaka 2009[21] diagnosed OSA using 3% ODI ≥5events/hr whilst Tahrani 2013[16] and Zhang 2014[23] diagnosed OSA based on AHI ≥5events/hr.