



# A meta-analysis of cohort studies including dose-response relationship between shift work and the risk of diabetes mellitus

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Received: 7 April 2019 / Accepted: 4 September 2019 / Published online: 11 September 2019  
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## Abstract

Previous reviews have suggested that shift work is associated with an increased risk of diabetes mellitus (DM); however, the results should be interpreted with caution due to differences in study designs and non-comprehensive literature searches. In addition, the quantitative dose-response relationship between years of shift work and DM risk is still unknown. We aimed to conduct an updated meta-analysis with cohort studies and to evaluate the relationship between the duration of shift work and the risk of DM in a dose-dependent manner. The PubMed and Web of Science databases were searched through 15 August 2019, and multivariate-adjusted relative risks (RRs) were pooled using random-effects models. Restricted cubic spline analysis with three knots was used to explore the relationship of years of shift work and risk of DM. Twelve cohort studies with 28 independent reports involving 244,266 participants and 15,906 DM cases were included. The summarized adjusted RR for the relationship between shift work and DM risk was 1.14 (95% CI 1.10 to 1.19;  $I^2 = 38.9\%$ ,  $P = 0.028$ ). The summary RR of a 5-year increase in shift work was 1.07 (95% CI 1.04 to 1.09), without heterogeneity ( $I^2 = 0.0\%$ ,  $P = 0.829$ ) for the female population. Shift work is associated with an increased risk of DM, and a strong and highly significant linear dose-response relationship between the duration of shift work and the risk of DM in women was observed. Further studies are needed to confirm the results, establish causality and elucidate the underlying mechanisms.

**Keywords** Shift work · Diabetes mellitus · Cohort · Meta-analysis · Dose-response relationship

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Dongming Wang and Zuxun Lu have contributed equally to this work.

**Electronic supplementary material** The online version of this article (<https://doi.org/10.1007/s10654-019-00561-y>) contains supplementary material, which is available to authorized users.

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## Introduction

Shift work, an occupational hazard factor involving irregular or unusual hours including night work and rotating shifts, is as common as smoking in Western countries, especially in Europe and North America. Shift work has been a potential health implication linked with sleep disorders, fatigue, metabolic disorders and a number of chronic

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diseases [1, 2], such as specific cancers [3, 4], cardiovascular diseases [5], metabolic syndrome [6], dementia [7] and diabetes mellitus (DM).

At present, many epidemiological studies on the relationship between shift work and DM risk have been conducted, and a previous systematic review [8] published in 2014 showed moderate evidence on an association between shift work and type 2 diabetes; another meta-analysis [9] that includes research up to April 2014 synthesized the association of shift work with DM risk. However, only seven cohort studies were included in the meta-analysis, and significant heterogeneity was observed ( $I^2=52.9\%$ ). In addition, two studies published in 2012 [10] and 2009 [11] were lost in the study, which may affect the reliability of the results. Moreover, most cohort studies before 2014 did not report risk estimates of different durations of shift work for DM risk, which were essential for dose-response analysis. Thus, it is still unknown how different quantities and years of shift work affect the risk of DM.

Therefore, this updated meta-analysis aims to comprehensively explore the relationship between shift work and the risk of DM; it includes a quantitative Dose-response method.

## Methods

### Search strategy and selection criteria

We identified published studies through PubMed and Web of Science from inception to August 15, 2019. “Diabetes”, “diabetes mellitus”, “type 2 diabetes”, “shift work”, “work shift”, and “night work” were used as medical subject heading terms in accordance with the MOOSE guidelines [12]. We did not apply any language restrictions. In addition, we searched the reference lists for all identified relevant original publications and relevant reviews.

Studies were identified on the basis of predefined inclusion criteria: the study design was cohort, the exposure of interest was shift work, the outcome was DM event, and the investigators reported relative risks (RRs) or hazard risks (HRs) with 95% confidence intervals (CIs). Additionally, non-human studies, clinical trials, cross-sectional studies, case-control studies, reviews, letters without sufficient data, and studies that examined other associations were excluded. If study populations were reported more than once, we used the result with the longest follow-up duration. After excluding duplicate studies, two investigators (WZL and DMW) independently reviewed all remaining articles by titles and abstracts and then by full texts. Any discrepancy between the two investigators was solved by discussion with the senior investigator (ZXL).

### Data extraction and quality assessment

Two investigators (WZL and DMW) participated in the collection of data for this meta-analysis. We extracted the following information from each eligible article: name of the first author, year of publication, follow-up time, study location (country), number of participants and DM events, sex and age of the study participants, definition and category of shift work, method of DM ascertainment (assessed by self-reports, death certificates, clinical examinations, or medical records), and covariates included in the adjusted models. We also extracted relevant data (number of participants or cases, RRs and 95% CIs) from text, figures, and tables.

Quality assessment was performed independently by two investigators (WZL and WYR) according to the Newcastle-Ottawa Quality Assessment Scale (NOS) [13], which is a validated scale for nonrandomized studies in meta-analyses. This scale awards a maximum of 9 points to each study: 4 for selection of participants and measurement of exposure, 2 for comparability of cohorts on the basis of the design or analysis, and 3 for assessment of outcomes and adequacy of follow-up. We designated scores of 0–3, 4–6, and 7–9 as low-, moderate-, and high-quality studies, respectively. When studies had several adjustment models, we extracted those that reflected the maximum extent of adjustment for potentially confounding variables.

To perform a Dose-response meta-analysis, we assigned the median or mean years of shift work in each category of duration to the corresponding RR for each study. If the mean or median duration per category was not reported, the midpoint of the upper and lower boundaries in each category was assigned. When the category was open-ended, we assumed that the years of shift work according to the open-ended \*1.2 times. Owing to the distinct cut-off points for categories in different articles, we computed an RR with a 95% CI for an increased duration of 5 years for each report.

### Statistical analysis

In this meta-analysis, the RRs and 95% CIs were considered to be the effect size for all studies, and the HRs were deemed equivalent to RRs. Any results stratified by sex, type or duration of shift work were treated as independent reports. The study consisting of two separate cohorts was also considered as two independent reports. Forest plots were produced to visually assess the RRs and corresponding 95% CIs across studies.  $I^2$  values were used to evaluate the heterogeneity across studies: values of 0–25% represented minimal heterogeneity, 26% to 75%

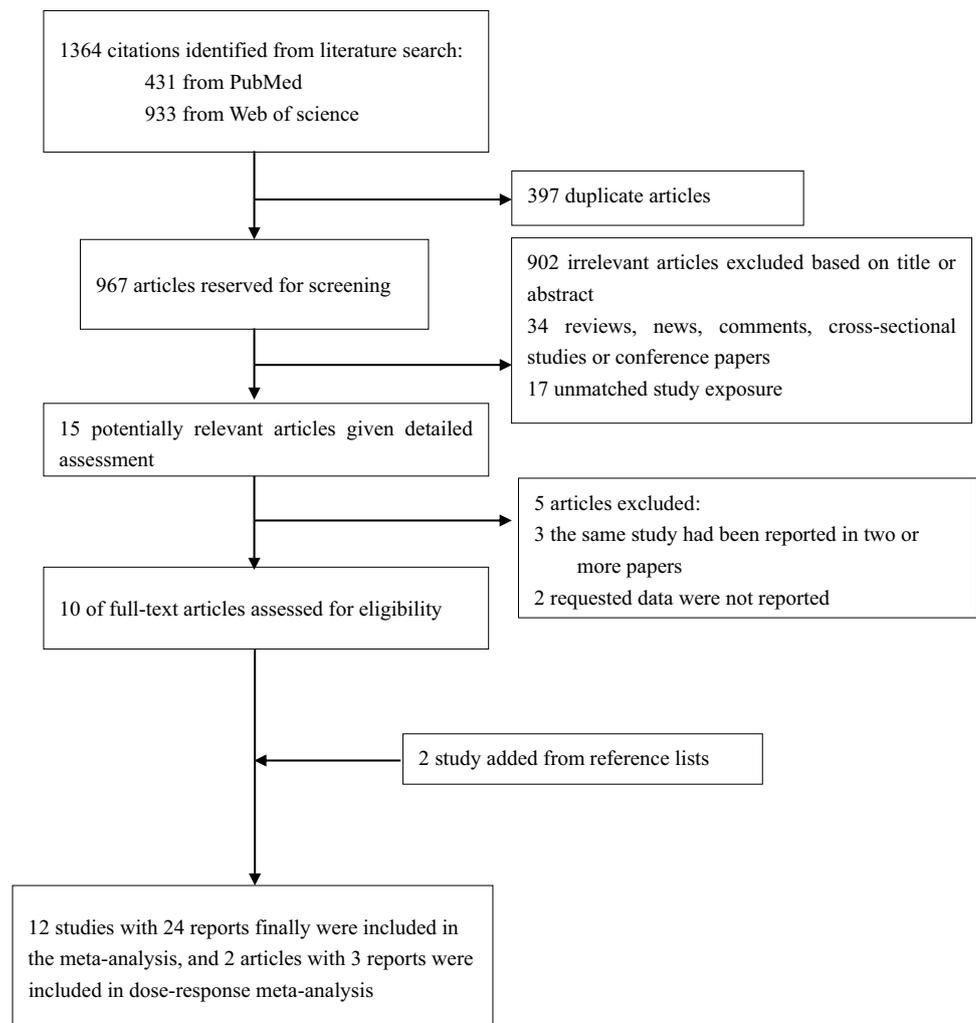
represented moderate heterogeneity, and greater than 75% represented substantial heterogeneity [14]. Approximately  $I^2 > 50\%$  was considered significant. Summary estimates of the RR/HR were performed using the Mantel–Haenszel random-effects models, which considered both within- and between-study variation [15].

Reports with RRs or HRs for at least three quantitative categories for duration of shift work were included in the Dose-response meta-analysis, and a fixed-effects Dose-response relationship described by Greenland and Longnecker [16] was used to calculate the trend from the correlated estimates for logRR across categories of shift work. The distributions of cases and participants and RRs and 95% CIs in each shift work category were extracted according to this method. In addition, we evaluated a potential curvilinear association between the years of shift work and the risk of DM using restricted cubic splines

with three knots at the 10th, 50th, and 90th percentiles of the distribution. The  $P$  value for non-linearity was calculated by testing the null hypothesis that the coefficient of the second spline is equal to zero.

Subgroup analyses were conducted that were stratified by age, location, follow-up time, and shift schedule and that were adjusted for age, BMI, physical activity, drinking, smoking, blood pressure, physical activity and history of diabetes mellitus. Publication bias was evaluated by inspection of the funnel plots for asymmetry with Egger's test and Begg's test [17, 18]. The trim-and-fill method was used to assess the impact of any potential publication bias [19]. Additional sensitivity analyses were performed by omitting one study at each time to test the robustness of the results and the influence of an individual study on heterogeneity. All statistical analyses were performed with Stata version 12.0 (Stata Corp, College Station, TX), and all tests were two sided with a significance level of 0.05.

**Fig. 1** Flow chart for the selection of eligible studies



## Results

### Study selection

Figure 1 shows the results of the literature research and study selection: 431 articles from PubMed and 933 articles from Web of Science prior to 15 August 2019. After the exclusion of duplicates and studies that did not fulfil the inclusion criteria, 15 remaining articles seemed to be relevant for this meta-analysis. After evaluating the full texts of these 15 publications, three articles were excluded because the same study had been reported [20–22], one article was excluded owing to lack of sufficient data [23, 24], and another two articles were retrieved from references lists [10, 11]. Finally, 12 articles were included in our meta-analysis. The quality score ranged from 7 to 9 with a median score of 8 for all cohorts, which suggested that the studies included in the meta-analysis were of high quality.

### Study characteristics and quality assessment

The main characteristics of these 12 eligible cohort studies with 24 independent reports are summarized in Table 1. The duration of follow-up ranged from 6.6 to 24 years. All studies were published between 1999 and 2018; two studies were conducted in Sweden [25, 26], four in Japan [10, 27–29], one in Belgium [30], two in the US [31, 32], two in Denmark [33, 34] and one in Germany [11]. The study in 2018 [32] included two cohorts—the Nurses' Health Study (NHS I) and the Nurses' Health Study II (NHS II). One cohort [31] reported the former shift work and different years of shift work; one cohort [29] reported two types of shift work (two-shift and three-shift); and one [33] reported evening shift, night shift and rotating shift, respectively. All studies used non-shift day workers as the referent category. The quality score of the included studies was 8 in nine studies and 7 in three studies with a median score of 8 for all cohorts, which suggested that the studies included in the present meta-analysis were of high quality.

### Association between shift work and risk of DM

Twelve cohort studies with 24 independent reports (involving 244,266 participants and 15,906 DM cases) were included in the association between shift work and risk of DM, and ten reports from 6 studies suggested a positive relationship between shift work and DM risk. The multivariable-adjusted relative risk of DM was 1.14 (95% CI 1.10 to 1.19) when shift workers were compared with

non-shift day workers using the random-effects model. We observed moderate heterogeneity among studies ( $I^2 = 38.9\%$ ,  $P = 0.028$ ) (Fig. 2).

### Dose-response analysis between years of shift work and DM risk

Three reports from two studies [31, 32] (involving 171,451 female participants and 12,701 DM cases) were included in the Dose-response meta-analysis. A curvilinear association was not found ( $P = 0.710$  for non-linearity); thus, generalized least squares for trend estimation of summarized Dose-response with a two-stage fixed-effect model assuming linearity was used to explore the relationship between years of shift work and DM risk. The summary risk estimates of DM for an increment of 5 years of shift work was 1.07 (95% CI 1.04 to 1.09) without heterogeneity ( $I^2 = 0.0\%$ ,  $P = 0.829$ ) (Fig. 3, Fig. S1).

### Subgroup analyses and sensitivity analyses

To explore the potential source of heterogeneity among the studies and examine the stability of the primary results, we conducted subgroup analyses by sex, location, follow-up time, shift schedule, whether adjustment for age, BMI, blood pressure, smoking, drinking, physical activity and history of diabetes mellitus. The associations of years of shift work with risk of DM were similar in subgroup analyses, which is shown in Table 2. Subgroup analysis by shift schedules indicated that different types of shift were all associated with an increased risk of DM. In addition, we conducted a sensitivity analysis to evaluate the effect of each study on the overall estimate by sequentially excluding one study in turn, which showed that none of individual studies could probably influence the summary of risk estimates in the present study (Fig. S2).

### Publication bias

Visual inspection of the funnel plot showed some asymmetry (Fig. 4). Both Egger's and Begg's tests suggested evidence of publication bias (Begg's Test:  $z = 2.48$ ,  $P = 0.014$ ; Egger's test:  $t = 4.30$ ,  $P < 0.001$ ). We used the trim-and-fill method to evaluate the effect of any potential publication bias and found that eight potentially missing studies could be needed to obtain funnel plot symmetry for DM risk (Fig. 5). The corrected RR using the trim-and-fill method was 1.12 (95% CI 1.07 to 1.17; random-effects model,  $P = 0.001$ ), which indicated that the correction for potential publication bias did not materially alter the pooled RR.

**Table 1** Characteristics of studies included in the meta-analysis

Study	Publication year	Country	Age	Sex	Follow-up	Definition of shift work	Type of work	Case ascertainment	Number of participants	Number of cases	Adjustment for covariates	Study quality
Teratani T et al.	2012	Japan	Mean = 42.3	Male	8	Job schedule type (Day-time, shift work)	Steel company	HbA1c $\geq$ 6.1% or taking any antidiabetic medication	8423	495	Tobacco consumption, alcohol consumption, age, BMI, mean arterial pressure, total serum cholesterol, aspartate aminotransferase, and creatinine	7
Suwazono Y et al.	2006	Japan	Day shift mean = 35.1 (9.9) alternating shift mean = 37.4 (8.8)	Male	6.69	Based on payment records for March of each year and was divided into day shifts, evening shifts, and night shifts.	Steel company	Diabetes identified through medical records and confirmed based on anglycated hemoglobin A1c $\geq$ 6.0% or medication	5629	246	BMI, blood pressure, cholesterol, creatinine, $\gamma$ -GTP, uric acid, drinking, Smoking, and exercise	8
Oberlinner C et al.	2009	Germany		38 Male	11	Fast-forward rotating 12-hour shifts with the day shift beginning at 06:00 h and the night shift at 18:00 h.	BASF production, research, and administrative employees	Hospital records or internal diagnostic findings	14,128	579	Age, job level, cigarette smoking, and alcohol intake.	8
Hansen AB et al.	2016	Danish	$\geq$ 40	Female	15	Question: Do you normally work in: (a) day, (b) evening, (c) night or (d) rotating shifts	Nurse organization	Record of diabetes in Diabetes Register, or date of death or emigration in CPR register	19,873	837	Age, smoking status, smoking intensity, physical activity, alcohol consumption, intake of fatty meat, marital status, employment status, acute myocardial infarction, hypertension, fruit, vegetables intake and BMI	8
Kawakami N et al.	1999	Japan	18–60	Male	8	Two or three shift work schedules including night shift, with a weekly clockwise rotation	Electrical company	Self-report and confirmed by WHO criteria	2194	34	Age, education, occupation, work time, job strain, social support, use of technology, BMI, alcohol consumption, smoking, physical activity, family history of DM	8

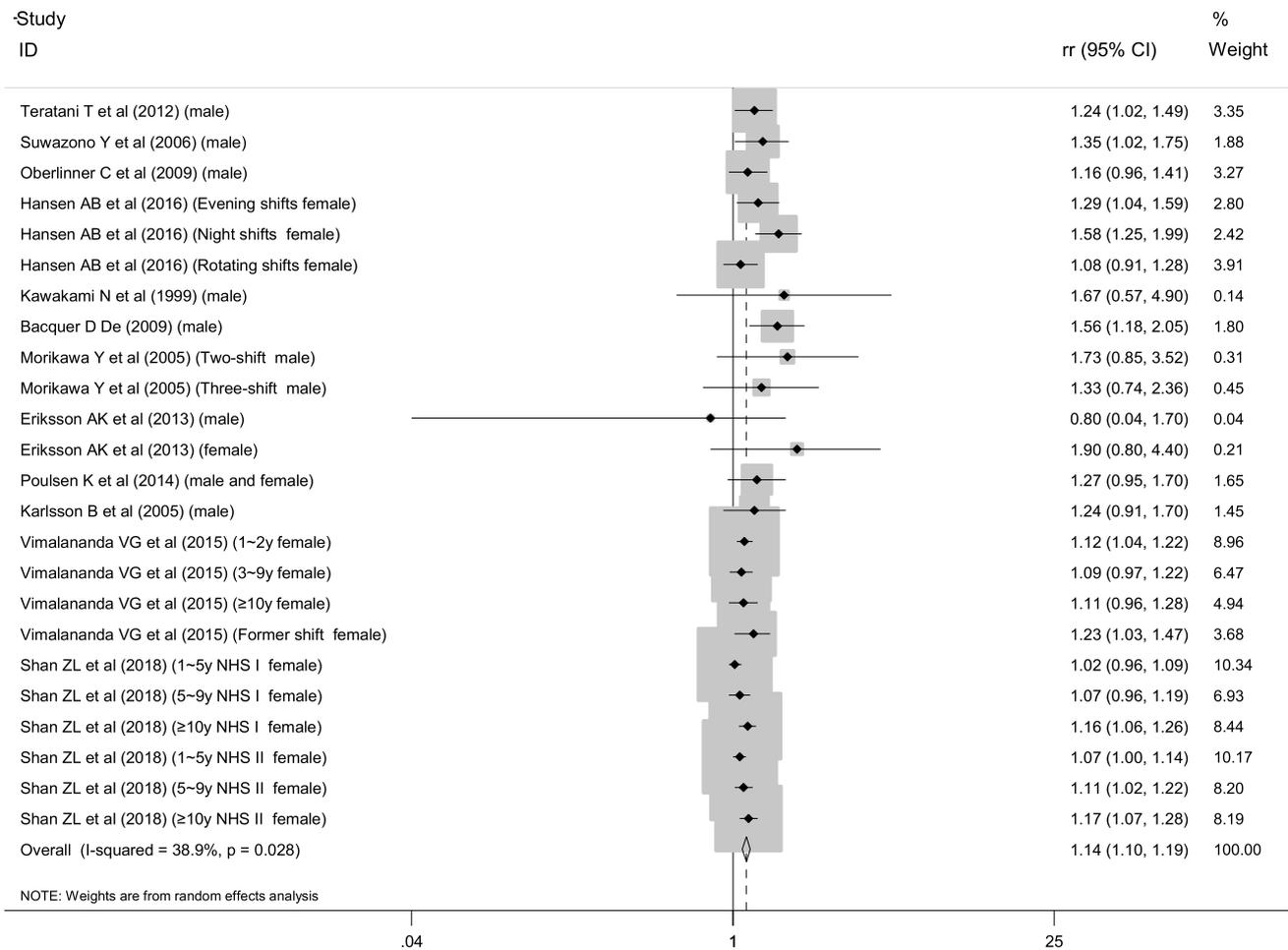
Table 1 (continued)

Study	Publi- cation year	Country	Age	Sex	Follow- up	Definition of shift work	Type of work	Case ascertain- ment	Number of par- ticipants	Num- ber of case	Adjustment for covariates	Study quality
Bacquer D De	2009	Belgium	35–59	Male	6.6	Shift workers worked in two or three rotat- ing shifts	Workers from nine different companies or public administra- tions in Belgium	Type 2 diabetes identified through self- reports and confirmed by a modification of the criteria of the Interna- tional Diabetes Federation	1529	364	Age, waist circumference, diastolic blood pressure and HDL cholesterol at the initial examination	8
Morikawa Y et al.	2005	Japan	19–49	Male	8	Rotating two-shift workers did day shifts and evening shifts, and three-shift workers did three-shift continuous (counter- clockwise) and three- shift non- continuous	Blue- and white- col- lar workers in sash and zipper factory	Diabetes identi- fied through health exami- nation and medical records and confirmed based on an HbA1c of $\geq 6.1$ or clinical judgment of hospital physi- cians	2860	87	Age, body mass index, family history of DM, health-related behavior, habitual drinking, lack of physical exercise	8
Eriksson AK et al.	2013	Sweden	35–56	Male and female	8–10	Did you do shift work?	Community- based population	Type 2 diabetes identified through self-report and medical checkup and confirmed by WHO criteria	5432	149	Age, sex, educational level, psychological distress, family history of DM, BMI, physical activity, smoking, and civil status	8
Poulsen K et al.	2014	Danish	30–69	Male and female	7	Self-reported, evening work, night work, and day work	Eldercare service employees	Self-reported and confirmed by a validated supplementary questionnaire including 6 items	7305	256	sex, age, ethnicity, family history of DM, work status, health status, BMI, physical activity, and smoking	7

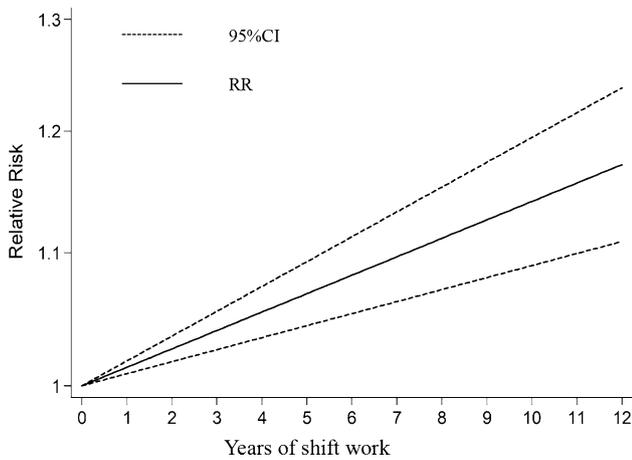
**Table 1** (continued)

Study	Publi- cation year	Country	Age	Sex	Follow- up	Definition of shift work	Type of work	Case ascertain- ment	Number of par- ticipants	Num- ber of case	Adjustment for covariates	Study quality
Karlsson B et al.	2005	Sweden	10–59	Male	22	Job title and workplace character- istics	Pulp and paper manu- facturing plants	Diabetes mortal- ity identified by medical records was confirmed by death certifi- cate diagnosis in the primary or contributory cause-of death fields based on ICD-6–10 codes or Diag- nosis Related Group codes	5442	158	Age, duration of employment	7
Vimalamanda VG et al.	2015	US	21–69	Female	8	Have you ever worked a night shift (graveyard shift, Mid- night to 8 AM)?	Subscribers of Essence, members of several African American profes- sional orga- nizations	Self-report	28,041	1786	Age, questionnaire cycle, family history of DM, education, neigh- borhood socioeconomic status, vigorous activity levels, smok- ing, alcohol, energy intake, dietary pattern, coffee, caffeinated coffee, soda consumption, and diet soda consumption, and BMI	8
Shan ZL et al.	2018	US	30–55	Female	24	“What is the total number of years dur- ing which you worked rotating night shifts (at least three nights per month in addition to days/ evenings in that month)?	Nurse	Self-report and confirmed by a validated supplementary questionnaire according to the National Diabetes Data Group criteria.	55,324	5474	Age, calendar year, ethnicity, marital status, living status, family history of DM, menopausal status, oral contraceptive use, alcohol drinking, total energy intake, smoking status, physical activity, Alternate Healthy Eating Index score, and BMI	8
Shan ZL et al.	2018	US	25–42	Female	22				88,086	5441		

**Inclusion criteria:** The study design was cohort, the exposure of interest was shift work, the outcome was DM event, and the investigators reported relative risks (RRs) or hazard risks (HRs) with 95% confidence intervals (CIs). **Exclusion criteria:** non-human studies, clinical trials, cross-sectional studies, case-control studies, reviews, letters without sufficient data, and studies that examined other associations. If study populations were reported more than once, we used the result with the longest follow-up duration. **Keywords:** diabetes, diabetes mellitus, type 2 diabetes, shift work, work shift, and night work



**Fig. 2** Pooled random effects RR and 95% CIs for the association of shift work and diabetes mellitus



**Fig. 3** Dose-response relationship plot between years of shift work and risk of diabetes mellitus

### Discussion

The present meta-analysis brought together and reanalyzed 244,266 individual participant data points for 15,906 cases with DM based on 12 cohort studies from 6 countries. We identified a clear and significant trend of increased DM risk with shift work in this study. Compared with individuals who had never been exposed to shift work, the risk of DM was increased by 14% for shift workers, and the relationship remained significant in most subgroup analyses. Our study thus could provide suggestions for companies' management schemes to protect the health of workers. Our study showed a higher risk of DM than that shown in Gan Y's study [9], in which the risk of DM increased by 9% for shift workers with seven cohort studies and four cross-sectional studies.

**Table 2** Subgroup analysis RR of diabetes mellitus

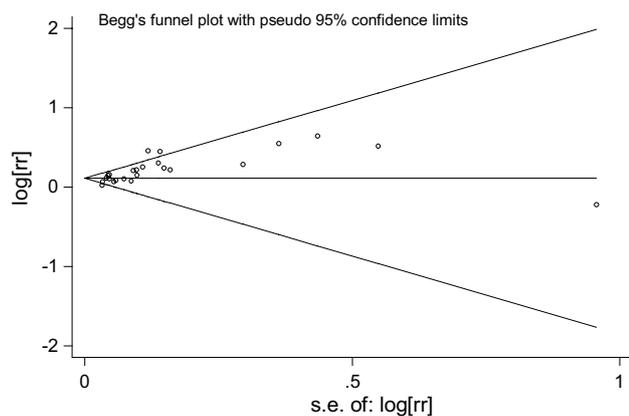
	No. of reports	RR	95% CI	$I^2$ (%)	$p$ value for heterogeneity
<i>Sex</i>					
Male	9	1.28	1.16 to 1.42	0.0	0.814
Female	14	1.21	1.08 to 1.17	46.9	0.027
Both	1	1.27	0.95 to 1.67	–	–
<i>Location</i>					
Asia	5	1.3	1.13 to 1.50	0.0	0.886
Europe	9	1.28	1.15 to 1.42	27.0	0.204
North American	10	1.10	1.06 to 1.14	20.6	0.253
<i>Follow-up</i>					
≥ 10	13	1.13	1.07 to 1.19	49.5	0.022
< 10	11	1.17	1.10 to 1.24	9.10	0.357
<i>Shift schedule</i>					
Rotating shift	10	1.11	1.06 to 1.16	48.2	0.072
Day shift	1	1.24	1.02 to 1.49	–	–
Night/evening shift	7	1.19	1.09 to 1.30	52.2	0.063
Mixed/unsure shift	6	1.31	1.12 to 1.54	0.0	0.953
<i>Controlling age in models</i>					
Yes	22	1.14	1.09 to 1.18	39.1	0.032
No	2	1.28	1.09 to 1.49	0.0	0.613
<i>Controlling BMI in models</i>					
Yes	21	1.13	1.09 to 1.18	36.1	0.051
No	3	1.29	1.08 to 1.54	33.5	0.222
<i>Controlling physical activity in models</i>					
Yes	20	1.13	1.09 to 1.17	36.7	0.052
No	4	1.26	1.12 to 1.41	1.50	0.385
<i>Controlling drinking in models</i>					
Yes	19	1.13	1.09 to 1.17	38.1	0.048
No	5	1.37	1.16 to 1.62	0.0	0.666
<i>Controlling smoking in models</i>					
Yes	22	1.13	1.09 to 1.17	33.3	0.066
No	2	1.41	1.13 to 1.76	14.1	0.281
<i>Controlling blood pressure in models</i>					
Yes	6	1.31	1.16 to 1.48	45.5	0.102
No	18	1.10	1.07 to 1.13	2.70	0.423
<i>Controlling family history of DM in models</i>					
Yes	15	1.10	1.07 to 1.14	10.5	0.335
No	9	1.27	1.17 to 1.39	21.0	0.257

BMI body mass index, DM diabetes mellitus

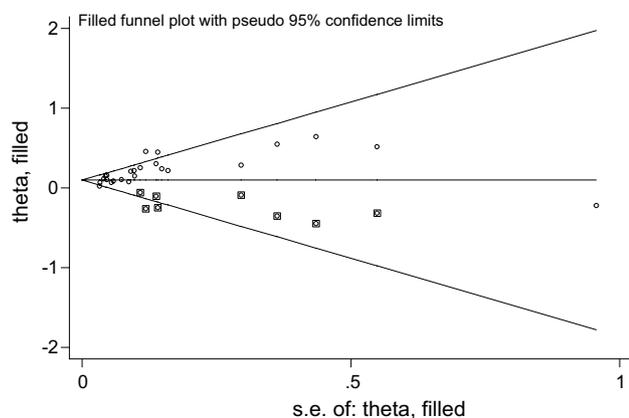
Our study may be more reliable due to limited cohort studies with high quality scores and lower heterogeneity across studies.

The Dose-response meta-analysis demonstrated that an increase in shift work of 5 years was associated with a 7% increase in the risk of DM, and the result was higher than that found in Pan A's study, which indicated that every 5-year increase of rotating night-shift work was associated

with a 5% elevated risk of type 2 diabetes [21]. However, our study was a meta-analysis that summarized more participants and could provide more information. To our knowledge, our study is the first Dose-response meta-analysis to evaluate the association between the duration of shift work and the risk of DM. The results revealed that shift work could probably increase the risk of DM in a Dose-response manner among women. The cut-off points for years of shift



**Fig. 4** Funnel plot for studies of shift work in relation to diabetes mellitus risk. The horizontal line represents the summary effect estimates, and the diagonal lines represent pseudo-95% CI limits



**Fig. 5** Filled funnel plot of RR from studies that investigated the association between shift work and the risk of diabetes mellitus. The circles alone are real studies and the circles enclosed in boxes are 'filled' studies

work were according to the report of the original studies, and we computed an RR with 95% CI for an increased year of shift work for each record. The duration of 5 years was merely a form of expression, and if it had been replaced by a duration of 1 year or 10 years, the value of RR would have changed accordingly while the significance would have remained the same.

The mechanisms linking shift work and DM risk may involve circadian rhythms in physiology and behavior [35], including the disturbance of the chronobiological rhythms [36], lower melatonin production [37], changes in blood pressure and blood lipids [30], worsening health-related lifestyle factors [38], activation of the stress system [39], insulin resistance [40, 41] and suppression of the gonadal, growth hormone and thyroid axes [42], which has been discussed in detail in previous publications [36, 43, 44].

There are several strengths in the present study. First, we included only cohort studies with high quality scores, which could ensure the accuracy of the results. Second, we conducted a Dose-response analysis to evaluate the association between shift work and the risk of DM, allowing us to quantify the linear relations. In addition, detailed subgroup analyses and publication bias analyses were conducted to evaluate the robustness of the pooled risk estimates, which reinforced the stability and reliability of the findings.

A few potential limitations of the present meta-analysis should also be noted. First, the definitions of shift work in all included studies were not consistent. Second, the type of shift work may change during the follow-up, but it was investigated one or two times in most studies. Third, adjusted confounding factors varied in the included studies, and it was unclear whether the adjusted RRs were actually valid. Finally, only three cohort studies were included in the Dose-response meta-analysis and were limited to women in the US, and it was still unclear whether the trend was similar in men or in other countries. Therefore, the results should be further confirmed by more studies conducted in different populations from other countries.

## Conclusions

In conclusion, our meta-analysis shows that shift work is an important risk factor for DM, and years of shift work is associated with an elevated risk of DM in a Dose-response manner in the female population. Additional prospective large-scale studies conducted in more countries or populations are needed to establish causality and elucidate the underlying mechanisms.

**Author contributions** WZL proposed the study. WZL, DMW and WYR performed the searching, data extraction, and quality assessment. ZXL helped to develop search strategies. WZL analyzed the data. WZL wrote the first manuscript; DMW, ZLC and GLY revised the draft. All authors contributed to reviewing or revising the paper and read and approved the final version.

**Funding** The study was supported by the Young Scientists Fund of the National Natural Science Foundation of China (81903291), the Fundamental Research Funds for the Central Universities (2019kfyXJJS032), China Postdoctoral Science Foundation (2019T120666), and Key project of Wuhan Municipal Health Committee (WG16B08). The funding source had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

## Compliance with ethical standards

**Conflict of interests** The authors declare no conflict of interest.

**Ethics** Data for the present meta-analysis were acquired through previously published articles, and the study did not involve participants or patients.

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