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REVIEW ARTICLES

Shift work and health outcomes: an umbrella review of systematic reviews and meta-analyses of epidemiological studies

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Study Objectives: Shift work is commonly increasing, and some physiological changes occur as workers sleep less and their circadian rhythms are disrupted. This umbrella review not only summarizes the evidence but also evaluates the validity of the associations of shift work with different health outcomes.

Methods: We searched the MEDLINE, Web of Science, and Embase databases from their inception to April 25, 2020. For each systematic review and/or meta-analysis, we estimated the summary effect size, the 95% confidence interval, the 95% prediction interval, the between-study heterogeneity, evidence of small-study effects, and evidence of excess-significance bias.

Results: Eight eligible systematic reviews and meta-analyses were identified, providing data on 16 associations. We observed highly suggestive evidence for associations between shift work and myocardial infarction (having ever vs having never done shift work) and diabetes mellitus incidence (per 5-year increment in shift work). Furthermore, we observed suggestive evidence for an association between shift work and diabetes mellitus incidence (having ever vs having never done shift work). Two health outcomes, including prostate cancer incidence (having ever vs having never done shift work and rotating night shift work vs daytime work) and colorectal cancer incidence (longest vs shortest shift work time), were only supported by weak evidence.

Conclusions: This umbrella review found that shift work was associated with several health outcomes with different levels of evidence. Associations for myocardial infarction and diabetes mellitus incidence were supported by highly suggestive evidence.

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Keywords: evidence, health outcome, shift work, umbrella review

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BRIEF SUMMARY

Current Knowledge/Study Rationale: During the past decades, an increasing body of evidence has suggested an association between shift work and several adverse health effects, including metabolic syndrome, overweight, and certain types of cancer. However, current studies on the relationship between these health outcomes and shift work have been inconsistent, making the overall interpretation of the results particularly complex.

Study Impact: Although shift work has been associated with a higher risk of several health outcomes in the literature, we only observed highly suggestive evidence for associations between shift work and myocardial infarction (having ever vs having never done shift work) and diabetes mellitus incidence (per 5-year increment in shift work) and suggestive evidence for an association between shift work and diabetes mellitus incidence (having ever vs having never done shift work). Several other health-related outcomes were inconsistent and showed signs of uncertainty and bias, thus requiring more confirmatory studies in the future.

INTRODUCTION

Shift work refers to a job schedule in which employees work hours other than the normal working schedule of 9 AM to 5 PM;[1] it comprises regular evening or night schedules, rotating shifts, split shifts, on-call or casual shifts, 24-hour shifts, irregular schedules, and other nonday schedules. A report from the International Labor Organization showed that almost 20% of the overall workforce is engaged in a shift work pattern, which is equivalent to nearly 0.7 billion workers globally.[2] It has further been reported that 15%–30% of workers in America and Europe are engaged in different degrees of shift work, and the trend is increasing rapidly.

Shift work forcefully disrupts the normal sleep-wake cycle, leading to short sleep times and excessive fatigue.[3] During the past decades, a growing body of evidence has suggested an association between shift work and several adverse health effects, including metabolic syndrome, overweight, and certain types of cancer.[4–7] In 2016, Kecklund and Axelsson[8] carried out a review summarizing the literature on shift work and its relation to health consequences. They highlighted the associations between shift work and several health outcomes, such as accidents, type 2 diabetes, weight gain, coronary heart disease, stroke, and cancer. However, their study and the previously published literature have not generated clear hierarchies of evidence across those factors, rendering the overall interpretation of the findings particularly complex.

Keeping this information in mind, we carried out an umbrella review of the evidence across existing systematic reviews and

meta-analyses of observational studies to systematically map the evidence of an impact of shift work on health outcomes. Our aim was first to provide an overview of the range and validity of the reported associations of shift work and health outcomes by evaluating whether there is evidence for biases in this literature. The second aim was to pinpoint the number of previously studied associations that have been synthesized with meta-analyses and have shown the strongest evidence. The strength of the evidence supporting these associations and hints of biases were evaluated using standardized approaches.[9]

METHODS

Umbrella review methods

We conducted an umbrella review, ie, a comprehensive and systematic search, which organized and evaluated the existing evidence from multiple systematic reviews and/or meta-analyses on a specific research topic.[10] An umbrella review synthesizes a large number of existing systematic reviews and/or meta-analyses on risk factors, rather than performing these systematic reviews from scratch. The protocol for this study was registered on PROSPERO; the registration number is CRD42020188537. We followed a standardized methodology and reported our findings according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses[11] of Observational Studies in Epidemiology recommendations.[12]

Literature search

Two independent investigators (Q.-J.W. and H.S.) comprehensively searched the published literature using the Web of Knowledge (incorporating Web of Science and MEDLINE) and Embase databases from their inception to April 25, 2020, for systematic reviews or meta-analyses of observational studies that evaluated the evidence of the effects of shift work on health. The search strategy used the keywords[13] ("meta-analysis" OR "systematic review") and ("shift work" OR "work shift" OR "night work" OR "shiftwork" OR "irregular hours" OR "rotating shift" OR "rotating hours"; **Table S1** in the supplemental material). No language restrictions were considered in the selection of eligible studies for this umbrella review. Furthermore, we conducted a manual search of the reference lists of the retrieved articles. A third investigator (Y.-H.Z.) arbitrated any differences that could not be resolved by consensus. Only data from published papers were used, and the study authors were not contacted.

Study selection and exclusion criteria

We included only meta-analyses or systematic reviews of observational studies in humans. Randomized controlled trials were unavailable for our research question. Meta-analyses and systematic reviews were included when they pooled any combination of relative risks, odds ratios (ORs), relative rates, or hazard ratios from studies investigating the association between shift work and any health-related outcome (eg, cardiovascular disease, cancer, death, obesity or overweight, severe mental illness, diabetes, and metabolic diseases). When standardized mean differences were reported, we transformed these estimates into ORs according to the formula suggested by Chinn.[14] Meta-analyses or systematic reviews that did not present study-specific data (risk estimates, 95% confidence intervals, the number of events and control patients, or the total population) were also excluded, as were cross-sectional studies.

If an article presented separate meta-analyses on more than one eligible outcome, then we assessed those separately. When more than 1 meta-analysis presented overlapping datasets on the same outcome, only the meta-analysis with the largest dataset was retained for the main analysis; however, we conducted sensitivity analyses to assess the concordance of the summary associations (direction, magnitude, and significance) in these duplicate meta-analyses. All of the above study selection and exclusion procedures were carried out by 2 independent investigators (Q.-J.W. and H.S.).

Data extraction

Data extraction was performed independently by 2 investigators (H.S. and Z.-Y.W.) using a custom-made data extraction form. Disagreements were re-evaluated by a third investigator (Y.-T.J.). When a meta-analysis or systematic review reported both summarized results and results divided according to subgroups, summarized results were preferred because they had a larger sample size. The following key study characteristics were extracted from each included systematic review and meta-analysis: the first author, publication year, study design, study population, unit of exposure comparison, number of included studies, meta-analysis metrics, total number of patients and control patients (cohort), health outcomes, reported maximally adjusted risk estimates (relative risks, ORs, or hazard ratios), and 95% confidence intervals. If a risk factor was examined in more than 1 level of comparison, then we extracted the data for the comparison with the largest number of component studies. For the primary studies from each systematic review and meta-analysis included in our analysis, the first author, number of patients and control patients (cohort), the maximally adjusted risk estimates (relative risks, ORs, or hazard ratios), and the corresponding 95% confidence intervals were extracted for further analysis (**Table S2** in the supplemental material). Any differences in extracted data between the 2 researchers were resolved by consensus.

Assessment of methodological quality of included studies

The methodological quality of the included meta-analyses was assessed using the validated (A Measurement Tool to Assess Systematic Reviews 2 (AMSTAR 2) instrument by 2 independent investigators (M.Z. and H.-Y.W.). Disagreements were re-evaluated by a third investigator (X.-H.H.). AMSTAR 2 measures 16 items, allows for a more comprehensive evaluation of systematic reviews, and focuses more on systematic reviews that include nonrandomized studies than the first AMSTAR (11 items).[15] AMSTAR 2 has been shown to be a reliable and valid tool for the quality assessment of systematic reviews and meta-analyses of both interventional and observational research,[16,17] which includes ratings for quality in the search, analysis, and transparency of a meta-analysis. For the rating item for the methodological quality of the analysis, we downgraded any

study that had used a fixed- rather than a random-effects model for producing a summary estimate. We considered the random-effects model as the most appropriate to be used in pooling estimates because the heterogeneity in study characteristics meant that we would not expect a single true effect size common to all studies. AMSTAR 2 scores are graded to be of high, moderate, low, or critically low quality.[16]

Statistical analysis

For each exposure and outcome pair, we calculated the summary effect and the 95% confidence interval using fixed- and random-effects methods. Furthermore, 95% prediction intervals for the summary random-effects estimates were reported, which indicated the true effects for 95% of the studies from the population of studies that were summarized or for similar (exchangeable) studies that might be conducted in the future.[18,19]

We used the I^2 statistic as an estimate of the proportion of variance reflecting true differences in effect size. Values exceeding 50% or 75% are considered to represent large or very large heterogeneity, respectively.[20] We assessed whether there was evidence for small study effects with the regression asymmetry test proposed by Egger and colleagues.[21] A P value of .10 or less in the regression asymmetry test with a more conservative effect in the largest study was considered evidence for small-study effects bias.[14]

We applied the excess significance test to investigate whether the observed number of studies with significant results ("positive" studies, $P < .05$) was different from the expected number of significant results. This method has been described in detail in previous studies.[22] Briefly, the expected number of studies with significant results was calculated in each meta-analysis based on the sum of the statistical power estimates for each component study.[22] Because the true effect size for any meta-analysis is unknown, we estimated the power of each component study using the effect size of the largest study in a meta-analysis.[22] The statistical power of each study was calculated with an algorithm from a noncentral t distribution.[23] Excess significance for single meta-analyses was defined at $P < .10$. The observed vs the expected comparison was examined separately for each meta-analysis, and it was also extended to groups, including several meta-analyses, after summing the observed and expected values from each meta-analysis. As described elsewhere, the number of expected positive (ie, significant data sets) studies can be compared with the observed number of significant studies through a chi-square–based test. The larger the difference between the observed and the expected values, the higher the degree of the excess of significance bias.

Association does not necessarily imply causation. For associations with convincing or highly suggestive evidence, we performed a sensitivity analysis, including only prospective cohort studies, to assess whether there was also evidence for the temporality of the association. All analyses were performed using STATA software, version 15 (StataCorp, College Station, TX).

Reviewing the existing evidence

We rated the claimed statistically significant ($P < .05$) associations between shift work and health outcomes as 1 of 5 levels: strong evidence required $P < 10^{-6}$, a number of patients > 1,000, $I^2 < 50\%$, $P < .05$ for the largest study in the meta-analysis, that the 95% prediction interval excluded the null value, the absence of small-study effects ($P > .1$ for the Egger test), and no excess significance bias ($P > .1$); highly suggestive evidence required $P < 10^{-6}$, a number of patients > 1,000, and $P < .05$ for the largest study in the meta-analysis; suggestive evidence required $P < 10^{-3}$ and a number of patients > 1,000; weak evidence required $P < .05$; and nonsignificant associations were those with $P > .05$.

RESULTS

Literature selection

Overall, the parallel reviews identified 1,423 unduplicated publications across 3 databases. After applying the inclusion and exclusion criteria, 8 publications[24–31] were identified and selected for inclusion (**Figure 1** and **Table S3** in the supplemental material).

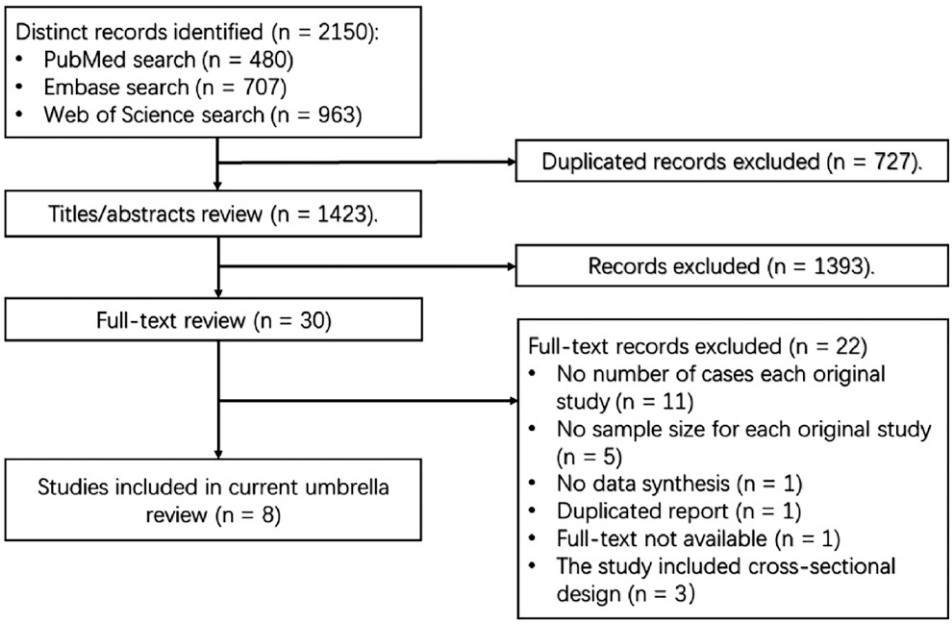
Characteristics of the included systematic reviews and meta-analyses

Overall, 8 eligible publications, including a total of 16 meta-analyses, were identified.[24–31] The publication dates of these 8 publications ranged from 2012–2020. **Table 1** summarizes these 16 independent meta-analyses that included 120 individual study estimates. Of these 120 individual studies, 100 (83%) were cohort studies and 20 (17%) were case-control studies. The median number of patients and populations included in each meta-analysis was 8,365 (range: 1,423 to 17,335) and 458,762 (range: 5,787 to 6,594,319), respectively. All associations included more than 1,000 patients in these 16 meta-analyses. The included studies covered 4 different types of shift work (shift work, rotating-night shift work, fixed-night shift work, and night shift work) and 11 major health outcomes (melanoma skin cancer, diabetes mellitus incidence, prostate cancer incidence, breast cancer incidence, colorectal cancer incidence, myocardial infarction incidence, coronary mortality, cerebrovascular mortality, cardiovascular events, cardiovascular mortality, and all-cause mortality). Two of these studies analyzed the data in a dose-response analysis (diabetes mellitus and prostate cancer incidence per 5-year increment in shift work),[28,30] and the remainder used categories of having ever vs having never done shift work,[24,26–28,30,31] shift work vs daytime work,[29] and the longest vs the shortest shift work time.[25]

Methodological quality assessment results

Table S4 in the supplemental material shows the quality assessment of the included meta-analyses using AMSTAR 2. Of the 8 publications, 1 was of moderate quality,[31] 1 was of low quality,[30] and 6 received a critically low-quality rating.[24–29] The low scores may result from 2 critical domains ("Did the review authors provide a list of excluded studies and justify the exclusions?" and "Did the review authors account for RoB [risk of bias] in individual studies when interpreting/discussing the results of the review?") and several noncritical flaws ("Did the

Figure 1—Flow chart of selection of studies for inclusion in umbrella review on shift work and health outcomes.



review authors explain their selection of the study designs for inclusion in the review?" and "Did the review authors report on the sources of funding for the studies included in the review?").

Summary effect size

With $P < .05$ taken as the threshold for statistical significance, the summary fixed-effects estimates were significant in 9 (56.3%) meta-analyses, whereas the summary random effects were significant in 6 meta-analyses (37.5%) (**Table 2**). At $P < .001$, 7 (43.8%) and 3 (18.8%) meta-analyses produced significant summary results using the fixed- and random-effects models, respectively. At a stricter threshold of $P < 10^{-6}$, we observed significant results of myocardial infarction and diabetes mellitus incidence when comparing having ever with having never done shift work. Furthermore, a significant result was observed for diabetes mellitus incidence in dose-response analyses, regardless of whether fixed- or random-effects models were used. The magnitude of the observed summary random-effects estimates ranged from 0.96 (relative risk) to 1.32 (OR).

The association of the largest study included in each meta-analysis was statistically significant in 5 meta-analyses, and the summary effect size of the largest studies was more conservative than the summary random effects in 11 meta-analyses (**Table 2**).

Between-study heterogeneity and prediction intervals

Half of the studies showed low heterogeneity ($I^2 \leq 50\%$). Four (25%) meta-analyses had large heterogeneity estimates ($50\% \leq I^2 \leq 75\%$), and 4 (25%) other meta-analyses had very large heterogeneity estimates ($I^2 > 75\%$) (**Table 3**). When we calculated the 95% prediction intervals, only 2 meta-analyses excluded null values (myocardial infarction and diabetes mellitus incidence in the cases of having ever vs having never done shift work).

Small-study effects and excess significance bias

Evidence for statistically significant small-study effects (Egger test $P < .10$, and random-effects summary estimate larger than the point estimate of the largest study in the meta-analysis) were found to be present in 6 meta-analyses for health outcomes, including cardiovascular mortality (having ever vs having never done shift work), diabetes mellitus incidence (having ever vs having never done shift work), prostate cancer incidence (having ever vs having never done shift work, per 5-year increment in shift work, rotating-night shift work vs daytime work, and having ever vs having never done night shift work; **Table 3**). Two meta-analyses had evidence of excess significance bias using the largest study estimate for the plausible effect size ($P < .10$), including diabetes mellitus incidence (per 5-year increment in shift work) and myocardial infarction incidence (having ever vs having never done shift work).

Risk factors with strong evidence of association

Each of the health outcomes identified as being associated with shift work was sorted into 1 of 5 groups according to the strength of reported evidence in the observational studies: strong, highly suggestive, suggestive, weak, or nonsignificant associations (**Table 4**). After applying our credibility criteria, 2 health outcomes—myocardial infarction incidence (having ever vs having never done shift work) and diabetes mellitus incidence (per 5-year increment in shift work)—presented a highly suggestive association with shift work, supported by more than 1,000 patients, $P < 10^{-6}$ under the random-effects model, and $P < .005$ of the largest study in the meta-analysis. Only diabetes mellitus incidence regarding having ever vs having never done shift work presented suggestive evidence. Three health outcomes, including prostate cancer incidence (having

Table 1—Main characteristics of included systematic reviews or meta-analyses that evaluate shift work and health outcomes.

Study	Exposure	Outcome	Patients	Sample Size	Study Design	n	Comparison	Effect Metric	Risk Estimate
Yousef et al, 2020[31]	Shift work	Melanoma skin cancer	17,038	3,579,147	Cohort and case-control	11	Ever vs never	RR	1.10 (1.05–1.16)
Li et al, 2019[30]	Shift work	Diabetes mellitus incidence	17,667	244,266	Cohort	24	Ever vs never	RR	1.14 (1.10–1.19)
Li et al, 2019[30]	Shift work	Diabetes mellitus incidence	12,701	171,451	Cohort	3	Per 5-year	RR	1.07 (1.04–1.09)
Gan, Li, et al 2018[28]	Shift work	Prostate cancer incidence	10,715	2,546,822	Cohort and case-control	16	Ever vs never	RR	1.23 (1.08–1.41)
Gan, Li, et al, 2018[28]	Shift work	Prostate cancer incidence	2,255	5,787	Case-control	4	Per 5-year	RR	1.06 (0.99–1.14)
Mancio et al, 2018[29]	Rotating night-shift work	Prostate cancer incidence	9,219	2,514,827	Cohort and case-control	9	Ever vs daytime work	RR	1.06 (1.01–1.12)
Mancio et al, 2018[29]	Fixed night-shift work	Prostate cancer incidence	6,702	332819	Cohort and case-control	4	Ever vs daytime work	RR	1.01 (0.81–1.26)
Du et al, 2017[27]	Night shift work	Prostate cancer incidence	8,638	2,489,307	Cohort	9	Ever vs never	RR	1.08 (0.99–1.17)
Travis et al, 2016[26]	Night shift work	Breast cancer incidence	16,649	1,633,298	Cohort	10	Ever vs never	RR	0.99 (0.95–1.03)
Wang, Ji, et al, 2015[25]	Night shift work	Colorectal cancer incidence	5,157	6,594,319	Cohort and case-control	11	Longest vs shortest	OR	1.32 (1.12–1.55)
Vyas et al, 2012[24]	Shift work	Myocardial infarction incidence	6,598	1,102,597	Cohort and case-control	10	Ever vs never	RR	1.23 (1.15–1.31)
Vyas et al, 2012[24]	Shift work	Coronary mortality	3,166	134,860	Cohort and case-control	9	Ever vs never	RR	1.08 (0.97–1.21)
Vyas et al, 2012[24]	Shift work	Cerebrovascular mortality	2,738	417,358	Cohort	4	Ever vs never	RR	1.12 (0.89–1.40)
Vyas et al, 2012[24]	Shift work	Cardiovascular events	1,423	30,452	Cohort	5	Ever vs never	RR	1.24 (0.81–1.89)
Vyas et al, 2012[24]	Shift work	Cardiovascular mortality	17,335	500,166	Cohort	5	Ever vs never	RR	1.14 (0.98–1.32)
Vyas et al, 2012[24]	Shift work	All-cause mortality	8,092	148,329	Cohort	8	Ever vs never	RR	1.04 (0.97–1.11)

OR = odds ratio, RR = risk ratio.

ever vs having never done shift work and rotating-night shift work vs daytime work) and colorectal cancer incidence (longest vs shortest shift work time), were supported by weak evidence, whereas the remaining 10 associations presented nonsignificant evidence. For associations supported by either class I or II evidence, we conducted additional sensitivity analyses based on a meta-analysis of prospective cohort studies to reassess the grading of the evidence. Therefore, 2 associations supported by highly suggestive evidence were performed.

DISCUSSION

Main findings

In this umbrella review, we provided an overview of the relationship between shift work and multiple health-related outcomes by summarizing the evidence from relevant systematic reviews and meta-analyses. Overall, there was highly suggestive evidence that shift work increased the risk of diabetes mellitus incidence[30] (per 5-year increment in shift work) and myocardial infarction incidence[24] (having ever vs having never done shift work). Diabetes mellitus incidence[30] (having ever vs having never done shift work) showed suggestive evidence regarding an association with shift work. Three associations were supported by weak evidence, including prostate cancer incidence (having ever vs having never done shift work and rotating-night shift work vs daytime work) and colorectal cancer incidence (longest vs shortest shift work time).[25,28,29]

Interpretation in light of the evidence

We found not only highly suggestive evidence in the dose-response analysis but also suggestive evidence in the categorical analysis of the association between shift work and diabetes mellitus incidence.[30] There were certain limitations,

Table 2—Description of 16 meta-analyses of shift work and health outcomes included in umbrella review.

Study	Exposure	Outcome	Comparison	Summary Effect Size (95% CI)				Random *P* Value[a]	Fixed *P* Value[b]
				Effect Metrics	Random Effects	Fixed Effects	Largest Study		
Yousef et al, 2020[31]	Shift work	Melanoma skin cancer	Ever vs never	RR	1.01 (0.90–1.14)	1.10 (1.05–1.16)	1.20 (1.10–1.30)	.805	.0003
Li et al, 2019[30]	Shift work	Diabetes mellitus incidence	Ever vs never	RR	1.14 (1.10–1.19)	1.12 (1.09–1.15)	1.02 (0.96–1.09)	2.733×10^{-11}	1.907×10^{-16}
Li et al, 2019[30]	Shift work	Diabetes mellitus incidence	Per 5-year	RR	1.07 (1.04–1.09)	1.07 (1.04–1.09)	1.06 (1.03–1.10)	2.659×10^{-8}	2.659×10^{-8}
Gan, Li, et al 2018[28]	Shift work	Prostate cancer incidence	Ever vs never	RR	1.23 (1.08–1.41)	1.10 (1.05–1.14)	1.04 (0.99–1.10)	.002	5.142×10^{-6}
Gan, Li, et al 2018[28]	Shift work	Prostate cancer incidence	Per 5-year	RR	1.06 (0.99–1.14)	1.02 (1.00–1.05)	1.01 (0.98–1.04)	.086	.037
Mancio et al, 2018[29]	Rotating night-shift work	Prostate cancer incidence	Ever vs daytime work	RR	1.11 (1.00–1.23)	1.06 (1.01–1.12)	1.02 (0.95–1.10)	.048	.026
Mancio et al, 2018[29]	Fixed night-shift work	Prostate cancer incidence	Ever vs daytime work	RR	0.96 (0.66–1.40)	1.01 (0.81–1.26)	1.10 (0.85–1.43)	.844	.931
Du et al, 2017[27]	Night shift work	Prostate cancer incidence	Ever vs never	RR	1.08 (0.99–1.17)	1.05 (1.00–1.11)	1.02 (0.95–1.10)	.077	.062
Travis et al, 2016[26]	Night shift work	Breast cancer incidence	Ever vs never	RR	0.97 (0.91–1.04)	0.99 (0.95–1.03)	1.00 (0.92–1.08)	.427	.636
Wang, Ji, et al, 2015[25]	Night shift work	Colorectal cancer incidence	Longest vs shortest	OR	1.32 (1.12–1.55)	1.14 (1.08–1.21)	1.03 (0.94–1.13)	.001	6.832×10^{-6}
Vyas et al, 2012[24]	Shift work	Myocardial infarction incidence	Ever vs never	RR	1.23 (1.15–1.31)	1.23 (1.15–1.31)	1.20 (1.09–1.31)	1.431×10^{-10}	1.431×10^{-10}
Vyas et al, 2012[24]	Shift work	Coronary mortality	Ever vs never	RR	1.08 (0.97–1.21)	1.07 (0.99–1.16)	1.03 (0.90–1.18)	.152	.093
Vyas et al, 2012[24]	Shift work	Cerebrovascular mortality	Ever vs never	RR	1.12 (0.89–1.40)	1.12 (0.99–1.28)	1.19 (1.01–1.40)	.328	.079
Vyas et al, 2012[24]	Shift work	Cardiovascular events	Ever vs never	RR	1.23 (0.80–1.89)	1.30 (1.13–1.49)	1.31 (1.06–1.62)	.335	.0003
Vyas et al, 2012[24]	Shift work	Cardiovascular mortality	Ever vs never	RR	1.14 (0.98–1.33)	1.04 (0.99–1.09)	1.02 (0.96–1.08)	.088	.147
Vyas et al, 2012[24]	Shift work	All-cause mortality	Ever vs never	RR	1.04 (0.97–1.11)	1.03 (0.98–1.09)	1.02 (0.93–1.11)	.327	.208

[a]*P* value of summary random-effects estimate. [b]*P* value of summary fixed-effects estimate. CI = confidence interval, OR = odds ratio, RR = risk ratio.

including the existence of a small study effect and the fact that the largest study included the null value regarding the association between shift work and diabetes mellitus incidence for the categorical analysis. In addition, the association of dose-response analysis failed our criteria for strong evidence, mainly because of the presence of excess significance bias. Our findings were consistent with the results of 2 meta-analyses of studies on the same topic, which were excluded based on related criteria.[32,33] Furthermore, the dose-response analyses, including 3 cohort studies carried out by Gao et al,[32] showed an increased risk of diabetes associated with longer shift work hours. Some potential biological mechanisms could explain the link between shift work and diabetes mellitus. For example, shift work causes workers to frequently change their sleeping time, which leads to sleep problems, such as poor sleep quality. Some studies have suggested that sleep deprivation and poor sleep quality may develop and exacerbate insulin resistance.[34,35] Stenvers et al[36] pointed out that the circadian clock can regulate food intake, energy consumption, insulin sensitivity, and glucose absorption, thus disrupting the rhythm of glucose metabolism. In addition, Qin et al[37] reported that the reduction of leptin and melatonin increased the risk of diabetes

Table 3—Evaluation of bias and heterogeneity in 16 meta-analyses of shift work and health outcomes.

Study	Exposure	Outcome	Comparison	I^2 (95% CI)	*P* Value[a]	Egger *P* Value[b]	95%PI	Observed[c]	Expected[c]	*P* Value[d]
Yousef et al, 2020[31]	Shift work	Melanoma skin cancer	Ever vs never	66.1% (36–82)	.0010	.084	0.73–1.42	4	3.9734	.9867
Li et al, 2019[30]	Shift work	Diabetes mellitus incidence	Ever vs never	38.9% (0–63)	.0278	.000	1.02–1.29	11	9.5283	.5392
Li et al, 2019[30]	Shift work	Diabetes mellitus incidence	Per 5-year	0.0% (0–90)	.7408	.185	0.92–1.24	3	0.2643	.0000
Gan, Li, et al 2018[28]	Shift work	Prostate cancer incidence	Ever vs never	82.7% (73–89)	.0000	.084	0.76–2.00	5	5.2780	—
Gan, Li, et al 2018[28]	Shift work	Prostate cancer incidence	Per 5-year	82.8% (56–93)	.0006	.052	0.79–1.42	1	1.3283	—
Mancio et al, 2018[29]	Rotating night-shift work	Prostate cancer incidence	Ever vs daytime work	50.1% (0–77)	.0417	.040	0.85–1.44	3	2.4825	0.7139
Mancio et al, 2018[29]	Fixed night-shift work	Prostate cancer incidence	Ever vs daytime work	33.0% (0–76)	.2150	.820	0.28–3.35	0	0.8057	—
Du et al, 2017[27]	Night shift work	Prostate cancer incidence	Ever vs never	24.0% (0–64)	.2304	.051	0.91–1.27	1	1.8309	—
Travis et al, 2016[26]	Night shift work	Breast cancer incidence	Ever vs never	46.4% (0–74)	.0521	.708	0.82–1.16	3	2.5049	.7178
Wang, Ji, et al, 2015[25]	Night shift work	Colorectal cancer incidence	Longest vs shortest	77.7% (60–87)	.0000	.111	0.80–2.18	5	5.1604	—
Vyas et al, 2012[24]	Shift work	Myocardial infarction incidence	Ever vs never	0.0% (0–62)	.4993	.297	1.14–1.33	5	1.5282	0.0107
Vyas et al, 2012[24]	Shift work	Coronary mortality	Ever vs never	28.6% (0–67)	.1906	.328	0.85–1.38	1	1.6197	—
Vyas et al, 2012[24]	Shift work	Cerebrovascular mortality	Ever vs never	50.3% (0–84)	.1102	.948	0.48–2.59	1	0.9553	.9582
Vyas et al, 2012[24]	Shift work	Cardiovascular events	Ever vs never	85.5% (68–93)	.0000	.820	0.27–5.60	4	2.6210	0.3779
Vyas et al, 2012[24]	Shift work	Cardiovascular mortality	Ever vs never	64.3% (6–86)	.0243	.057	0.73–1.79	1	1.5037	—
Vyas et al, 2012[24]	Shift work	All-cause mortality	Ever vs never	35.5% (0–71)	.1453	.978	0.88–1.23	1	1.5236	—

[a]*P* value of *Q* test. [b]From Egger regression asymmetry test. [c]Observed and expected number of significant studies using effect of largest study (smallest SE) of each meta-analysis as plausible effect size. [d]*P* value of excess significance test. All statistical tests were 2-sided. CI = confidence interval, PI = prediction interval, SE = standard error.

mellitus. Notably, melatonin secretion in shift workers, especially in night shift workers, is often inhibited.

Our findings suggested that the association between shift work and myocardial infarction incidence was supported by highly suggestive evidence.[24] This association failed our criteria for strong evidence, mainly because of the excess significance bias. Compared with previous umbrella reviews, which examined associations between single risk factors and health outcomes,[38,39] the meta-analysis we included[24] failed only 1 of our criteria and not multiple criteria, indicating that the presence of bias in this literature may be relatively modest. The present meta-analysis included 4 cohort and 6 case-control studies. We observed that shift work was associated with an increased risk of myocardial infarction in all 4 cohorts. Shift work is disruptive to circadian rhythm, impairs sleep quality, and affects work-life balance. Insomnia, commonly reported among night shift workers, is an independent risk factor for myocardial infarction.[40] Insomnia may increase the risk of myocardial infarction through metabolic or endocrine changes, through increased sympathetic activation and hypertension, or through elevated levels of proinflammatory cytokines.[41,42] Hypertension and myocardial infarction are closely related in many ways, and a previous study has shown that shift work increases the risk of hypertension.[43]

There was weak evidence that prostate cancer incidence (shift work vs nonshift work and rotating-night shift work vs daytime work) or colorectal cancer incidence (longest shift work time vs shortest shift work time) were associated with

Table 4—Evidence-rating results based on the results of statistical analyses of the 16 associations.

Study	Association Between Shift Work and Health Outcomes	Evidence Rating	Random-Effects *P* Value[a]	Patients > 1,000	Largest Study Relative Risk Estimate *P* < .05	I^2 < 50%	Small Study Effects	95% PI Excluding Null Value	Excess Significance
Yousef et al, 2020[31]	Melanoma skin cancer in shift work vs nonshift work	No association	-	+	+	-	-	-	-
Li et al, 2019[30]	Diabetes mellitus incidence in shift work vs nonshift work	Suggestive	+ + +	+	-	+	+	+	-
Li et al, 2019[30]	Diabetes mellitus incidence in per 5-year	Highly suggestive	+ + +	+	+	+	-	-	+
Gan, Li, et al 2018[28]	Prostate cancer incidence in shift work vs nonshift work	Weak	+	+	-	-	+	-	-
Gan, Li, et al 2018[28]	Prostate cancer incidence in per 5-year	No association	-	+	-	-	+	-	-
Mancio et al, 2018[29]	Prostate cancer incidence in rotating night-shift work vs daytime work	Weak	+	+	-	-	+	-	-
Mancio et al, 2018[29]	Prostate cancer incidence in fixed night-shift work vs daytime work	No association	-	+	-	+	-	-	-
Du et al, 2017[27]	Prostate cancer incidence in night shift work vs non-night-shift work	No association	-	+	-	+	+	-	-
Travis et al, 2016[26]	Breast cancer incidence in night-shift work vs non-night-shift work	No association	-	+	-	+	-	-	-
Wang, Ji, et al, 2015[25]	Colorectal cancer incidence in longest time vs shortest time	Weak	+	+	-	-	-	-	-
Vyas et al, 2012[24]	Myocardial infarction incidence in shift work vs nonshift work	Highly suggestive	+ + +	+	+	+	-	+	+
Vyas et al, 2012[24]	Coronary mortality in shift work vs nonshift work	No association	-	+	-	+	-	-	-
Vyas et al, 2012[24]	Cerebrovascular mortality in shift work vs nonshift work	No association	-	+	+	-	-	-	-
Vyas et al, 2012[24]	Cardiovascular events in shift work vs nonshift work	No association	-	+	+	-	-	-	-
Vyas et al, 2012[24]	Cardiovascular mortality in shift work vs nonshift work	No association	-	+	-	-	+	-	-
Vyas et al, 2012[24]	All-cause mortality in shift work vs nonshift work	No association	-	+	-	+	-	-	-

[a]*P* value calculated using random-effects model; +++: $P < 10^{-6}$; +: $P < .05$; –: $P > .05$. For other items: + = yes, – = no. PI = prediction interval.

shift work.[25,28,29] These meta-analyses had some limitations, including the presence of a small-study effect, large or very large heterogeneity, or a 95% prediction interval containing the null value. These biases may degrade the evidence and lead to cautious and prudent conclusions. Further studies are needed to indicate the relationship between shift work and these outcomes.

Strengths and limitations

This umbrella review is the first to provide such a comprehensive critical evaluation of published systematic reviews and meta-analyses of the links between shift work and various health outcomes. A total of 16 associations were rigorously rated for robustness and effectiveness based on the results of a series of statistical analyses. The methodological quality of the systematic reviews was assessed using the AMSTAR 2 checklist, which is a major update of the former version, AMSTAR.

There are several limitations worth mentioning. First, as mentioned earlier, most of the methods in the systematic review were considered to be of critically low quality, as assessed by the AMSTAR 2 checklist. Most of the included studies did not justify the exclusion of potentially eligible studies (item 7) and did not account for the risk of bias in individual studies when interpreting or discussing the results of systematic reviews and meta-analyses (item 13), which are all critical domains of AMSTAR 2, and these limitations contributed to the negative ratings. Moreover, the included studies should consider the study design of individual studies (item 3) and report the source of funding for the primary studies (item 10) because too many noncritical items lower the rating. However, there is no clear conclusion as to how low-quality or critically low-quality meta-analysis should be handled.[9] Second, because the present umbrella review only included observational studies, the reliability depended directly on the included meta-analyses and indirectly on the original studies. It is impossible to control for the bias in the original studies. Simultaneously, further analysis was not possible because of the lack of data on specific shift work types and shift work duration in these systematic reviews and meta-analyses. However, there has been no randomized controlled trial linking shift work to health outcomes. Last, more than half of the associations did not include sufficient studies (at least 10) to enable excess significance tests and Egger tests to identify the origins of biases.[44]

CONCLUSIONS

Although shift work has been associated with a higher risk of several health outcomes in the literature, only the associations between shift work and myocardial infarction, along with diabetes mellitus, were supported by highly suggestive or suggestive evidence. Several other health-related outcomes were inconsistent and showed signs of uncertainty and bias, requiring additional confirmatory studies in the future.

ABBREVIATIONS

AMSTAR 2, A Measurement Tool to Assess Systematic Reviews 2
OR, odds ratio

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