The Relationship Between Shift Work and Metabolic Risk Factors

A Systematic Review of Longitudinal Studies

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Context: Although the metabolic health effects of shift work have been extensively studied, a systematic synthesis of the available research is lacking. This review aimed to systematically summarize the available evidence of longitudinal studies linking shift work with metabolic risk factors.

Evidence acquisition: A systematic literature search was performed in 2015. Studies were included if (1) they had a longitudinal design; (2) shift work was studied as the exposure; and (3) the outcome involved a metabolic risk factor, including anthropometric, blood glucose, blood lipid, or blood pressure measures.

Evidence synthesis: Eligible studies were assessed for their methodologic quality in 2015. A best-evidence synthesis was used to draw conclusions per outcome. Thirty-nine articles describing 22 studies were included. Strong evidence was found for a relation between shift work and increased body weight/BMI, risk for overweight, and impaired glucose tolerance. For the remaining outcomes, there was insufficient evidence.

Conclusions: Shift work seems to be associated with body weight gain, risk for overweight, and impaired glucose tolerance. Overall, lack of high–methodologic quality studies and inconsistency in findings led to insufficient evidence in assessing the relation between shift work and other metabolic risk factors. To strengthen the evidence, more high-quality longitudinal studies that provide more information on the shift work schedule (e.g., frequency of night shifts, duration in years) are needed. Further, research to the (mediating) role of lifestyle behaviors in the health effects of shift work is recommended, as this may offer potential for preventive strategies.
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Context

Shift work has become an inevitable part of society. It has been estimated that about one in five workers in Europe perform shift work involving night work.[1] There is growing concern that shift work involving chronic disruption of circadian rhythms contributes to the development of negative health effects, including cardiovascular disease (CVD), metabolic disorders, and cancer.[2] In recent decades, the association between shift work on health has been extensively studied, with most consistent results for breast cancer and CVD.[3,4]

Metabolic disorders, including CVD and Type 2 diabetes, have a high prevalence in developed countries. Worldwide, 347 million people have diabetes, and WHO predicts diabetes to be the seventh leading cause of death by 2030.[5,6] CVD, presently the first-leading cause of death, caused an estimated 17.3 million deaths in 2008, representing 30% of all global deaths.[7] Considering the chronicity and high prevalence of these diseases and the

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high prevalence of shift work, a causal relation between shift work and metabolic disorders would be of great public concern.

Several reviews[8–10] have been performed to investigate the impact of shift work on metabolic risk factors, such as overweight, hypertension, and glucose and lipid metabolism. The 2011 systematic review on body weight change conducted by van Drongelen et al.,[10] for example, identified eight cohort studies that met their inclusion criteria and found strong evidence for an association between shift work and body weight gain in unadjusted analyses. However, after adjusting for potentially relevant confounders, sufficient evidence was not apparent. Insight into the effect of shift work on metabolic risk factors will be useful for secondary prevention, as these risk factors appear before actual disease is noticeable. As such, risk factors are intermediate outcome measures in the relationship between shift work and metabolic diseases. Although the metabolic health effects of shift work have been studied, a systematic synthesis of the available research is currently lacking. This review aimed to systematically summarize the available evidence from longitudinal studies analyzing the effects of shift work on (physiologic) risk factors for various metabolic disorders.

Evidence Acquisition

Literature Search and Selection

A literature search was performed in 2015 with the help of an experienced librarian. The electronic search was performed in MEDLINE, followed by other electronic databases, including Embase, BIOSIS Previews, and SciSearch. In the search strategy, a frequently applied time frame of the past 20 years was used (1995 through March 2015). The full search strategy used for MEDLINE can be found in the Appendix (available online). In addition to the electronic search, key publications (eight reviews) as well as included studies were checked for relevant references. The obtained titles and abstracts were all screened for eligibility as defined by the criteria for inclusion by two reviewers independently (DL and KP).

Inclusion Criteria

Criteria for studies to be included in this review were as follows:

1. a longitudinal design (either retrospective or prospective);
2. the study population involved a working population where a shift working group was compared to with non-shift working group;
3. the health outcome involved a metabolic risk factor; and
4. publication in English.

Based on identified risk factors for CVD and Type 2 diabetes,[11–13] the metabolic risk factors in this review were as follows:

1. body weight or body composition;
2. disrupted glucose metabolism;
3. disrupted lipid metabolism; and
4. blood pressure.

As this review focused on the metabolic risk factors, and not the metabolic disease, studies that examined the relation between shift work and the disease, such as metabolic syndrome, diabetes, or CVD, were excluded.

Data Extraction

Two reviewers (DL and KP) independently extracted data using a predefined form. The following data were extracted: study design, study population, sample size, follow-up duration, assessment of shift work, assessment of metabolic risk factor, statistical methods, included confounders, and main findings.

Methodologic Quality Assessment

All studies that met the inclusion criteria were assessed by the two reviewers (DL and KP) independently on their methodologic quality or risk of bias following a predefined checklist (Table 1). The checklist was based on previously used checklists,[14–16] but for the purpose of this review, specific items on shift work exposure were added. The items referred to either informativeness (five items) or validity/precision (11 items). The reviewers scored the item as positive (+) if the item was met, negative (−) if the item was not met, and unclear (?) if insufficient information was provided. In case of insufficient information (?), the first author or contact person of the article was contacted by e-mail to provide additional information. In a meeting, the two reviewers discussed their scorings and tried to achieve consensus. The total quality score was calculated by counting the number of items scored positively on the validity/precision criteria. Studies were regarded as "high quality" if at least 75% of these items were met; otherwise, the study was considered "low quality."[17]

Data Analyses

After summarizing the included studies, it appeared that the studies were heterogeneous, especially with regard to the measurement of shift work and the outcome under study. Moreover, the statistical analyses varied between the studies, resulting in different types of effect sizes (ORs and regression coefficients) making statistical pooling impossible. Therefore, to synthesize the methodologic quality of the studies and to be able to draw conclusions regarding the relationship between shift work and metabolic risk, data were summarized qualitatively per metabolic risk factor using a best-evidence synthesis. The best-evidence system consists of three levels of evidence[10,15,16]:

1. strong evidence in the case of consistent findings in multiple (two or more) high-quality studies;
2. moderate evidence in case of consistent findings in one high-quality study and at least one low-quality study, or in the case of consistent findings in multiple low-quality studies; or
3. insufficient evidence in the case of only one study available or inconsistency in findings between studies.

Analogous to earlier systematic reviews,[10,15,16] consistency was defined if at least 75% of the studies showed a similar result, as

Table 1. Criteria List for Assessment of the Methodological Quality of Cohort Studies[15–17]

Criteria	I, V/P
Study population and participation (baseline)	
1. Adequate description of sampling frame, recruitment methods, period of recruitment, and place of recruitment	I
2. Participation rate at baseline at least 80%, or if the nonresponse was not selective	V/P
3. Adequate description of baseline study sample for key characteristics	I
Study attrition	
4. Provision of the exact *n* at each follow-up measurement	I
5. Provision of exact information on follow-up duration	I
6. Response at short-term follow-up was at least 80% of the *n* at baseline and response at long-term follow-up was at least 70% of the *n* at baseline	V/P
7. Information on not selective nonresponse during follow-up measurement	V/P
Data collection	
8a. Adequate measurement of shift work	V/P
8b. Are the compared research groups clearly defined?	V/P
8c. Is exposure to shift work measured using appropriate tools?	V/P
8d. Is there relevant information on shift work schedules, patterns and duration included?	I
9. Adequate measurement of the metabolic health outcome	V/P
Data analyses	
10. The statistical model used was appropriate and point estimates with measures of variability must have been provided	V/P
11. The number of cases was at least 10 times the number of the independent variables	V/P
12. Important confounders were identified and have been adjusted for	V/P
13. No selective reporting of results	V/P

I, criterion on informativeness; V/P, criterion on validity/precision.

defined by statistical significance ($p<0.05$). In the synthesis, low-quality studies were disregarded if there were high-quality studies.

Evidence Synthesis

Study Selection

Figure 1 shows the flow diagram of the literature search. The electronic search resulted in 367 hits. Of these, the large majority (n=318) was excluded based on reading titles and abstracts, leaving 49 articles describing potentially relevant studies. After a check in key publications, one reference was added. Thus, 50 full-text articles were retrieved and further checked for eligibility. One extra publication was added manually afterwards, resulting in 39 publications describing 22 studies that met the inclusion criteria. Sixteen publications[18–33] reported on separate studies. The remaining six studies were described in two or more publications. A total of 11 publications[34–44] described the results of data used from a historic cohort of male workers from a Japanese steel company, who underwent annual health checkups during 1991–2005. Data were used over a 10- and 14-year period. Despite differences in follow-up period or outcome measure, these publications were all treated as one study. Three other publications[45–47] used data of Japanese workers based on a healthcare database of a manufacturing corporation. The mean follow-up time of the included workers differed by outcome under study, but overall, the research methods were similar. Therefore, these three publications were considered one study. This was also done for two publications[27,48,49] reporting on the relation of shift work and metabolic risk factors using data from retired workers from a motor company in China, and two publications[50,51] describing results from data of Dutch workers starting a new job. Also, three publications of Morikawa and colleagues[52–54] were considered one study, because the same study population was used. Finally, Akbari et al.[55] and Gholami-Fesharaki

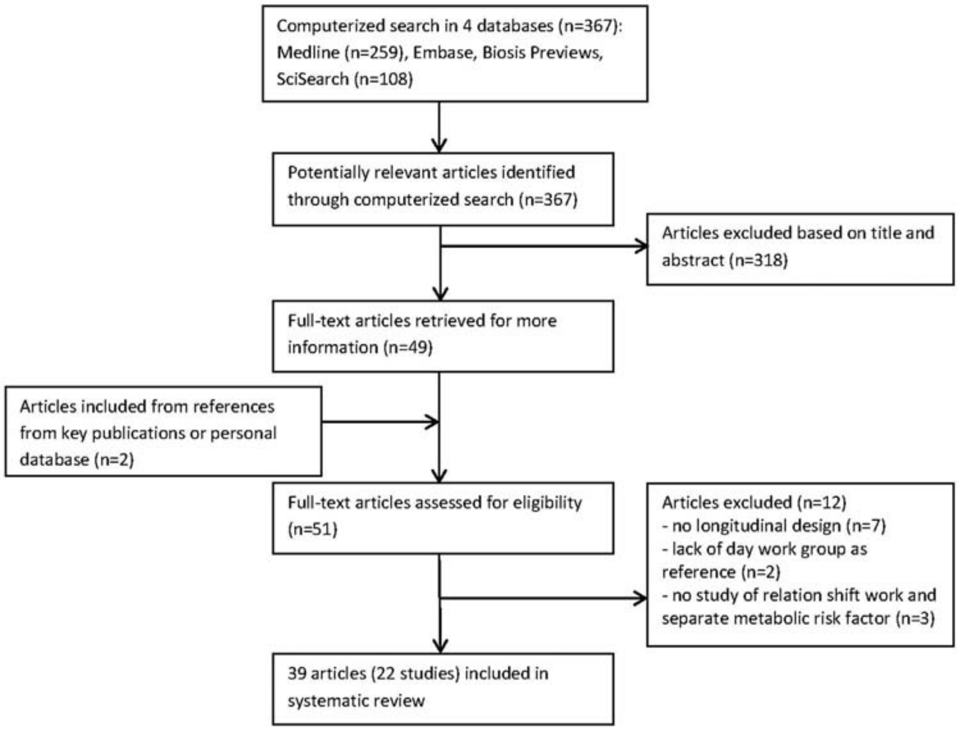

Figure 1. Flow diagram of literature search and selection of studies in review.

and colleagues[56] used data of male workers from the same company in Iran with a different follow-up period and analyzed the relation between shift work and cholesterol and blood pressure, respectively. Another study of Gholami-Fesharaki et al.[32] additionally analyzed the data from another company on blood pressure and was therefore considered as a separate study.

Appendix Table 1 (available online) provides the description of the 22 studies that met the inclusion criteria. The study population was diverse between studies, and differed in sample size and occupational groups. The sample size ranged from <85 workers[20] to 107,663 workers.[33] Studied occupational groups were, among others, nurses, steel workers, factory workers but also white collar workers such as employees from a local government. Shift work was defined in various ways, but mostly included night shifts.

Of the 22 studies,[21,32,34–49,52–56] seven studies were of high quality. The majority of studies scored negatively on the item related to the measurement of shift work (Item 8C, Table 2). Overall, most studies had used appropriate statistical models, adjusting for important confounders (Items 10 and 12, Table 2).

Relation Between Shift Work and Body Weight–Related Outcomes. Seventeen studies, of which four[39,43,46,49,54] were of high quality, studied the relationship between shift work and body weight–related outcomes (Table 3). Several body weight–related outcomes were studied, including body weight, BMI, overweight, and waist circumference. Eleven studies examined the relation between shift work and body weight or BMI. The majority of the studies (n=8) found a positive relation between shift work and body weight/BMI, which was confirmed by the two high-quality studies[39,43,54] (Table 3). Based on their analyses using data of factory workers, Morikawa and colleagues[54] found increased BMI in those workers who moved from day work to shift work (β=0.052, p=0.04), as well as in those who were stable shift workers (β=0.061, p=0.02) compared with stable day workers over a period of 10 years. The other high-quality study, on Japanese steel workers using a study period of 14 years, also showed shift work to be significantly associated with BMI increases.[39,43] Based on the consistent findings between the two high-quality studies, there was strong evidence for a relation between shift work and body weight or BMI. Furthermore, eight studies, of which two were of high quality,[46,49] studied the effect of shift work on overweight, defined by BMI cut off points of 25 or 30 or based on waist circumference ($\geq$90 or $\geq$94 cm for men, $\geq$80 cm for women). Overall, most studies (n=7) found shift work to be a significant predictor of overweight, although two[22,31] of these found mixed results in subgroups (by age group or sex). Both high-quality studies showed consistent results, in that shift work was

Table 2. Scorings on Risk of Bias Validity/Precision Items (Table 1) Per Study

	2	6	7	8a	8b	8c	9	10	11	12	13	Total scoring[a]	Quality rating[b]
Akbari (2015)[55]	?	1	1	1	1	?	1	1	1	1	1	9	High
Gholami-Fesharaki (2014)[56] (Occ Med)	1	1	1	1	1	1	1	1	1	1	1	11	
Gholami-Fesharaki (2014)[32] (Atherocl)	?	1	1	1	1	1	1	1	1	1	1	10	High
Biggi (2008)[18]	?	?	0	1	1	?	?	1	1	1	1	6	Low
De Bacquer (2009)[19]	0	0	0	1	1	0	1	1	1	1	1	7	Low
Geliebter (2000)[20]	1	NA[c]	NA	1	1	0	0	0	1	1	1	6	Low
Guo (2013)[48]	1	NA	NA	1	0	0	1	1	1	1	1	7	High
Guo (2015)[49]	1	NA	NA	1	0	0	1	1	1	1	1	7	
Hannerz (2004)[30]	1	1	0	0	0	0	0	1	0	0	0	3	Low
Hublin (2010)[21]	1	1	1	1	0	0	1	1	1	1	1	10	High
Itani (2011)[31]	0	NA	NA	0	0	0	1	1	1	1	1	5	Low
Kubo (2011)[46]	1	1	1	1	1	1	0	1	1	1	1	10	High
Kubo (2013)[45]	1	1	1	1	1	1	?	1	1	1	1	10	
Oyama (2012)[47]	?	1	1	1	1	1	1	1	1	1	1	10	
Li (2011)[22]	?	?	0	0	0	0	0	0	1	0	1	2	Low
Lieu (2012)[23]	1	?	0	1	1	0	0	1	1	1	1	7	Low
Lin (2009)[24]	0	?	0	1	1	0	1	0	1	0	1	5	Low
Morikawa (1999)[52]	0	1	1	1	1	0	1	1	1	1	1	9	High
Morikawa (2005)[53]	1	1	0	1	1	0	1	1	1	1	1	9	
Morikawa (2007)[54]	1	1	1	1	1	0	1	1	1	1	1	10	
Murata (1999)[25]	?	1	0	0	1	?	1	0	1	1	1	6	Low
Nabe-Nielsen (2011)[26]	1	0	0	1	1	0	0	1	0	1	1	6	Low
Niedhammer (1996)[27]	0	1	1	1	1	0	0	1	1	1	1	8	Low
Pan (2011)[33]	1	1	0	1	1	0	0	1	1	1	1	8	Low
Thomas (2010)[28]	0	0	0	1	0	0	1	1	1	1	1	6	Low
Van Amelsvoort (1999)[50]	0	1	0	1	1	0	0	1	1	1	1	7	Low
Van Amelsvoort (2004)[51]	0	1	0	1	1	0	1	0	1	1	1	7	
Zhao (2012)[29]	0	0	0	1	1	0	0	1	1	1	1	6	Low
Dochi (2008)[34]	1	1	0	1	1	1	1	1	1	1	1	10	High
Dochi (2009)[35]	1	1	0	1	1	1	1	1	1	1	1	10	
Uetani (2011)[44]	1	0	0	1	1	1	1	1	1	1	1	9	
Suwazono (2009)[38]	1	1	0	1	1	1	1	1	1	1	1	10	
Suwazono (2010)[42]	1	1	0	1	1	1	1	1	1	1	1	10	
Oishi (2005)[36]	1	1	0	1	1	1	1	1	1	1	1	10	
Sakata (2003)[37]	1	1	0	1	1	1	1	1	1	1	1	10	

(continued on next page)

Table 2. Scorings on Risk of Bias Validity/Precision Items (Table 1) Per Study *(continued)*

	2	6	7	8a	8b	8c	9	10	11	12	13	Total scoring[a]	Quality rating[b]
Suwazono (2008)[40]	1	1	0	1	1	1	1	1	1	1	1	10	
Suwazono (2006)[41]	1	?	0	1	1	1	1	1	1	1	1	9	
Suwazono (2008)[39]	1	?	0	1	1	1	1	1	1	1	1	9	
Tanaka (2010)[43]	1	?	0	1	1	1	1	1	1	1	1	9	

[a]Total scoring on the items on validity/precision.
[b]High quality: ≥75% positive items, low quality: <75% positive items.
[c]These items were not applicable in retrospective studies; the quality rating was based on valid scorings.

significantly related with being overweight (risk ratio=1.14, 95% CI=1.01, 1.28)[46] and abdominal obesity,[49] leading to strong evidence for shift work and the risk for overweight. There were only two studies, both of low quality, on the relation between shift work and waist circumference.[28,50,51] Because of mixed results, there was insufficient evidence for the relation between shift work and waist circumference.

Relation Between Shift Work and Glucose Metabolism. Nine studies[18,19,22,24,28,38,41,42,47,49,53,54] examined the relation between shift work and glucose metabolism. Most of them (n=7)[19,22,24,41,47,49,53] investigated the effect of shift work on hyperglycemia or impaired glucose tolerance, defined by elevated (non-)fasting glucose and hemoglobin A1c (HbA1c) levels. Also, four studies[18,28,38,42,54] examined the relation with glucose or HbA1c as a continuous measure. Across these four studies, including two high-quality studies, inconsistent results were seen (Table 3). One high-quality study did not find a significant relation of shift work in blue-collar workers on HbA1c levels,[54] whereas the other high-quality study on Japanese steel workers showed shift work to be significantly associated with four different HbA1c endpoints.[38,57] The latter study also showed a dose–response relation between the duration of shift work and HbA1c increases. Conflicting results among the few high-quality studies yielded insufficient evidence for a positive relation between shift work and blood glucose, including HbA1c. Of the four high-quality studies[41,47,49,53] on the relation between shift work and hyperglycemia, three found a significant impact of shift work. Oyama et al.[47] reported an increased risk for the incidence of impaired glucose tolerance (HbA1c ≥5.9%); two- and three-shift system workers had a higher risk than daytime workers (hazard ratio [95% CI] for two- and three-shift groups, 2.62 [2.17, 3.17] and 1.78 [1.49, 2.14], respectively). These findings were supported by Suwazono and colleagues,[41] who showed that alternating shift work is a significant risk factor for HbA1c ≥6.0%. Also, Guo et al.[49] observed significant associations between shift work duration and fasting glucose level ≥5.5 mmol/L. However, another high-quality study, by Morikawa et al.,[53] did not show two- and three-shift workers to be at increased risk for elevated HbA1c levels compared to daytime workers. Because 75% of the high-quality studies showed an impact of shift work, there was strong evidence for shift work as a predictor for impaired glucose tolerance.

Relation Between Shift Work and Lipid Metabolism. Ten studies, of which four[34,44,49,54,55] were of high quality, investigated the relation between shift work and blood lipid profile. Several outcome measures were used, including total, high-density lipoprotein (HDL), and low-density lipoprotein cholesterol and triglycerides. Total cholesterol was used in six studies,[18,28,35,44,51,54,55] of which three were of high quality. Overall, mixed results were seen between the studies (Table 3). The high-quality study of Dochi and colleagues[35] found an overall significant effect of shift work resulting in 20%–45% increases in total cholesterol in Japanese steel company workers. However, using the same study population and follow-up period (14 years), Uetani et al.[44] showed shift work to be associated with cholesterol increase in non-overweight workers but not in overweight workers. The other high-quality study[54] found that those moving from day to shift workers over 10 years did not show increased total cholesterol levels compared to stable day workers. The absence of a significant relation between shift work pattern and cholesterol was also reported in the study by Akbari and colleagues.[55] Based on the inconsistencies in study findings, there is insufficient evidence for a positive relation between shift work and total cholesterol. For both HDL cholesterol and triglycerides, seven studies were identified, but only one[49] was of high quality. That high-quality study did not observe a significant risk for elevated HDL cholesterol or triglyceride levels per 10-year increase of shift work. The remaining studies,[18,19,22,24,28,51] all of low quality, showed conflicting

Table 3. Evidence for the Relation Between Shift Work and Metabolic Risk Factors

Outcome	Effect of shift work[a] +	Effect of shift work[a] 0	Effect of shift work[a] –	Best evidence synthesis
Weight related measure				
BMI, body weight	Geliebter (2000)[20]; Van Amelsvoort (1999, 2004)[50,51]; Biggi (2008)[18]; **Morikawa (2007)**[54]; Pan (2011)[33]; **Suwazono (2008)**[39]; **Tanaka (2010)**[43]; Thomas (2010)[28]; Zhao (2012)[29]	Nabe-Nielsen (2011)[26]; Niedhammer (1996)[27]; Hannerz (2004)[30]; Thomas (2010)[28]	Nabe-Nielsen (2011)[26]	Strong
Waist circumference	Thomas (2010)[28]; Van Amelsvoort (1999)[50]	Thomas (2010)[28]; Van Amelsvoort (2004)[51]		Insufficient
Obesity (defined by BMI or waist circumference)	Itani (2011)[31]; **Kubo (2011)**[46]; Li (2011)[22]; Van Amelsvoort (1999)[50]; **Guo (2015)**[49]; Lin (2009)[24]; Pan (2011)[33]	Itani (2011)[31]; Li (2011)[22]; De Bacquer (2009)[19]		Strong
Blood glucose				
Blood glucose, HbA1c	**Suwazono (2009, 2010)**[38,42]; Thomas (2010)[28]	Biggi (2008)[18]; **Morikawa (2007)**[54]; Thomas (2010)[28]		Insufficient
Impaired glucose tolerance, hyperglycemia	De Bacquer (2009)[19]; Li (2011)[22]; **Guo (2015)**[49]; **Oyama (2012)**[47]; **Suwazono (2006)**[41]	Li (2011)[22]; Lin (2009)[24]; **Morikawa (2005)**[53]		Strong
Blood lipids				
Total cholesterol	Biggi (2008)[18]; **Dochi (2009)**[35]; Thomas (2010)[28]; **Uetani (2011)**[44]	**Akbari (2015)**[55]; **Morikawa (2007)**[54]; Thomas (2010)[28]; **Uetani (2011)**[44]; Van Amelsvoort (2004)[51]		Insufficient
HDL, LDL, triglycerides	Li (2011)[22]; Van Amelsvoort (2004)[51]; De Bacquer (2009)[19]; Biggi (2008)[18]; Thomas (2010)[28]	**Guo (2015)**[49]; Li (2011)[22]; Lin (2009)[24]; Thomas (2010)[28]; Van Amelsvoort (2004)[51]		Insufficient
Hypercholesterolemia	**Dochi (2008)**[34]			Insufficient
Blood pressure				
Systolic and/or diastolic blood pressure	**Suwazono (2008)**[40]	**Gholami-Fesharaki (2014)**[32]; **Gholami-Fesharaki (2014)**[56]; **Biggi (2008)**[18]; **Morikawa (2007)**[54]; Murata (1999)[25]; Van Amelsvoort (2004)[51]		Insufficient
Hypertension	De Bacquer (2009)[19]; **Guo (2013)**[48]; **Kubo (2013)**[45]; Li (2011)[22]; Lieu (2012)[23]; Lin (2009)[24]; **Morikawa (1999)**[52]; **Oishi (2005)**[36]/**Sakata (2003)**[37]	Biggi (2008)[18]; **Hublin (2010)**[21]; Li (2011)[22]; Lieu (2012)[23]; **Morikawa (1999)**[52]; **Oishi (2005)**[36]		Insufficient

Note: References in bold are high quality studies.
[a]0 = no relation; + = positive relation; – = negative relation. A study can appear in multiple columns per outcome measure, for example in case of + relation in non-overweight and 0 relation in overweight workers (e.g., Uetani[44]), or in different age groups (e.g., Morikawa[52]).
HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

results, with some finding a significant influence of shift work on HDL cholesterol and triglycerides, which was not confirmed by others. Therefore, insufficient evidence for shift work as a predictor for adverse changes in HDL cholesterol and triglycerides was concluded. Only one study[34] of high quality investigated the relation between shift work and hypercholesterolemia (>220 mg/dL, 5.7 mmol/L). Although an increased risk for the onset of hypercholesterolemia was found, owing to the lack of more studies, there is insufficient evidence for shift work as a predictor for hypercholesterolemia.

Relation Between Shift Work and Blood Pressure. Fifteen studies were identified that examined the relation between shift work and systolic or diastolic blood pressure, of which seven were of high quality.[21,32,36,37,40,45,48,52,54,56] The outcomes under study involved hypertension or systolic or diastolic blood pressure (as a continuous outcome measure). Ten studies, of which five were of high quality,[21,36,37,45,48,52] investigated whether shift work is a risk factor for hypertension. There were inconsistencies in the findings for this outcome, both when including all studies and when focusing on high-quality studies only. In the study[36,37] among Japanese steel company workers, mixed results were observed, depending on the definition of hypertension. That is, shift work appeared to increase the risk for hypertension defined by either an elevated systolic blood pressure ($\geq$160 mmHg) or an elevated diastolic blood pressure ($\geq$100 mmHg) but did not lead to increased risk as defined by systolic hypertension only. Heterogeneous findings were also observed in the high-quality study of Morikawa et al.[52] Depending on the age group, shift work increased the risk for hypertension, particularly with the younger shift worker group (aged 18–29 years) being at increased risk compared with day workers (risk ratio=3.6, 95% CI=1.4, 9.1). In summary, given the mixed findings, there was insufficient evidence for shift work as a predictor for hypertension. For systolic or diastolic blood pressure as a continuous outcome, there were seven studies overall showing no relation with shift work (Table 3). Of the four high-quality studies,[32,40,54,56] only one[40] found shift work to be related to increases in blood pressure. Following the best-evidence system, insufficient evidence was assigned for a relation between shift work and blood pressure.

Discussion

Based on the best-evidence system applied in this review, there was strong evidence for an effect of shift work on body weight gain, the risk of overweight, and impaired glucose tolerance. However, insufficient evidence was found for a relationship between shift work and other metabolic outcomes, including lipid metabolism and blood pressure.

The insufficient evidence was also apparent in previous reviews on this topic. For example, Esquirol and colleagues[9] observed mixed results between studies on the effect of shift work on hypertension and blood cholesterol. With respect to body weight, the review by van Drongelen et al.,[10] which also rated the quality of the studies and applied a similar synthesis of findings, found strong evidence for a relationship between shift work and body weight gain in unadjusted analyses. When adjusting for confounders, including sociodemographics, physical activity, and body weight at baseline, inconsistencies in findings were apparent, however, leading to insufficient evidence.[10] Apart from the separate metabolic risk factors, studies investigating the risk of developing metabolic diseases, such as CVD[4,58,59] and metabolic syndrome,[9,58,60,61] have been reviewed. Yet, no unambiguous conclusion about the influence of shift work can be drawn owing to inconsistencies. To illustrate, a meta-analysis showed shift work to be associated with cardiovascular outcomes, including myocardial infarction and ischemic stroke,[4] whereas Frost and colleagues[59] in their systematic review concluded that there is limited epidemiologic evidence for a causal relation between shift work and ischemic heart disease. For metabolic syndrome, two recent reviews[60,61] have drawn contrasting conclusions. A qualitative synthesis[60] concluded that there was insufficient evidence for the relationship between shift work and prevalent metabolic syndrome, whereas a meta-analysis[61] showed an increased pooled risk of metabolic syndrome for ever being exposed to shift work and an even higher risk in workers who had long exposure to night shifts. In the comparison between the present and other reviews, it is important to note that these reviews have used different methods or used different criteria for inclusion and thereby summarized other and more-recent studies. The present review adds to the literature on the health effects of shift work by systematically summarizing the available evidence on the various metabolic risk factors rather than one risk factor or the appearance of the disease.

A number of sources of inconsistencies could explain the differences in findings of the studies, such as the study quality, follow-up duration, and definition and measurement of shift work. With respect to the latter, it appeared that the items on shift work measurement and description were scored poorly. Although some studies used company registrations, other studies used questionnaires and assessed shift work dichotomously, and often information on the type and duration of shift work was missing. It is important to characterize the shift work schedule in as much detail as possible, including, for instance, frequency of night shifts; direction of rotation (clockwise or counterclockwise); and speed of rotation (number of consecutive nights).[62] Not just night shifts disturb sleep; in some cases, morning shifts disturb sleep patterns even more so than night shifts, because difficulty is experienced in initiating sleep early enough to obtain adequate sleep and because of the anticipation of stress related to waking up early.[63] This is especially true for late chronotypes[64] and for subjective outcome measures, such as feeling rested.[65] Also, leisure and social time is reduced when performing morning shifts owing to the early bedtime.[63] As different work schedules are expected to have different health consequences, it is recommended that future research take into account details of shift work as well as the sensitivity of the individual toward shift work. Although most studies performed adjusted analyses to examine the relation between shift work and metabolic risk factors, the included confounders differed. After sociodemographic variables, the role of lifestyle behavior is important to consider. The few available studies[66,67] linking shift work with lifestyle found poorer activity and diet behaviors in shift workers compared with day workers. Some studies have indeed taken these behaviors into account in the analysis. Nonetheless, it is questionable whether adjustment for lifestyle behaviors is appropriate and will not lead to an underestimation or disappearance of the true effect between shift work and health effects, because lifestyle behaviors including the timing of food behaviors have been suggested as one of the mechanisms underlying the health effects of shift work.[68,69] This potential mediating role of lifestyle behaviors has been hypothesized, but has not been tested to date. It is therefore recommended that more research be performed on this role of lifestyle behaviors.

Limitations

The results of this systematic review need to be interpreted with caution because of the limited number of high-quality studies per outcome and the heterogeneity in the design of the studies. Thus, the present review indicates that more high-quality research is needed to increase current knowledge on this topic. A strength of this review is the systematic approach used to identify relevant studies, appraise the methodologic quality of studies, and summarize the results. To draw conclusions on the available evidence, a best-evidence system was used taking into account the number and methodologic quality of the studies. Despite this being a widely accepted method, the sensitivity of the rating system should be considered. For example, the addition of just one more high-quality study can change the conclusion substantially. Moreover, no standard cut off points for assigning a study as high or low quality exists. Previous reviews have applied arbitrarily chosen cut offs of 50% or 75%. In the present review, the more conservative cut off of at least 75% was chosen to define a study as high quality. It is plausible that the use of other cut off points can change the conclusion. Another (preferred) method to compile the study results is by a meta-analysis. However, the heterogeneity was too large for pooling the data. More specifically, the definition and measurement of shift work and the outcome measures under study differed too much to be able to validly calculate a pooled effect size. In this case, a qualitative synthesis of the literature is appropriate.[70] The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach, endorsed by Cochrane Collaboration, is also recommended for determining the quality of evidence. It describes the extent of confidence the review authors have in the estimated effect size.[71] As this implies a meta-analysis, the GRADE approach was not followed. Although a systematic search was performed in several databases and references of relevant publications were checked, some studies might have been missed.

Conclusions

Shift work seems a risk factor for some, but not all, metabolic risk factors. Overall, a lack of high-quality studies with a longitudinal design and the inconsistency in study findings led to insufficient evidence with respect to the relation between shift work and blood lipids and blood pressure. To strengthen the evidence, more studies of high methodologic quality and a longitudinal nature are needed that provide detailed information on the exposure to shift work.

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Appendix

Supplementary data

Supplementary data associated with this article can be found at http://dx.doi.org/10.1016/j.amepre.2015.11.013.