Shift work and cardiovascular diseases: current evidences and guidelines for prevention.

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STATEMENT SLIDE

I have no conflicts of interest to disclose

INTRODUCTION

Old and **recent** large cohorts' studies provide evidence of the increased risk of cardiovascular diseases (CVD) among people working with a shifting schedule of work (SW) compared to a regular daily work (DW) (*A. Knutsson et al. Lancet 1986; T. Åkerstedt et al. Scand J Work Environ Health 1984); (L. Torquati et al SJEH 2018; JM Ferguson et al SJEH 2019; C. Vetter et al JAMA 2016; M.Cheng et al Occup. Med. 2019).*

The **recent studies** confirm that many questions remain unanswered about relationship (confounders and mediators) between shiftwork (SW) and CVD.
However, they often have old quality problems (i.e. selection bias, insufficient or incorrect control of confounders, and imprecise exposure information) *(M. Harma, SJEH 2018).*

No evidence-based guidelines internationally accepted are available to drive interventions aimed at reducing this preventable risk factor for cardiovascular mortality and morbidity, but only recommendations by experts in the field *(AH. Garde, SJEH 2020).*

KEY POINTS

What we already know about CVD and shiftwork.

What are the major gaps to be filled.

How we can address the lack of knowledge.

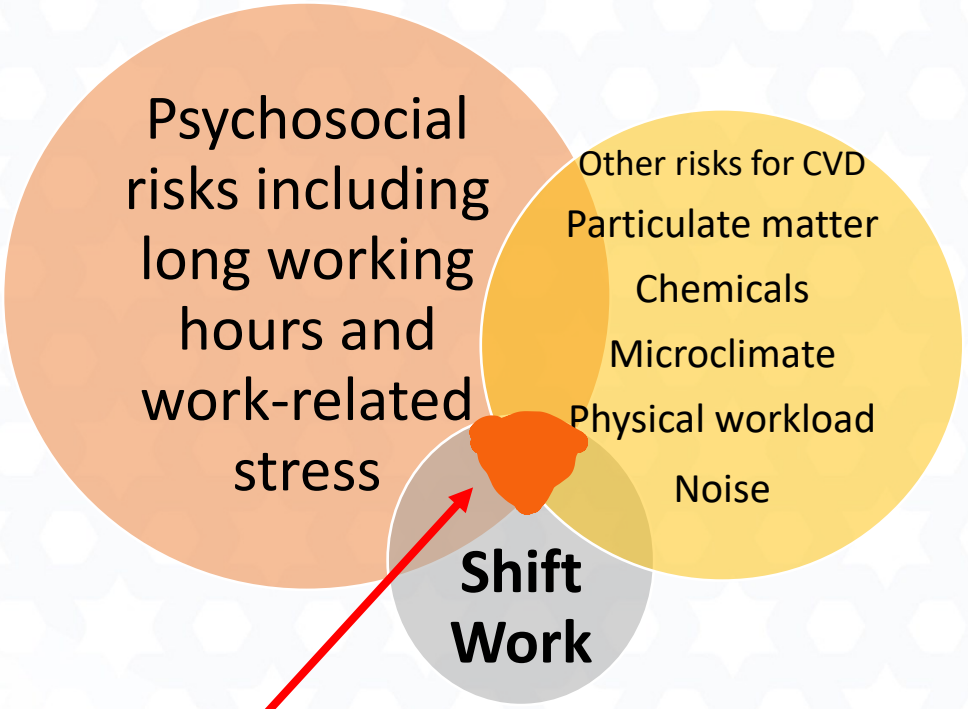
What can we do by now to prevent CVD in shift workers? It is time to start with wide and shared intervention in working place?

What we already know about CVD and SW: epidemiology and complexity

Shift work and night work is increasing world-wide and involve different sectors i.e., social and health care sector, hotels and restaurants, retail and sales, public administration and defence, transportation and manufacturing.

- Around 40 hours/week in SW in Europe;
- Over than 70h/week in SW in many companies of China and Africa and other rapidly developing countries.

Industrial Health 2021, **59**, 285–292
T. Anttila et al.



Combined and multiple risk factors for CVD increases complexity

What we already know about CVD and SW: dose-response relationship

The relative risk (RR) of Ischemic Heart Disease (IHD) rose with increasing duration of reported exposure to shift work.
A significant risk of IHD was associated with an exposure of 11-15 years (RR = 2·2, p 0·04) and of 16 to 20 years (RR = 2·8, p 0·03). The association was independent of age and smoking history.

The RR of IHD fell sharply after 20 years of shift work. This was ascribed to the pronounced positive selection that had taken place in this group.

TABLE I—RELATIVE RISK OF ISCHAEMIC HEART DISEASE IN DIFFERENT EXPOSURE CATEGORIES

—	Years of shift work					
	0	2–5	6–10	11–15	16–20	21–
RR	1·0	1·5	2·0	2·2	2·8	0·4
Proportion with IHD	9/110	3/58	7/60	10/81	10/52	4/122
Person-years	1414·5	776·0	751·0	928·0	647·0	1722·5
p-values	..	NS	NS	0·04	0·03	NS

"The trend up to 20 years of exposure was significant: partial r = 0.12 ($p < 0.05$) when age was held constant".

A. Knutsson et al. The Lancet , 1986

TABLE II—BACKGROUND VARIABLES

Variable	Day workers	Shift workers	p
Age (1968)	42·0 ± 15·2	39·3 ± 12·5	NS
Married (1982/83)	69%	61%	NS
Widowed (1982/83)	5%	5%	NS
Divorced (1982/83)	7%	14%	0·035
Smokers and ex-smokers (1968)	50%	74%	0·000
Smoking (g) (1968)	4·7 ± 7·5	8·5 ± 9·6	0·000
Smoking (g) (1982/83)	3·6 ± 7·1	5·5 ± 8·3	0·034
Hypertension (1982/83)	19%	22%	NS

N = 472 – 504. *t* test or χ^2-test as appropriate.
Findings other than percentages and p value given as mean ± SD.

TABLE III—MULTIPLE LOGISTIC REGRESSION ON ISCHAEMIC HEART DISEASE DURING 0–20 YEARS' EXPOSURE TO SHIFT WORK

Predictor	Coefficient	Coeff/SE	p
Age	0·0907	5·01	0·001
Years of shiftwork	0·0774	2·58	0·01
Constant	−6·88	−6·91	0·001

The **main predictor** of IHD was **age** and the next was **duration of exposure** to shift work.

What we already know about CVD and SW: dose-response relationship

7.1% incremental risk CVD for every five years of shift work exposure after the first five years.

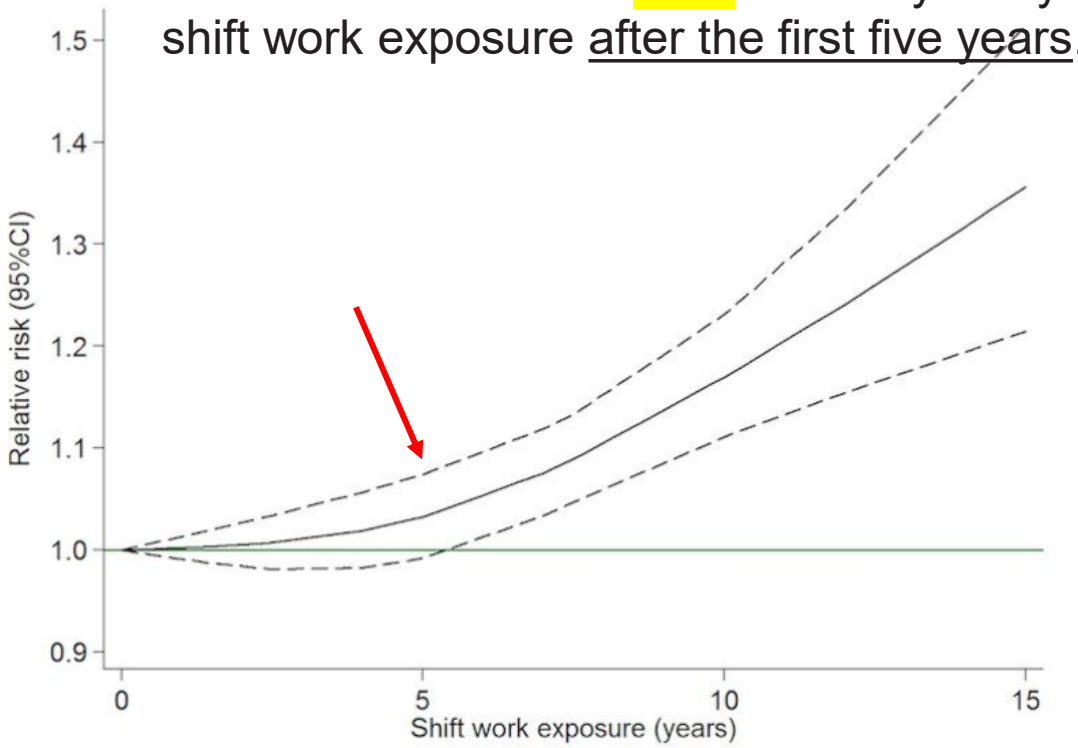


Figure 3. Dose-response relationship between years of shift work and risk of any CVD event. Relative risk was calculated with 16 estimates from N=5 cohort studies including N=13440 cases of CVD events. Dashed lines indicate 95% confidence interval.

Torquati et al , SJWEH 2018

0.9% increase of the risk of IHD for each 1-year increase in shift work exposure

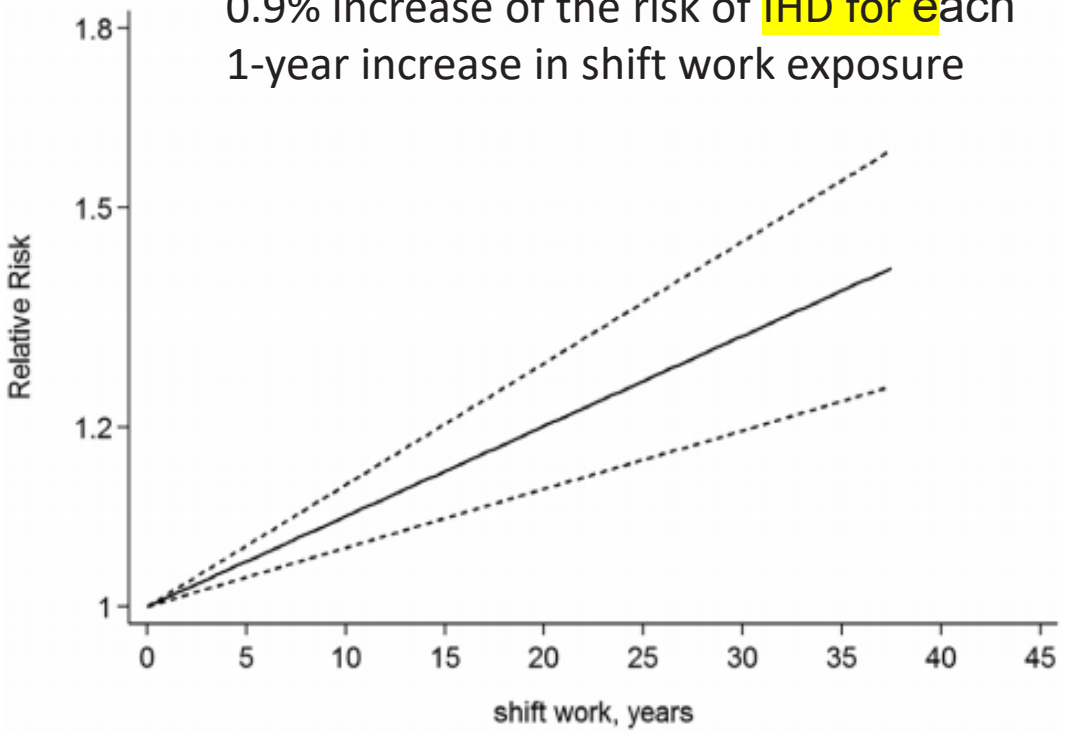


Figure 2. Relative risk for ischaemic heart disease by years of shift work based on the results of the dose–response meta-analyses. Solid line represents the estimated relative risk, while the dotted lines represent the 95% CIs.

Cheng et al , Occup. Med 2019

Systematic reviews: risk of bias and quality of the studies

Table 4| **Summary of findings: is shift work associated with an increased risk of cardiovascular events?***

Outcomes	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	No of participants (studies)	Relative effect (95% CI)	Quality of evidence (GRADE)
Myocardial infarction	Not likely†	No serious inconsistency‡	No serious indirectness§	No serious imprecision¶	Not likely**	1 082 977 (10)	1.23 (1.15 to 1.31)	Moderate††⊕⊕⊕O
Coronary events	Not likely†	Inconsistency‡‡	No serious indirectness§	No serious imprecision¶	Not likely**	1 530 070 (28)	1.24 (1.10 to 1.39)	Low††⊕⊕ OO
Ischaemic stroke	Not likely†	No serious inconsistency‡	No serious indirectness§	No serious imprecision¶	Undetected§§	80 787 (2)	1.05 (1.01 to 1.09)	Moderate†† ⊕⊕⊕O

†Median Downs and Black score for included studies was 60% (interquartile range 34-86%).
‡I^2=0%.
§Population, outcome, and intervention were consistent with question of interest, although individual studies varied.
¶No of events and participants studied in review is large, and confidence interval does not include null value.
**Estimates adjusted for publication bias did not differ from observed estimates.
††Dilution effect of single time point exposure ascertainment allows upgrading of evidence.
‡‡I^2=85%.
§§Publication bias could not be tested for two studies.

M.V. Vyas et al BMJ 2012

Table 2. Risk of bias assessment

Study	Risk of bias per item: Major Domain 1	2	3	4	5	Minor Domain * 1	2	3	4	5	Overall risk of bias
Cohort studies											
Allesøe et al 2010 (36)	1	1	0	0	0	U	U	0	0	0	High
Biggi et al 2008 (40)	0	0	0	0	0	U	U	0	U	U	Low
Brown et al 2009 (17)	0	1	0	0	0	U	U	0	0	0	Moderate
Ervasti et al 2016 (27)	1	1	0	0	0	U	U	0	0	0	High
Fujino et al 2006 (37)	1	1	0	0	0	U	U	0	0	0	High
Gu et al 2015 (16)	0	1	0	0	0	U	0	0	0	0	Moderate
Hublin et al 2010 (26)	1	1	0	0	0	U	0	0	U	0	High
Natti et al 2012 (38)	1	1	0	0	0	U	0	0	0	0	High
Tüchsen et al 2006 (33)	0	1	0	0	0	U	U	0	U	0	Moderate
Vetter et al 2016 (18)	0	1	0	0	0	0	0	0	0	0	Low
Virkkunen et al 2006 (30)	0	1	0	0	0	U	U	0	0	0	Moderate
Virkkunen et al 2007 (31)	0	1	0	0	0	U	U	0	0	U	Moderate
Wang et al 2015 (39)	0	1	0	0	0	U	1	0	0	0	Moderate
Wang et al 2016 (34)	0	1	0	0	0	U	U	0	0	0	Moderate
Yong et al 2014 (19)	0	0	0	0	0	0	0	0	U	0	Low
Case-control studies											
Cheng et al 2014 (41)	1	1	0	0	1	U	0	0	0	0	High
Ellingsen et al 2007 (32)	0	0	0	0	1	U	U	0	U	U	Moderate
Hermansson et al 2007 (35)	1	1	0	0	0	U	U	0	U	U	High
Hermansson et al 2015 (29)	0	1	0	0	0	U	U	0	U	0	Moderate
Kim et al 2013 (28)	1	1	0	0	0	0	U	0	0	0	High
Yadegarfar et al 2007 (20)	0	0	0	0	0	0	0	0	0	0	Low

* Risk of bias due to: (1) shift work exposure definition, (2) exposure assessment, (3) reliability of assessments, (4) confounders assessment, (5) analysis methods in the study (research-specific bias), (1a) blinding of assessors, (2a) attrition, (3a) selective reporting, (4a) funding, (5a) conflict of interest. 1 = high risk, 0= low risk; U= unclear.

Torquati et al , SJWEH 2018

Sensitivity analysis:

Studies with low, intermediate, or high risk of bias from either unreliable exposure assessment, insufficient adjustment for confounders, analytical methods, blinding of assessors, attrition, selective reporting, or funding.

Methodological shortcomings of the studied bias types seemed not explain the positive overall findings.

What we already know about CVD and SW: other studies and gaps

Association between rotating night shift work and risk of coronary heart disease among women

Main Outcomes and Measures—Incident CHD, i.e. non-fatal myocardial infarction, CHD death, angiogram-confirmed angina pectoris, coronary artery bypass grafting (CABG), stents, and angioplasty.

Design, Setting and Participants—Prospective cohort study of 189,158 initially healthy women followed over 24 years in the Nurses' Health Studies (NHS (1988-2012): N=73,623, and NHS2 (1989-2013): N=115,535).

Conclusions

Among women who worked as registered nurses, longer duration of rotating night shift work was associated with a statistically significant, but small absolute increase in CHD risk. Further research is needed to explore whether the association is related to specific work hours and individual characteristics.

C. Vetter et al

JAMA. 2016 April 26; 315(16): 1726–1734. doi:10.1001/jama.2016.4454.

Mechanisms and Role of Mediators

Circadian disruption

1. Misalignment between circadian oscillation of variables/functions regulated by the endogenous clock (day-night or light-dark synchronized) and the continuous changes of time of sleep, wake and work.
2. The degree of desynchronization seems to be related with the number of consecutive night shift: changes in amplitude, duration, and timing of biological rhythms (melatonin, cortisol, markers of autonomic control) and objective or subjective proxies of changed circadian rhythm.

SW

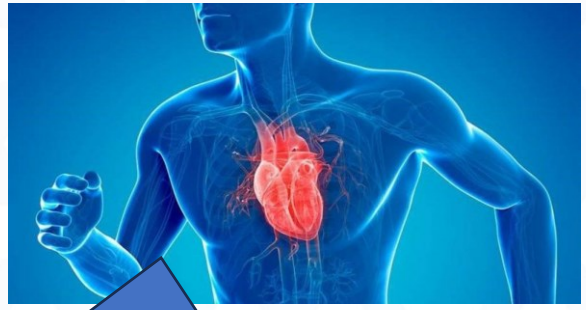
Autonomic unbalance, inflammation, insulin resistance

1. Sleep disorders (quality and duration)
2. Diet (irregular, low quality)
3. Smoking and alcohol
4. Leisure physical activity (?)

AGE

Hypertension
Dyslipidemia
Overweight/obesity
Diabetes
Metabolic syndrome

CVD



Mechanisms and Role of Mediators: Autonomic Nervous system Unbalance

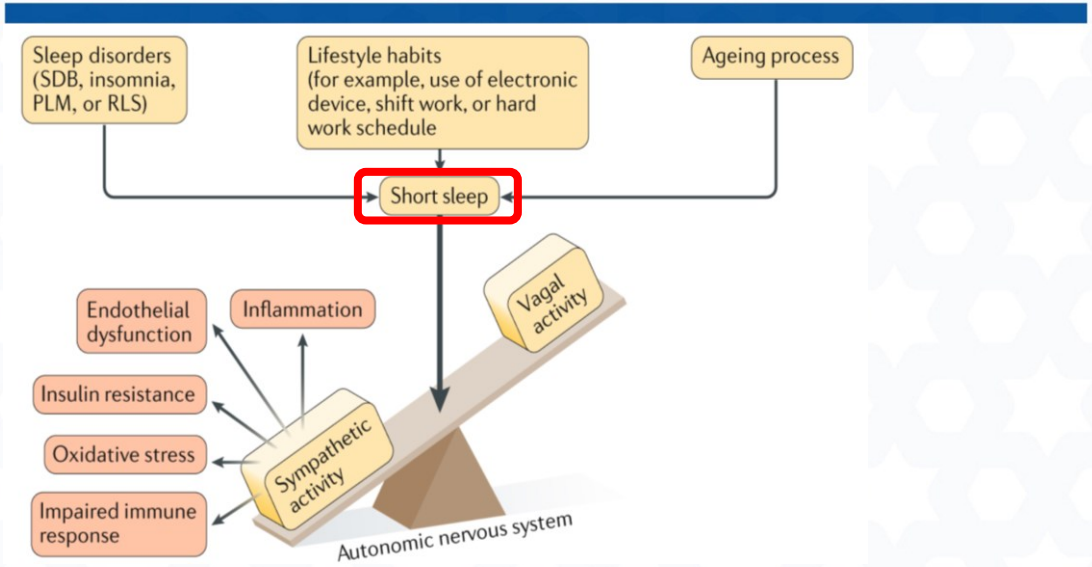
The status of the ANS, although often ignored by clinicians, is a ***major determinant of cardiovascular health and prognosis and strongly affected by circadian misalignment***.

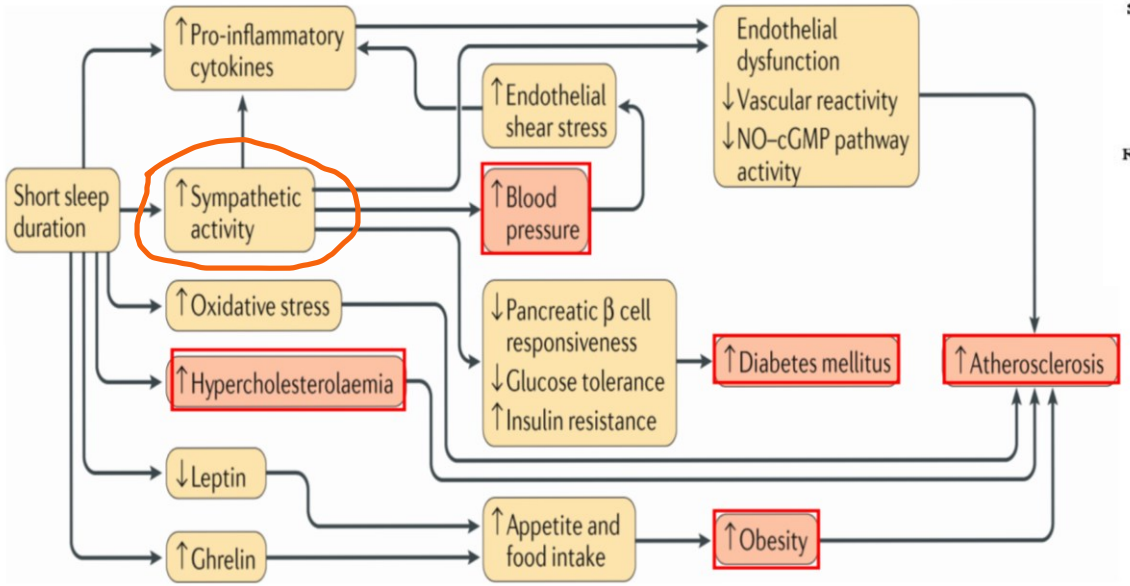
The sympathetic and parasympathetic balanced activity is crucial to control visceral functions such as:

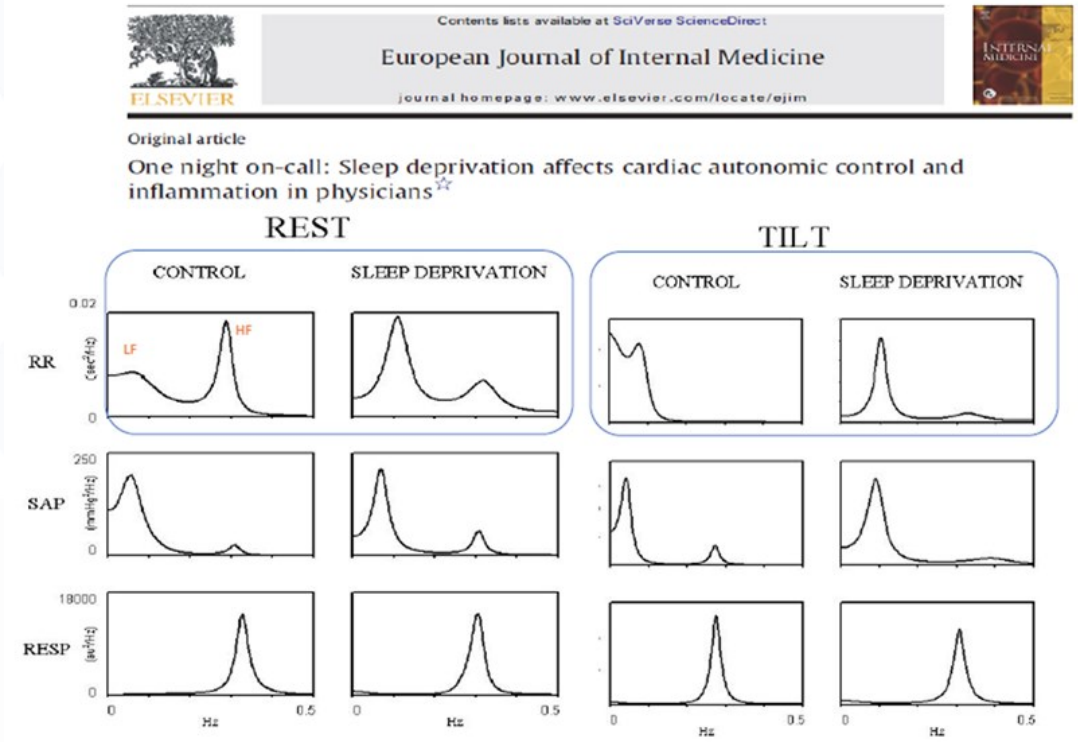
- Heart rate/stroke volume
- Blood pressure
- Gastroenteric motility and secretion
- Body temperature
- Energy expenditure
- Other essential functions

Un unbalance of ANS functioning also promoted by a circadian misalignment may impair responses to environmental stimuli and promote acute and chronic diseases.

Mechanisms and Role of Mediators: Autonomic Nervous system Unbalance






Contents lists available at SciVerse ScienceDirect
European Journal of Internal Medicine
journal homepage: www.elsevier.com/locate/ejim

Original article

One night on-call: Sleep deprivation affects cardiac autonomic control and inflammation in physicians☆

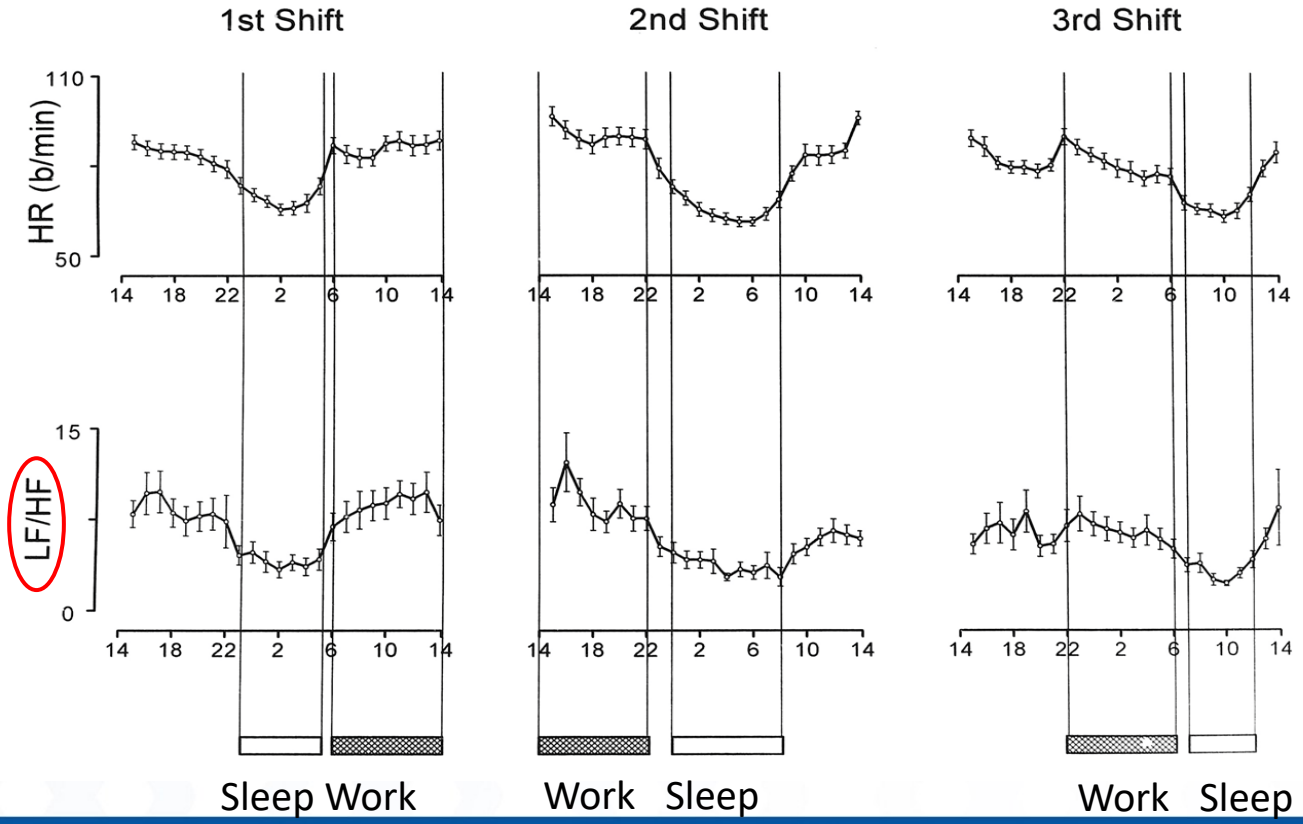
Tobaldini et al. Nat Rev Cardiol 2019

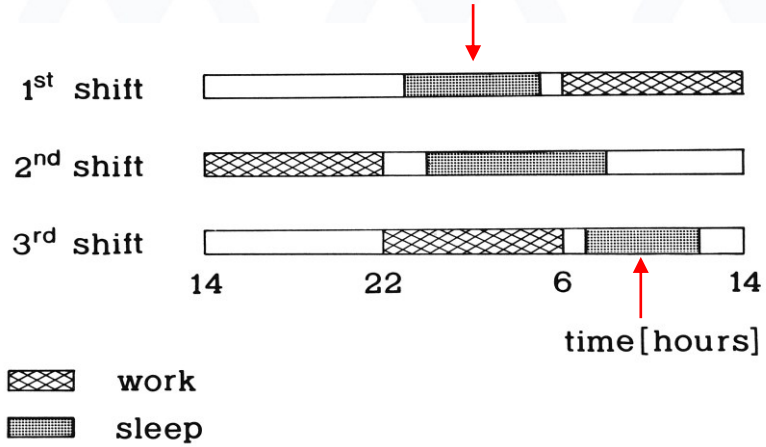
Mechanisms and Role of Mediators: Autonomic Nervous system Unbalance

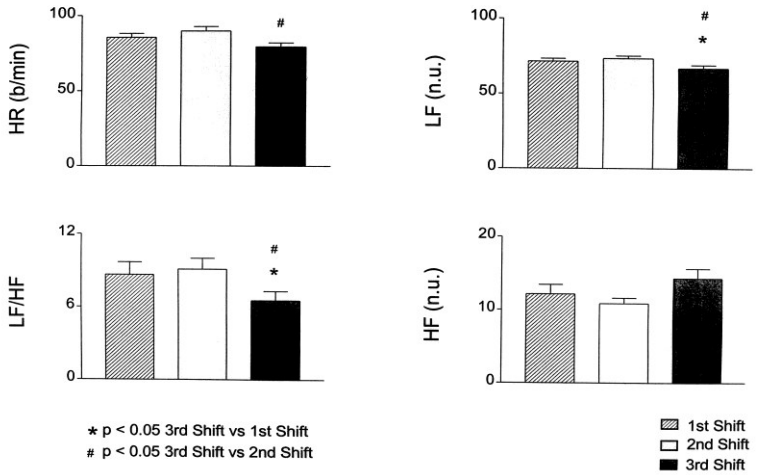
Circulation American Heart Association. Learn and Live.
Circulation 2000;102;1912-1916

Modifications of Cardiac Autonomic Profile Associated With a Shift Schedule of Work

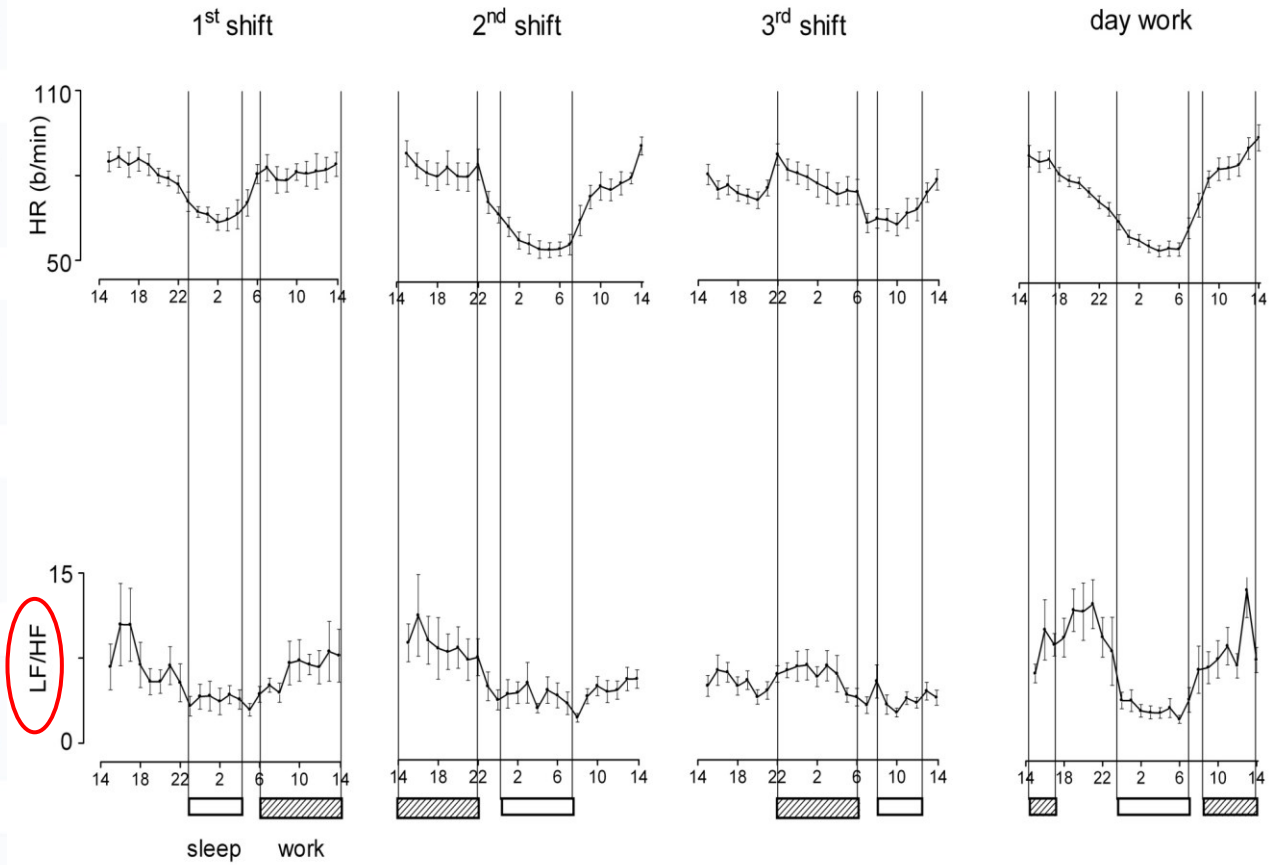
Raffaello Furlan, MD; Franca Barbic, MD; Simona Piazza, MD, PhD; Mauro Tinelli, MD, PhD; Paolo Seghizzi, MD; Alberto Malliani, MD

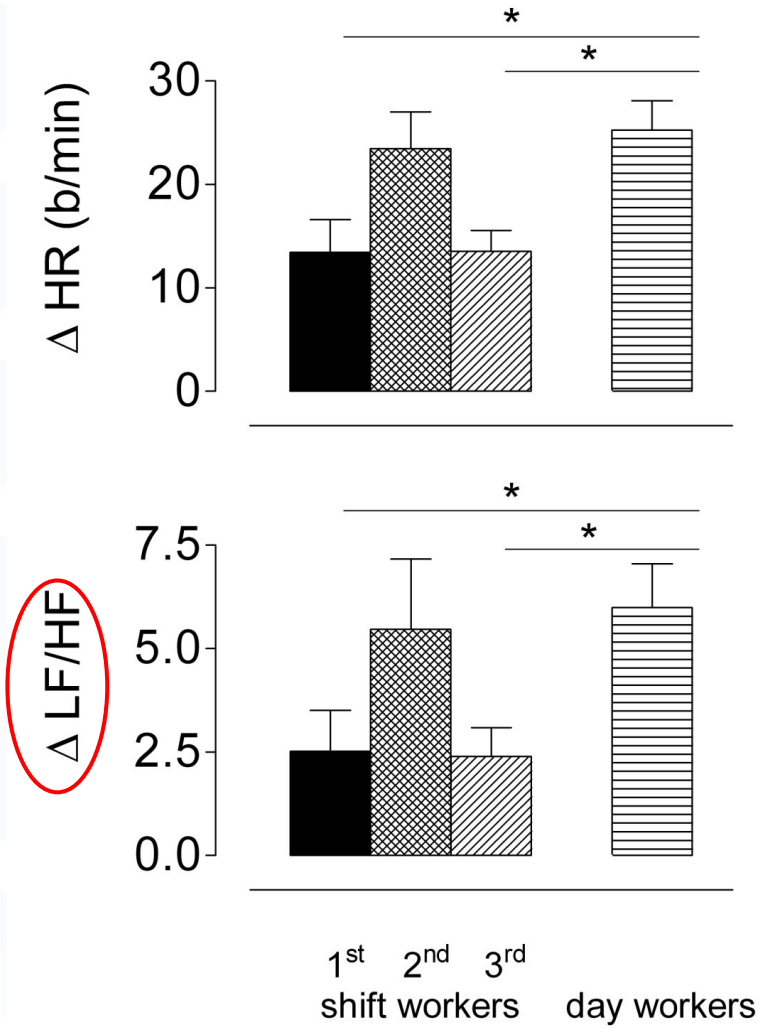






Mechanisms and Role of Mediators: Autonomic Nervous system Unbalance





F. Barbic F. et al Ergonomia IJE&HF, 2007; 29 (3-4): 199-204.

Autonomic Nervous System Unbalance and Chronic Sleep Deprivation in SW

The amplitude of 24-hour oscillations of cardiac sympatho-vagal modulation indexes were reduced in SW during the morning and nigh shift compared to what observed in habitual DW *(Barbic et al al. Ergonomia 2007*).

Of interest, this 24-hour oscillatory pattern is like to what previously observed in hypertensive and ischemic patients *(Guzzetti et al al. J Hypertens 1991; Lombardi et al. Am Heart J. 1992*) and in aging.

The reduced amplitude of 24-hour oscillations of the indexes of cardiac autonomic modulation observed in SW, and the continuous changes of the time of Max and Min represent a risk of CVD in this population.

The chronic sleep deprivation potentially associated with the shift schedule of work, may promote a long-lasting sympathetic overactivity leading to acute and chronic cardiovascular disease and metabolic syndrome.

Mechanisms and Role of Mediators: Myocardial Infarction severity, dyslipidemia, overweight, smoke

Disruption of Circadian Rhythms by Shift Work Exacerbates Reperfusion Injury in Myocardial Infarction

JACC VOL. 79, NO. 21, 2022
MAY 31, 2022:2097–2115

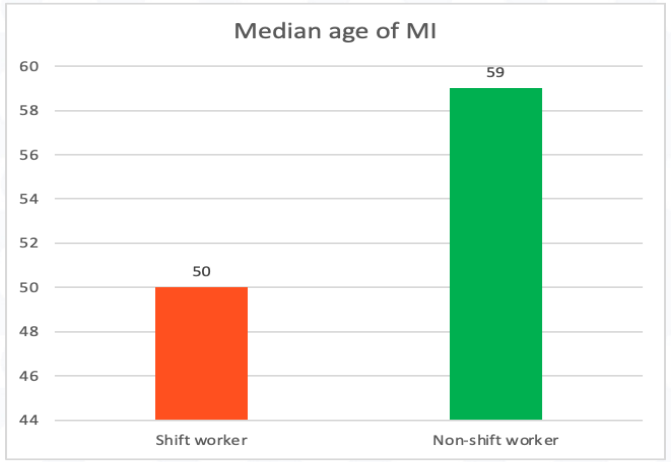
OBJECTIVES This study sought to investigate the impact of shift work on reperfusion injury, a major determinant of clinical outcomes in AMI.

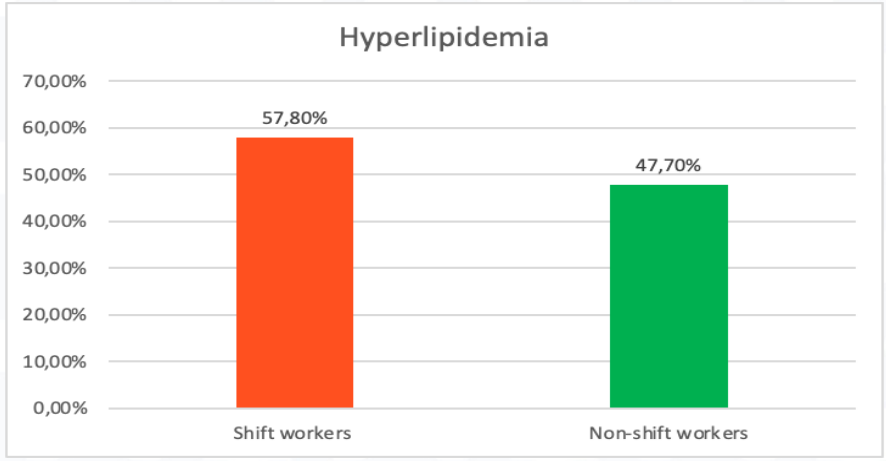
RESULTS Of 706 patients enrolled in the EARLY-MYO-CMR registry, 412 patients with STEMI were ultimately included. Shift work was associated with increased CMR-defined infarct size ($\beta = 5.94\%$; 95% CI: 2.94-8.94; $P < 0.0001$). During a median follow-up of 5.0 years, shift work was associated with increased risks of MACE (adjusted HR: 1.92; 95% CI: 1.12-3.29; $P = 0.017$). Consistent with clinical findings, shift work simulation in mice and sheep significantly augmented reperfusion injury in AMI. Mechanism studies identified a novel nuclear receptor subfamily 1 group D member 1/cardiotrophin-like cytokine factor 1 axis in the heart that played a crucial role in mediating the detrimental effects of shift work on myocardial injury.

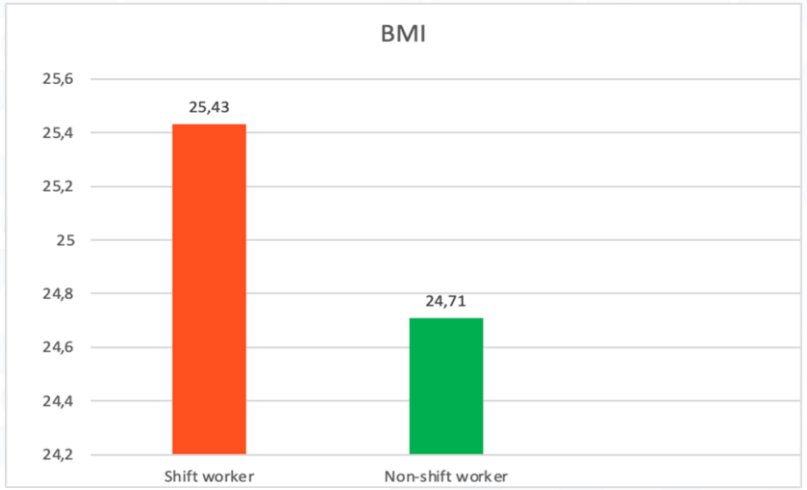
CONCLUSIONS The current study provided novel findings that shift work increases myocardial infarction reperfusion injury. It identified a novel nuclear receptor subfamily 1 group D member 1/cardiotrophin-like cytokine factor 1 axis in the heart that might play a crucial role in mediating this process. (Early Assessment of Myocardial Tissue Characteristics by CMR in STEMI [EARLY-MYO-CMR] registry; NCT03768453) (J Am Coll Cardiol 2022;79:2097–2115) © 2022 by the

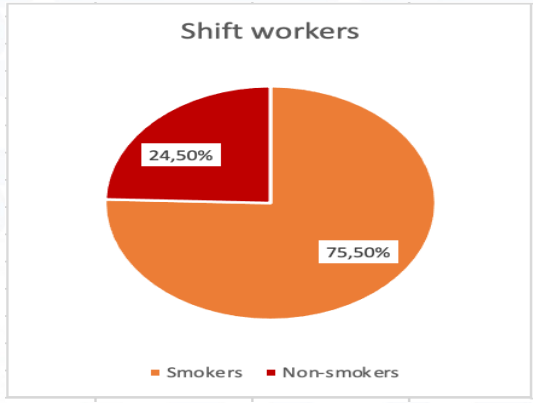
Yichao Zhao et al.

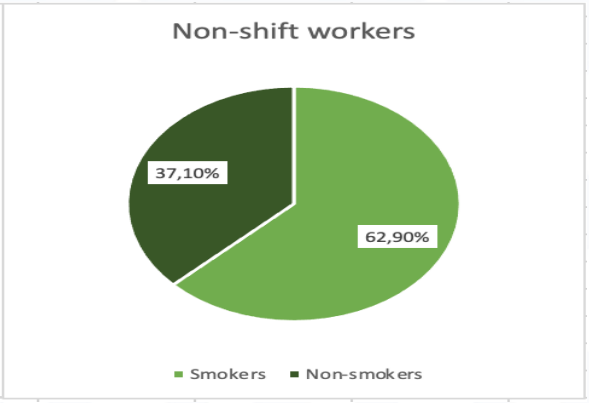
Mechanisms and Role of Mediators: Myocardial Infarction severity, age, dyslipidemia, overweight, smoke











Zhao *et al*

Shift Work and Reperfusion Injury

JACC VOL. 79, NO. 21, 2022

MAY 31, 2022:2097-2115

Mechanisms and Role of Mediators: Old and New insight in role of Hypertension

A longitudinal study on the relationship between shift work and the progression of hypertension in male Japanese workers

Mitsuhiro Oishi[a], Yasushi Suwazono[a], Kouichi Sakata[a], Yasushi Okubo[b], Hideto Harada[a], Etsuko Kobayashi[a]. Mirei Uetani[a] and Koii Nogawa[a]

Journal of Hypertension 2005, Vol 23 No 12

Shift work was found to be an independent risk factor for the progression of hypertension, particularly **diastolic** (adjusted for HbA1c and other significant factors i.e job schedule type, age, BMI, total cholesterol, creatinine, and g-GTP). **DAP** is strongly related with **sympathetic** efferent discharge to the vessels *(Barbic et al Physiol Meas. 2015)*.

Night and rotational work exposure within the last 12 months and risk of incident hypertension

by Ferguson JM, Costello S, Neophytou AM, Balmes JR, Bradshaw PT, Cullen MR, Eisen EA *Scand J Work Environ Health 2019*

1. Novel definitions of night work and rotational work and their associations with risk of incident hypertension
2. 2151 workers at eight aluminium manufacturing facilities
3. Followed from 2003 through 2013 for incident hypertension
4. Recent night and rotational work may both be associated with higher rates of incident hypertension.

Ferguson et al, 2019 (47)	Cohort study of aluminum manufacturing workers (2003–2013)	Hypertension	Average % night shifts/month in the past year			
			0	26	1	Reference
			>0–5	34	2.47	1.12–5.44
			>5–50	98	2.40	1.04–5.55
			>50–95	42	3.21	1.32–7.80
			>95–100	15	3.71	1.24–11.09

AH Garde et al SJWEH; 2020 Discussion Paper

Role of diet: quality and timing

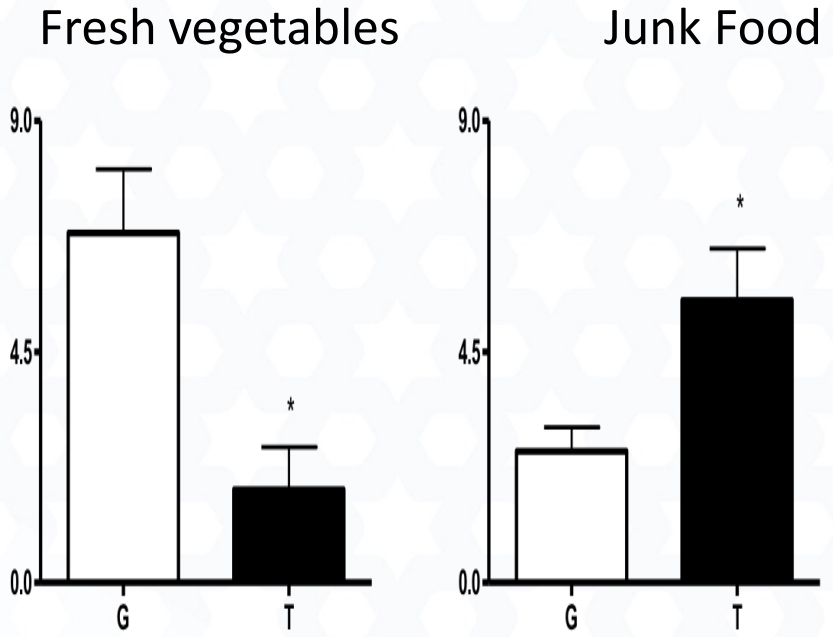
SWs has increased energy intake and weight gain; SW disturbs sleep and may increase smoking.

Shift workers have a similar diet quality but higher energy intake than day workers

Hulsegge G et al Scand J Work Environ Health 2016;42(6):459-468

PILOT - Eating time in a 3-shift workers (SW) and in a daily workers (DW) of a cement plant during a week of observation by a food diary.

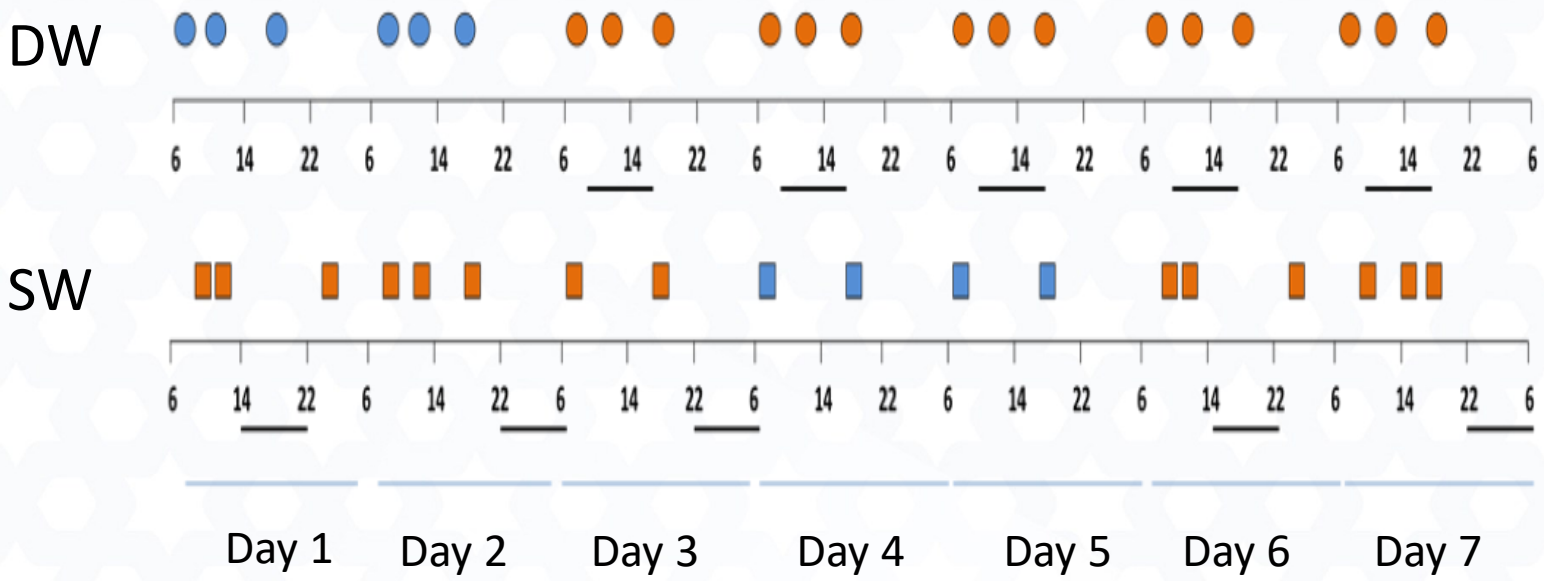
	Day workers	Shift workers	*p* value
Vegetables	6,8±3,5	1,8±2,4	0,005
Junk Food	2,6±1,3	5,5±2,9	0,019
Meat	4,5±1,6	5,6±3,4	0,409
Fruit juices and drinks	0,7±0,8	3,2±3,2	0,052
Spirits	2,1±1,6	3,7±4,6	0,379



Minonzio et al, Proceeding of Italian Congress of Occupational Medicine. Rome, 2020

Role of diet: quality and timing

PILOT - Eating time in a 3-shift workers (SW) and in a daily workers (DW) during a week of observation by a diary



Red: Work
Blue: Rest

Minonzio et al, Proceeding of Italian Congress of Occupational Medicine. Rome, 2020

Restricting food access to the active phase may accelerate adaptation of circadian rhythms in core body temperature and locomotor activity.

People would better cope with rotating shift work if they fixed their eating to the daytime.

Avoid caffeine almost 7 hours before sleeping time, also during night shift.

Assume warm beverage during the night to contrast the reduction of body temperature and increase vigilance.

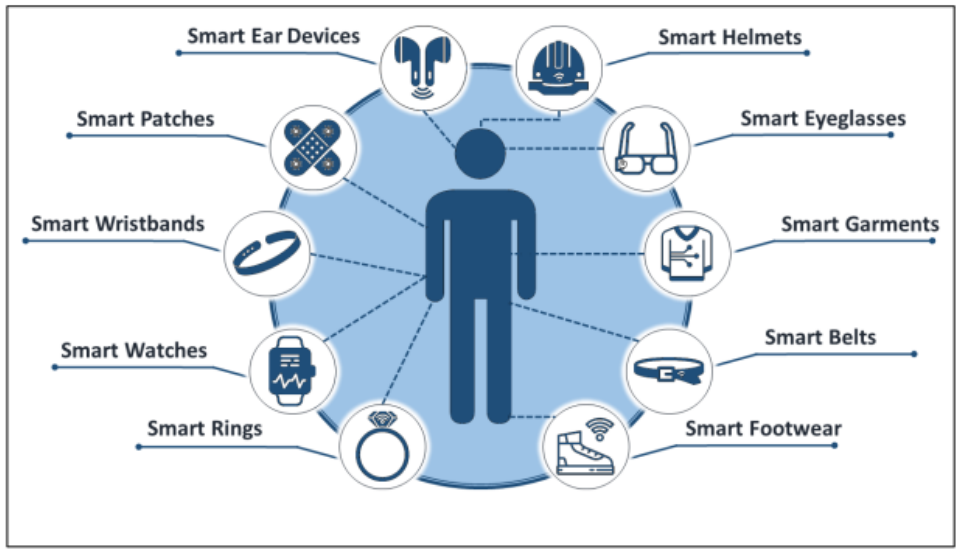
Hulsegge G et al SJWEH 2016;42(6):459-468
Potter and Wood Front. Nutr. 2020

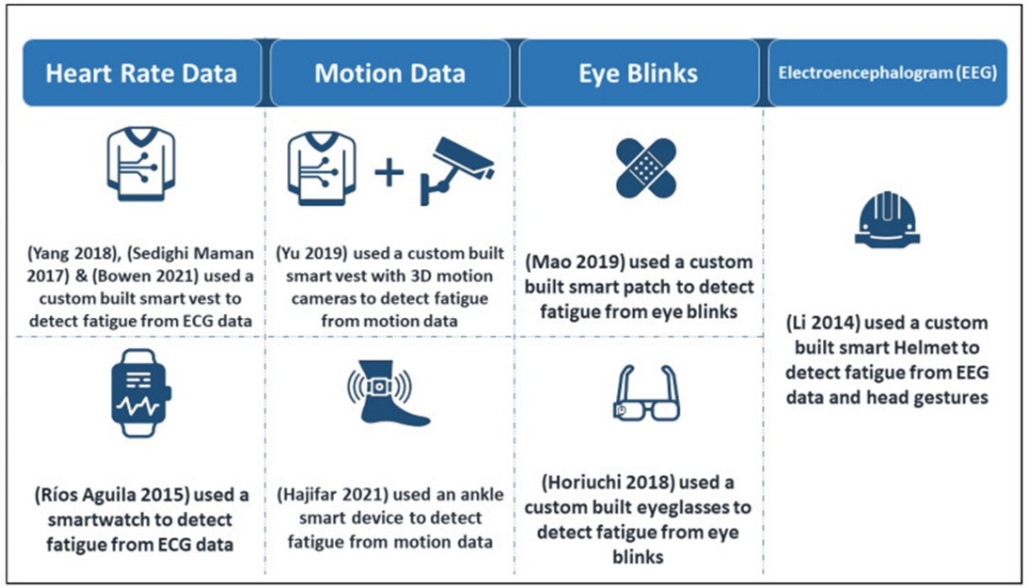
How we can address the lack of knowledge: future studies.

1. Should be based on **precise** and preferably repeated **information on exposure** combined with long, preferably registry-based follow-up. The use of register-based exposure information on working hours, like payroll data, is recommended if a sufficient proportion of working life is covered (*M. Harma et al 2018*).
2. Should be planned according with **high quality** and **risk of bias control** to avoid unusable results (GRADE)
3. Should address **gender and sex differences** in SW exposure and CVD outcomes, also considering work-life balance and extra work family-load.
4. Search for **individual/social/cultural determinants** that may predict the occurrence and severity of CVD in the presence of SW well defined exposure. Big data analysis by artificial intelligence may be used to:
   - Identify **hypersusceptible individuals** that should be quickly removed from risk also to prevent post-retirement disability.
   - Identify **individual determinants** that may be considered **protective against the risk.**

How we can address the lack of knowledge.

5. **Wearable devices** and **artificial intelligence technology** may provide opportunities to identify in an early phase signs of individual circadian disruption, early sign of fatigue, low quality of sleep and sleep deprivation in SW.





6. Search for **age-dependent threshold** in SW exposure intensity and duration.

7. Larger sample sizes to investigate **the effects of diet composition and timing** on a range of round-the-clock postprandial responses.

It is time to start with wide and shared intervention in working place?

How to schedule night shift work in order to reduce health and safety risks

Garde AH et al. *Scand J Work Environ Health*. 2020

In early 2020, 15 experienced shift work researchers participated in a workshop where they identified relevant scientific literature within their main research area to suggest preventing interventions .

1. ≤3 consecutive night shifts;
2. shift intervals of ≥11 hours;
3. ≤9 hours shift duration.
4. Forward-rotating schedules appear to have the most advantages: M-E-N *(D..Shiffer et al IJERPH 2018*)
5. Pregnant women should not work more than one night shift in a week (In Europe night work is not allowed during pregnancy)

It is time to start with wide and shared intervention in working place?

A new Precise Prevention Approach: Individual differences in response to shift work, according to age and chronotype (ie, how the circadian system embeds itself into the 24-hour day) are crucial and should be considered.

The role of age and shift exposure duration: Advanced ageing is associated with earlier chronotype, reduce 24-oscillation of cardiovascular autonomic control, alterations in circadian rhythmicity and sleep–wake homeostasis, increased CVD risk and higher morbidity and mortality in general (Fisher D et al PlosOne 2017).
Quick returns are associated with increased risk for sleep problems and fatigue among those aged ≥50.

The role of **other concomitant CVD risks**.

Considering mechanisms and mediators involved:

1. Provide **training** on the risks, promote **healthy diet** (quality and time) by providing **facilities in working place**.

2. Improve work environment according with **circadian synchronizers implementation** (light; exercise; food and beverage).

3. **Age and co-morbidity**: modify shifting schedule to adequately manage elderly workers and workers affected by mild CV impairment (early detection by monitoring). Early identification of people with low tolerance to SW and stop to exposure (age-related rotation).

CONCLUSION

Even if the relations between SW and CVD including coronary heart disease have been studied for a long time several gaps have to be filled.

Advanced technologies may furnish novel insights for workplace intervention aimed at reducing the effect of SW in CVD.

It is time to provide Evidence Based Guidelines that summarize the huge knowledges on SW and CVD that are available by now.

ACKNOWLEDGEMENTS & REFERENCES

- R. Furlan
- M. Minonzio
- D. Shiffer
- F. Dipaola
- A. Porta
- E. Tobaldini
- N.Montano
- S. Stranges
- J. Wei He
- E. Riboli
- A. R. Zamuner
- N. Magnavita
- I. Capitanelli
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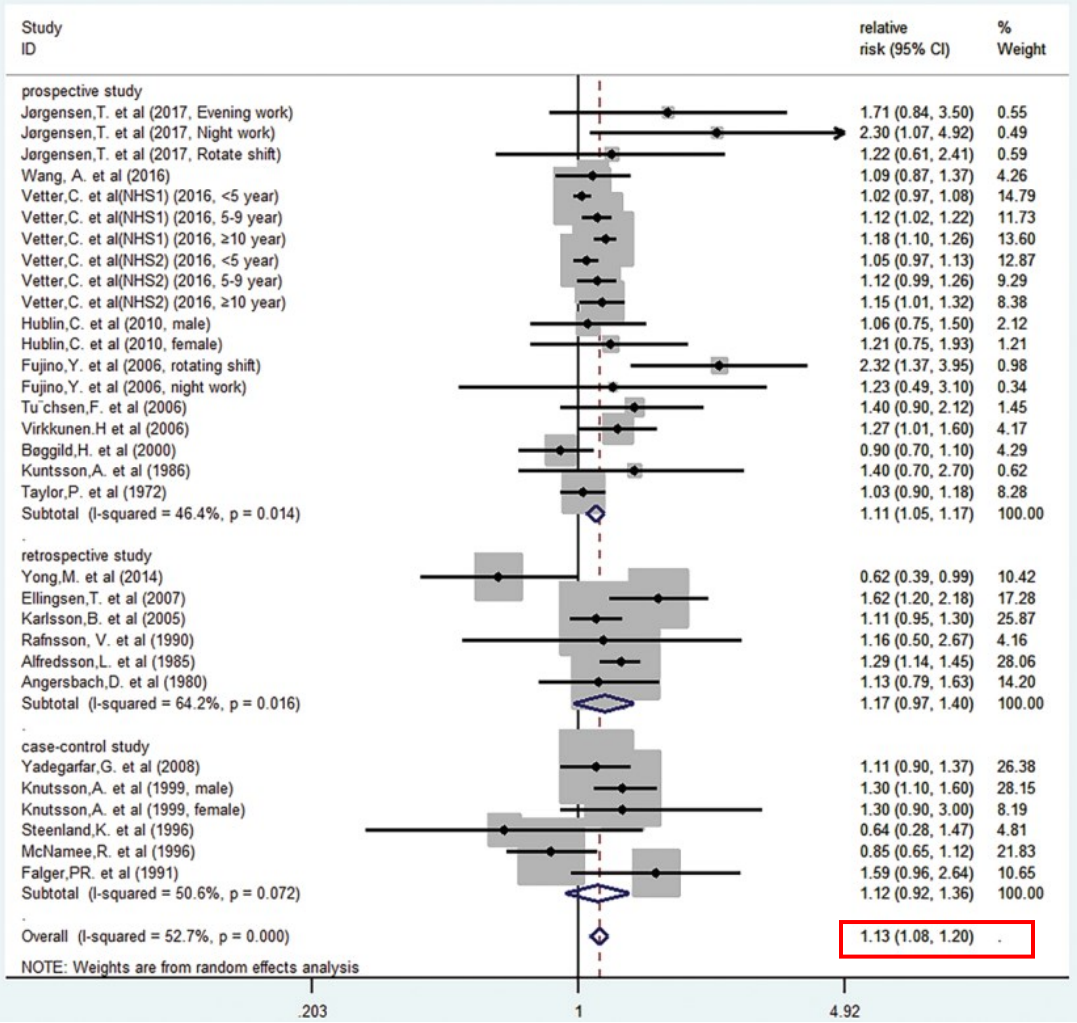
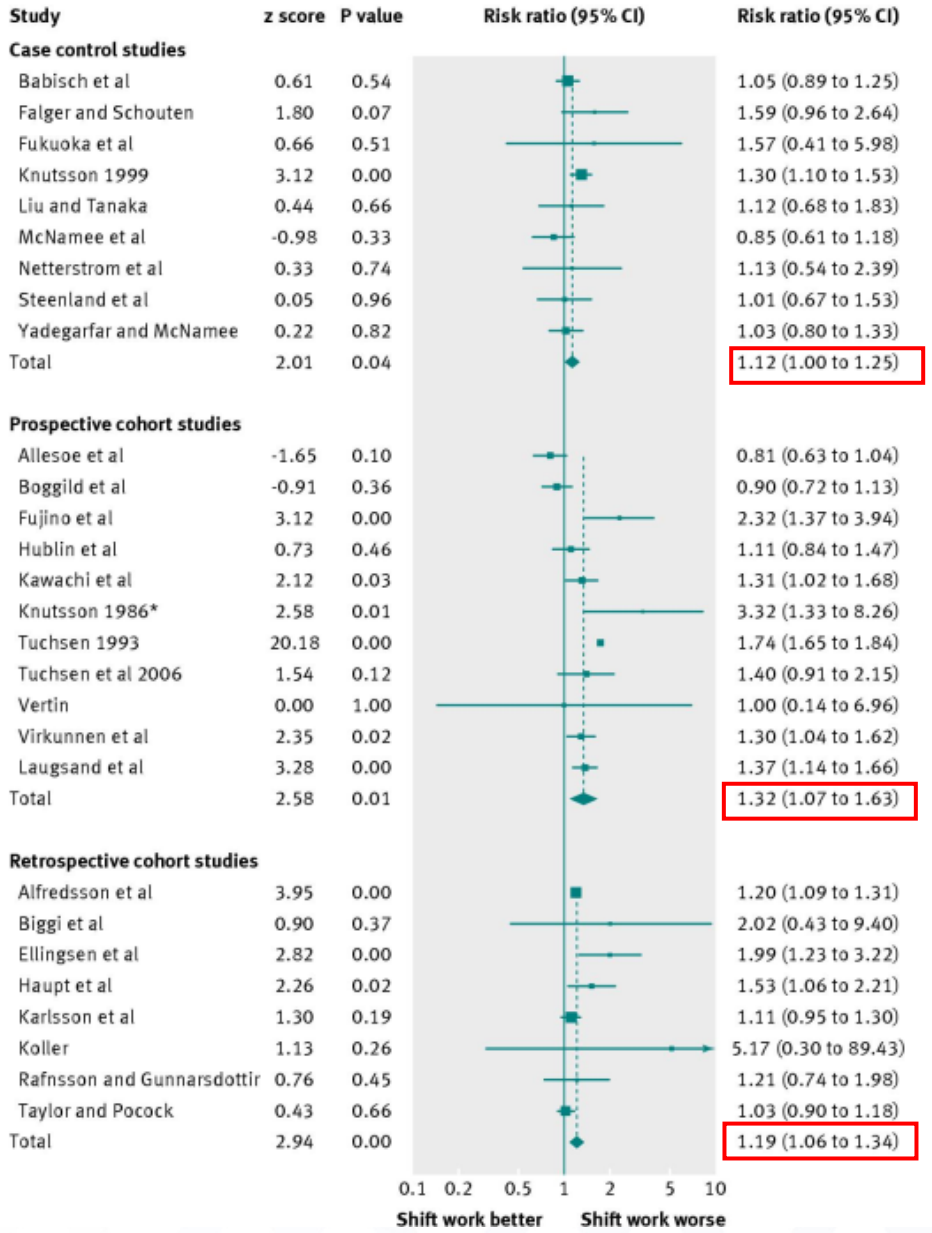
Metanalysis



Pooled random-effects RR and 95% CIs for the association of shift work and ischaemic heart disease by the study design.

M. CHENG *ET AL.*: SHIFT WORK AND ISCHAEMIC HEART DISEASE

Occupational Medicine 2019;**69:**182–188



Meta-analysis of coronary events. Studies were combined using a random effects generic inverse variance model after stratification by study design. *Risk ratio and 95% confidence interval recalculated from original study data over duration of follow-up

M.V. Vyas et al BMJ 2012