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BRIEF COMMUNICATION

Cumulative Exposure to Long Working Hours and Occurrence of Ischemic Heart Disease: Evidence From the CONSTANCES Cohort at Inception

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BACKGROUND: Long-working hours (LWH) are a probable risk factor for ischemic heart diseases (IHD); however, no previous study has considered duration of exposure to LWH when addressing this topic. We aimed to determine the association between cumulative exposure to LWH and IHD while accounting for relevant confounders.

METHODS AND RESULTS: In this retrospective study, we included all baseline participants from the French population-based cohort CONSTANCES. Part-time employees and those who reported a cardiac event in the 5 years before LWH exposure were excluded. From self-administered questionnaires and clinical examinations, we obtained participants' age, sex, body mass index, occupational status, smoking habits, high blood pressure, diabetes mellitus, familial history of cardiovascular disease, dyslipidemia, exposure to LWH, and its duration. We defined LWH as working for >10 hours daily for at least 50 days per year. The main outcome was reported history of IHD, ie, myocardial infarction or angina pectoris, during a clinical examination. Of 137 854 included participants, 69 774 were men. There were 1875 cases (1.36%) of IHD, and exposure to LWH was reported by 42 462 subjects (30.8%) among whom 14 474 (10.50%) reported exposure for at least 10 years. Overall, exposure to LWH for ≥10 years was associated with an increased risk of IHD, adjusted odds ratio (aOR) 1.24 (1.08–1.43), *P*=0.0021. In stratified analyses, this effect was not observed in women, but was significant amongst men, aOR 1.28 (1.11–1.48), *P*=0.0008.

CONCLUSIONS: This large population-based study supports an association between cumulative exposure to LWH and IHD in men. Future research should consider relevant strategies for reducing LWH exposure and duration.

Key Words: cumulative exposure ■ epidemiology ■ ischemic heart disease ■ long working hours

See Editorial by Alpert and Rieder

Ischemic heart disease is the leading cause of death and disability worldwide, a major driver of the global burden of disease. The workplace has received increasing attention as a setting for preventing cardiovascular disease.[1]

Among several occupational risk factors, much evidence suggests that long working hours (LWH) increase the risk of ischemic heart diseases (IHD): a recent meta-analysis showed that LWH increased the risk of IHD in both men and women.[2] However, a recent

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Nonstandard Abbreviations and Acronyms

ANR	National Agency for Research (in French)
aOR	Adjusted odds ratio
IHD	Ischemic heart disease
LWH	Long working hours

study from Denmark did not find any association,[3] and a recent Japanese study showed associations in men only.[4] Exposure to LWH in all these studies was defined as hours per week of LWH (intensity), rather than years of LWH (duration).[5] Our study sought to fill this gap by using a large general population cohort to investigate associations between cumulative exposure to LWH and IHD.

METHODS

Per the Transparency and Openness Promotion Guidelines, the methods used in the analysis will be made available at demand though the data are under restriction (country regulation). We used baseline data that included retrospective exposure and outcome information from the French CONSTANCES study. This active cohort includes randomly selected adults aged 18 to 69 years who are covered under France's National Health Insurance (representing >80% of the French population).[6] Participants are recruited from 21 health screening centers across France. From 2012 to 2018, baseline cohort data on LWH, IHD, and relevant health behaviors and comorbidities, were collected from self-administered questionnaires and clinical histories from baseline clinical examinations conducted by study physicians. Analyses were restricted to those employed full-time for >6 months.

Age, sex, smoking habits, occupational/social position, and work hours were obtained from the questionnaires. LWH were defined as ≥10 hours of daily work for at least 50 days per year (commuting time excluded). Participants reported if they were exposed to LWH and for how long. Following previously published analyses,[7] LWH were assessed in 3 categories of exposure: no exposure, exposure of <10 years, and exposure of >10 years.

From the baseline clinical examinations, we obtained body mass index, history of IHD (myocardial infarction or angina pectoris, and age of occurrence), history of diabetes mellitus, hypertension, dyslipidemia (hypercholesterolemia or hypertriglyceridemia), and family history of cardiovascular events, which included history of myocardial infarction or stroke among the participants' parents (before 65 years for mother and 55 years for father).

Reported IHD was the main outcome. During the clinical examination, the study physician asked several standardized questions about the participant's health as well as his/her medical history. If the participant answered positively for history of myocardial infarction and/or angina pectoris, the study physician asked for precision about the age of diagnosis. We excluded subjects who had missing data on LWH or a record of IHD before being exposed to LWH. We used logistic regression models to describe the association between LWH and IHD (further defined by including or excluding angina pectoris in the models). Models were adjusted for age, sex, occupation, body mass index, smoking habits, high-blood pressure, diabetes mellitus, dyslipidemia, and familial history of cardiovascular disease. Analyses stratifying by sex, age, and occupational/social position were also performed. We additionally examined a 5-year duration step for LWH, with a 5-year lag and checked with a Cox model (time continuous). Statistical analyses were performed using SAS software (version 9.4© SAS Institute Inc., Cary, NC, USA).

All study participants gave informed consent before enrolling in the study. CONSTANCES was approved by the Institutional Review Board of the National Institute for Medical Research (Inserm).

RESULTS

There were 162 115 subjects who reported working for at least 6 months. From this group 18 508 (11.4%) were excluded for a history of predominantly part-time jobs, and 5727 (4.0%) were excluded for missing data on duration of LWH. There were additional exclusions for reported occurrence of IHD before LWH's exposure (26 cases, 0.02%) and for any cardiac event before 5 years of exposure (55 subjects, 0.04%). In total, 137 854 participants were included.

Table 1 shows the characteristics of study participants, with 1875 cases (1.4%) of IHD (myocardial infarction or angina pectoris). Exposure to LWH was reported by 42 462 subjects (30.8%); 14 474 reported exposure to LWH for at least 10 years (10.5%).

Overall, LWH were associated with increased odds of IHD (Table 2). Being exposed to LWH for >10 years was significantly associated with IHD, adjusted odds ratio (aOR) 1.24 (1.08–1.43), P=0.0021. This association was stronger when excluding angina pectoris, aOR 1.31 (1.11–1.56), P=0.0017. Sex differences were observed: while exposure to LWH was significantly associated with IHD amongst men in all tested models, these associations were not found in women when considering angina pectoris—aOR 0.90 (0.55–1.49), P=0.69 or excluding angina pectoris—aOR 0.82 (0.41–1.65), P=0.57. Results

Table 1. Characteristics of the Study Population (n=137 854)

	LWH		
	No (n=107 604)	Yes (<10 y) (n=15 777)	Yes (≥10 y) (n=14 473)
Continuous variables, mean (SD)			
Age, y	48.1 (13.3)	42.4 (12.6)	54.8 (10.2)
Body mass index, kg/m²	25.0 (4.4)	24.8 (4.4)	26.1 (4.3)
Categorical variables, n (%)			
Sex			
Men	50 887 (47.3)	8793 (55.7)	10 094 (69.7)
Women	56 717 (52.7)	6984 (44.3)	4379 (30.3)
Occupation/social position			
Manager, CEO, skilled jobs	31 810 (29.6)	6489 (41.1)	7134 (49.3)
High-skilled white collar workers	31 095 (28.9)	3749 (23.8)	3316 (22.9)
Low-skilled white collar workers	25 725 (23.9)	2907 (18.4)	1540 (10.6)
Blue collar workers	11 064 (10.3)	1418 (9.0)	1237 (8.6)
Smoking habits			
No smoker	49 421 (45.9)	6345 (40.2)	5377 (37.2)
Current/former smoker <30 pack-years	43 109 (40.1)	7510 (47.6)	6529 (45.1)
Current/former smoker ≥30 pack-years	3917 (3.6)	543 (3.4)	1217 (8.4)
High blood pressure diagnosed			
No	94 937 (88.2)	14 500 (91.9)	11 838 (81.8)
Yes	12 667 (11.8)	1277 (8.1)	2635 (18.2)
Diabetes mellitus diagnosed			
No	104 893 (97.5)	15 444 (97.9)	13 838 (95.6)
Yes	2711 (2.5)	333 (2.1)	635 (4.4)
Dyslipemia diagnosed			
No	98 405 (91.5)	14 824 (94.0)	12 260 (84.7)
Yes	9199 (8.5)	953 (6.0)	2213 (15.3)
Familial history of cardiovascular diseases			
No	96 791 (90.0)	14 374 (91.1)	12 730 (88.0)
Yes	10 813 (10.0)	1403 (8.9)	1743 (12.0)
History of IHD (including angina pectoris)			
No	106 305 (98.8)	15 630 (99.1)	14 044 (97.0)
Yes	1299 (1.2)	147 (0.9)	429 (3.0)
History of myocardial infarction (excluding angina pectoris)			
No	106 819 (99.3)	15 689 (99.4)	14 197 (98.1)
Yes	785 (0.7)	88 (0.6)	276 (1.9)

CEO indicates chief executive officer; IHD, ischemic heart disease; LWH, long working hours.

were similar without adjusting for diabetes mellitus and high blood pressure, exposure to LWH was associated with IHD (including angina pectoris) $aOR_{LWH\geq 10\ years}$ 1.25 (1.08–1.43), P=0.0018.

No important changes in results were found after stratifying by age and occupation/social position (Table 3). The same analyses using a 5-year step showed an increase in association starting at 10 years of exposure to LWH (Table S1) Results were also confirmed when using a 5-year lag for LWH, when considering and excluding angina pectoris, aOR 1.18 (1.03–1.36) and 1.25 (1.05–2.14), respectively. Similar results were obtained when using a Cox-model (Table S2).

DISCUSSION

Previous meta-analyses indicated that working long hours (≥55 hours per week versus 35 to 40 hours per week) was associated with an elevated risk of IHDs of 13% after adjusting for age, sex, and socioeconomic status.[2] To our knowledge, our study is the first to examine the effect of cumulative exposure to LWH (exposure years) on IHD, and found a modest increase

Table 2. Associations Between Cumulative Exposure to LWH and Occurrence of IHD (Odds Ratio and 95% CIs), Among All, Men Only, and Women Only

	Cases: n (%)	Model I	Model II	Model III	Model IV
LWH					
IHD (including angina pectoris)					
No	1299 (1.2)	1.00	1.00	1.00	1.00
Yes (<10 y)	147 (0.9)	1.04 (0.86–1.26)	1.00 (0.81–1.23)	0.99 (0.80–1.23)	1.00 (0.81–1.24)
Yes (≥10 y)	429 (3.0)	1.38 (1.22–1.56)	1.26 (1.10–1.44)	1.25 (1.09–1.43)	1.24 (1.08–1.43)
IHD (excluding angina pectoris)					
No	785 (0.7)	1.00	1.00	1.00	1.0
Yes (<10 y)	88 (0.6)	0.98 (0.77–1.25)	0.93 (0.72–1.22)	0.93 (0.71–1.21)	0.94 (0.71–1.23)
Yes (≥10 y)	276 (1.9)	1.47 (1.26–1.71)	1.34 (1.13–1.58)	1.32 (1.11–1.56)	1.31 (1.11–1.56)
LWH among men					
IHD (including angina pectoris)					
No	1050 (2.06)	1.00	1.00	1.00	1.00
Yes (<10 y)	130 (1.48)	1.06 (0.87–1.30)	1.02 (0.82–1.27)	1.03 (0.82–1.30)	1.04 (0.83–1.31)
Yes (≥10 y)	401 (3.97)	1.38 (1.22–1.57)	1.29 (1.12–1.48)	1.29 (1.11–1.49)	1.28 (1.11–1.48)
IHD (excluding angina pectoris)					
No	650 (1.28)	1.00	1.00	1.00	1.00
Yes (<10 y)	80 (0.91)	1.02 (0.79–1.31)	0.97 (0.73–1.28)	0.98 (0.73–1.30)	0.99 (0.74–1.32)
Yes (≥10 y)	263 (2.61)	1.49 (1.27–1.74)	1.37 (1.16–1.63)	1.36 (1.14–1.63)	1.36 (1.14–1.62)
LWH among women					
IHD (including angina pectoris)					
No	249 (0.44)	1.00	1.00	1.00	1.00
Yes (<10 y)	17 (0.24)	0.89 (0.52–1.54)	0.86 (0.49–1.53)	0.79 (0.45–1.41)	0.79 (0.44–1.40)
Yes (≥10 y)	28 (0.64)	1.28 (0.84–1.95)	0.94 (0.57–1.54)	0.91 (0.55–1.50)	0.90 (0.55–1.49)
IHD (excluding angina pectoris)					
No	135 (0.24)	1.00	1.00	1.00	1.00
Yes (<10 y)	8 (0.11)	0.72 (0.33–1.56)	0.66 (0.29–1.53)	0.61 (0.27–1.41)	0.61 (0.26–1.41)
Yes (≥10 y)	13 (0.30)	1.08 (0.59–1.97)	0.85 (0.43–1.71)	0.82 (0.41–1.66)	0.82 (0.41–1.65)

Model I: adjusted for age, occupation/social position, and sex (if not stratified on it). Model II: model I+additionally adjusted for body mass index, and smoking habits. Model III: model II+additionally adjusted for high blood pressure, diabetes mellitus, and dyslipidemia. Model IV: full model=model III+additionally adjusted for familial history of cardiovascular diseases. IHD indicates ischemic heart disease; LWH, long working hours.

in occurrence of IHDs among male employees who were exposed to LWH for ≥10 years, after controlling for sociodemographic variables, smoking, comorbidities, and family history. Precise sedentary lifestyle was not available, alternatively body mass index was used as a proxy.[8] Few epidemiological studies have examined potential associations of cumulative exposure to psychosocial or organizational work factors with cardiovascular diseases: a study from New York indicated that systolic blood pressure was higher among men employed for ≥25 years who were exposed to job strain for 50% of their work life[9]; another study from Stockholm reported that employees had lower risk of IHD when they had more years of good managerial leadership.[10] Our group recently showed similar findings on cumulative exposure to LWH and stroke.[7]

Though current evidence on explanations linking LWH with IHD is limited, 2 major pathways have been proposed for observed associations.[11] The first is that LWH may promote unhealthy behaviors that increase cardiac risk, such as smoking, poor diet, and lack of exercise. Chronic psychosocial stress responses or work shift define a second pathway, as LWH may lead to excessive activation of the autonomic nervous system or immune system and thus increase cardiac risk.

Men, but not women, showed an increase in IHDs risk with LWH in our study. These observed differences have several possible explanations, including lack of statistical power given the low numbers of IHDs events among women with LWH in our sample, and exclusion of participants with predominantly part-time job may also contribute to these differences (more women with part-time jobs). The observed sex differences in our study and others are worth future exploration to examine other potential explanations including differently gendered work and sex-specific

Table 3. Stratified Analyses by Age and Occupation/Social Position for Associations Between Cumulative Exposure to LWH and Occurrence of IHD (Odds Ratio and 95% CIs)*

	LWH	Cases: n (%)	IHD (Including Angina Pectoris)	IHD (Excluding Angina Pectoris)
Age				
<50 y	No	113 (0.20)	1.00	1.00
	Yes (<10 y)	21 (0.19)	1.02 (0.59–1.76)	0.92 (0.47–1.81)
	Yes (≥10 y)	15 (0.32)	1.12 (0.59–2.15)	1.35 (0.66–2.77)
≥50 y	No	1186 (2.34)	1.00	1.00
	Yes (<10 y)	126 (2.83)	0.97 (0.77–1.22)	0.93 (0.69–1.26)
	Yes (≥10 y)	414 (4.22)	1.23 (1.07–1.42)	1.29 (1.08–1.54)
Occupation/social position				
Manager, CEO, skilled jobs	No	348 (1.09)	1.00	1.00
	Yes (<10 y)	37 (0.57)	0.93 (0.63–1.35)	0.75 (0.45–1.24)
	Yes (≥10 y)	197 (2.76)	1.20 (0.98–1.46)	1.23 (0.96–1.58)
High-skilled white collar workers	No	376 (1.21)	1.00	1.00
	Yes (<10 y)	48 (1.28)	1.28 (0.90–1.81)	1.34 (0.87–2.05)
	Yes (≥10 y)	93 (2.80)	1.17 (0.89–1.54)	1.19 (0.85–1.67)
Low-skilled white collar workers	No	185 (0.72)	1.00	1.00
	Yes (<10 y)	23 (0.79)	1.23 (0.74–2.05)	1.31 (0.70–2.48)
	Yes (≥10 y)	31 (2.01)	1.24 (0.79–1.94)	1.60 (0.95–2.70)
Blue collar workers	No	259 (2.34)	1.00	1.00
	Yes (<10 y)	18 (1.27)	0.64 (0.37–1.12)	0.52 (0.25–1.10)
	Yes (≥10 y)	67 (5.42)	1.50 (1.07–2.12)	1.50 (0.99–2.27)

CEO indicates chief executive officer; ICH, ischemic heart disease; and LWH, long working hours.

*Adjusted for body mass index, smoking habits, high blood pressure, diabetes mellitus, dyslipidemia, and familial history of cardiovascular diseases (plus sex and occupation/social position for age stratification, and sex and age for occupation/social position stratification).

worker survivor effects,[12] changes in work trajectory attributable to child-rearing, diagnostic biases, and other cultural and biological differences.[13] For our analyses, however, the number of women is too low to allow any interpretation.

There are some limitations. Even if we used baseline data from a cohort, this study is retrospective and so, information and common variable bias are always possible; however, in this multi-purpose cohort, the risk of this was reduced by using several mechanisms (different questionnaires and clinical examinations) to collect information on exposure to LWH and IHD. Current and retrospective exposure to LWH was first collected as part of the baseline questionnaire alongside other factors, such as biomechanical and social exposure variables; then, the occurrence of a cardiovascular event was obtained during a medical interview (clinical examination). From the detailed responses to specific questions on past exposure and disease, we were also able to exclude prior IHDs and perform a sensitivity analysis of the exposure disease relationship, using a 5-year lag.

Most variables used, including the main outcome and the exposure, are self-reported. While for cohort studies, objective, prospective measures are considered the gold standard, a recent study has indicated that the validity and reproducibility of self-reported past working hours were generally high when compared with employment records.[14] Further studies might use job coding and job exposures matrices that will be developed in the future. For IHD, there is evidence that self-reports and medical records have consistent positive agreement that is considered acceptable for large epidemiological studies.[15] Moreover in our cohort, IHD was defined by a physician who examined each participant, following protocol guidelines in place to improve diagnostic consistency. Though the clinician could not check medical records for past events, misclassification probably had a low impact on the diagnosis: in this cohort, diabetes mellitus that was recorded during the same examination protocol as our outcome, had high agreement with administrative data.[16] We also captured alternate names for IHD (ie, myocardial infarction with or without angina pectoris) that should provide additional reassurance of our analyses and variable definitions. We used logistic regression models rather than time-dependent ones (such as, Cox) as consistent with the structure of our data collection at baseline, and which gave similar results. Further studies in the future are recommended.

The main strength of this study is the large sample size. CONSTANCES is a population-based cohort of randomly selected adults enrolled in the National Health Insurance system, which covers >80% of the French population. The cohort is diverse in occupation and social status. Also noteworthy, is that we found a considerable association between exposure to LWH and IHD, even after adjusting for age, a time variant (variable) that may have reduced the strength of the association. This further highlights the independent effects of LWH.

In conclusion, this large-scale epidemiological study found moderate yet robust associations between cumulative exposure to LWH and occurrence of IHD among men. Intervention and implementation research should address the reduction of cumulative exposure to LWH as a step towards attenuating the global burden of work-related IHD.[11] Further studies with detailed occupational exposure information (including duration and intensity) and lifestyles, with prospective design will be relevant.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Materials

Tables S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. Sensitivity analysis for associations between cumulative exposure to long working hours and occurrence of ischemic heart disease with a five-year step (ORs and 95 % CIs)*.

Long working hours	Ischemic heart disease (including angina pectoris)	Ischemic heart disease (excluding angina pectoris)
No	1.00	1.00
Yes (<5 years)	0.90 (0.66-1.23)	0.79 (0.53-1.20)
Yes (≥5 and <10 years)	1.09 (0.83-1.44)	1.06 (0.76-1.50)
Yes (≥10 and <15 years)	1.18 (0.90-1.56)	1.38 (1.00-1.90)
Yes (≥15 and <20 years)	1.42 (1.08-1.87)	1.37 (0.97-1.93)
Yes (≥20 years)	1.22 (1.03-1.44)	1.28 (1.04-1.58)

*Adjusted for age, sex, occupations, body mass index, smoking habits, high-blood pressure, diabetes, dyslipidemia, and familial history of cardiovascular diseases

Table S2. Sensitivity analysis for associations between cumulative exposure to long working hours and occurrence of ischemic heart disease using Cox regression models (Hazard ratios and 95 % CIs)*.

	Ischemic heart disease (including angina pectoris)	Ischemic heart disease (excluding angina pectoris)
Long working hours all		
No	1.00	1.00
Yes (<10 years)	1.00 (0.83-1.21)	0.94 (0.73-1.21)
Yes (≥10 years)	1.21 (1.07-1.37)	1.28 (1.10-1.50)
Long working hours among men		
No	1.00	1.00
Yes (<10 years)	1.04 (0.85-1.27)	0.99 (0.76-1.29)
Yes (≥10 years)	1.25 (1.10-1.41)	1.32 (1.13-1.55)
Long working hours among women		
No	1.00	1.00
Yes (<10 years)	0.80 (0.45-1.40)	0.62 (0.27-1.40)
Yes (≥10 years)	0.91 (0.55-1.51)	0.82 (0.40-1.68)

*Adjusted for age, sex (if not stratified on sex), occupations, body mass index, smoking habits, high-blood pressure, diabetes, dyslipidemia, and familial history of cardiovascular diseases