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Direct and Indirect Effects of Prolonged Exposure to Long Working Hours on Risk Stroke Subtypes in the CONSTANCES Cohort

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Dear Sir:

Long working hours (LWH) have been identified as a leading cause of work-related mortality and morbidity.¹ Although their associations with health effects are low to moderate, the high prevalence of LWH makes them a significant occupational health risk.² Earlier evidence has suggested elevated risk of stroke among workers with prolonged exposure to LWH, but differentiating stroke subtypes and causal pathways have become a key focus of research.² Particularly, a couple of recent studies have highlighted a potential difference in association regarding ischemic and hemorrhagic stroke.^{3,4} The aim of this study was to estimate the direct and indirect effects of exposure to LWH on the risk of ischemic and hemorrhagic stroke through cardiovascular risk factors using structural equation models.

Baseline data from CONSTANCES (CONSultants des Centres d'Examens de Santé), a French population-based cohort were used. Details on the cohort are available elsewhere.⁵ All participants who had completed the baseline questionnaires and who were identified in the National Health Data System (Système National des Données de Santé, SNDS) were included. Partici-

pants with a personal history of stroke before their inclusion were excluded. All study participants provided written informed consent prior to enrollment with appropriate institutional review (Angers University Hospital Ethics Committee, approval #2021-186). For CONSTANCES, all procedures have been approved by the Institutional Review Board (IRB) of the French Institute of Health (Inserm) (Opinion n°01-011, then n°21-842), and authorized by the by the French Data Protection Authority ("Commission Nationale de l'Informatique et des Libertés," CNIL) (Authorization #910486).

Age, sex, smoking habits, family and personal history of cardiovascular diseases, socio-professional status according to the French classification, and exposure to LWH were collected from the questionnaire at baseline. LWH were defined as self-reported working time ≥ 10 h/day for at least 50 days/year. Duration of exposure to LWH was categorized by a period of every 5 years. The initial health examinations by medical professionals and the linkage to SNDS were used to identify diabetes, dyslipidemia (hypercholesterolemia or hypertriglyceridemia), and high blood pressure status according to validated algorithms (Supplementary Table 1). The SNDS is a national healthcare database and con-

tains data from the hospital discharge database and healthcare related reimbursement in France. Cases of stroke were retrieved during the follow-up period (until 2022) using the SNDS database and were categorized as hemorrhagic (I60–I62 except for I60.4/I60.5/I62.1) or ischemic (I63–I64 except for I63.6) using the International Classification of Diseases 10 (ICD-10). Only the first new case of stroke during the follow-up was considered.

Associations between LWH and stroke were examined using crude and adjusted multinomial logistic regression models, adjusting for cardiovascular variables. All analyses were stratified on sex. Missing data were imputed in a sensitivity analysis using multivariate imputation by chained equations. A conceptual structural equation model was created based on current knowledge between LWH and cardiovascular risk factors, which were considered as mediators in this analysis (Supplementary Figure 1). This method allows for studying the relation between variables, especially identifying mediating factors, testing hypothesized

structures, and assessing complex relationships between variables through their correlations.⁶ The aim is to construct, based on a hypothesized graph of measured and latent variables as well as their causal links, the linear model that most closely yields the observed matrix of cross-correlations between variables. The quality of the model is roughly reflected in how much correlation is explained by the model. Variables were standardized or binarized for categorical data. Adequation of models was estimated using usual indicators (root mean square error of approximation, standardized root mean square residual, comparative fit index, and Tucker–Lewis Index). Direct and indirect effects were estimated from the models and 95% confidence interval with bootstrapping. All analyses were carried out using R software (version 4.3.0; R Foundation for Statistical Computing, Vienna, Austria) with the following packages: compareGroups, mice, lavaan, and manyome.

From 2012 to 2022, 174,925 participants were free of stroke

Table 1. Multivariable multinomial regression analysis according to stroke subtypes

	Male		Female	
	Ischemic stroke	Hemorrhagic stroke	Ischemic stroke	Hemorrhagic stroke
	Adjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)
Age (yr)	1.08 (1.06–1.09)	1.08 (1.05–1.10)	1.06 (1.04–1.08)	1.04 (1.01–1.07)
Body mass index				
25–30 kg/m ² (vs. <25 kg/m ²)	0.81 (0.62–1.07)	0.90 (0.55–1.46)	1.14 (0.73–1.76)	0.86 (0.48–1.55)
≥30 kg/m ² (vs. <25 kg/m ²)	0.72 (0.48–1.06)	0.61 (0.29–1.31)	1.71 (1.05–2.79)	0.89 (0.43–1.85)
High blood pressure status				
Yes (vs. No)	1.41 (1.06–1.86)	1.73 (1.04–2.89)	2.01 (1.33–3.03)	1.73 (1.00–3.03)
Diabetes status				
Yes (vs. No)	1.06 (0.69–1.63)	1.14 (0.53–2.46)	0.60 (0.22–1.66)	1.33 (0.46–3.84)
Dyslipidemia status				
Yes (vs. No)	1.06 (0.82–1.38)	1.13 (0.71–1.80)	1.07 (0.72–1.59)	1.46 (0.85–2.51)
Familial history of cardiovascular diseases				
Yes (vs. No)	1.29 (0.83–2.00)	0.73 (0.26–1.99)	1.11 (0.60–2.08)	1.53 (0.73–3.22)
Smoking				
<30 pack-years (vs. 0 pack-years)	1.09 (0.83–1.43)	0.85 (0.54–1.36)	1.04 (0.72–1.52)	1.13 (0.67–1.89)
≥30 pack-years (vs. 0 pack-years)	1.64 (1.10–2.46)	0.67 (0.27–1.63)	1.73 (0.79–3.83)	3.52 (1.52–8.14)
Occupation				
Self-employed/chief executive officer/professional (vs. High-skilled white-collar)	1.11 (0.82–1.52)	1.16 (0.67–2.03)	0.71 (0.43–1.19)	0.97 (0.48–1.94)
Low-skilled white-collar (vs. High-skilled white-collar)	1.34 (0.88–2.05)	1.24 (0.56–2.74)	0.97 (0.64–1.47)	1.47 (0.81–2.66)
Blue-collar (vs. High-skilled white-collar)	1.45 (1.00–2.11)	1.43 (0.72–2.85)	0.71 (0.25–1.99)	2.35 (0.87–6.36)
Long working hours exposure				
5–10 years (vs. <5 years)	0.87 (0.48–1.57)	2.75 (1.38–5.49)	1.38 (0.64–2.99)	2.25 (0.95–5.31)
10–15 years (vs. <5 years)	1.18 (0.69–2.00)	2.36 (1.11–5.02)	0.29 (0.04–2.09)	1.16 (0.28–4.80)
≥15 years (vs. <5 years)	1.16 (0.85–1.58)	1.08 (0.58–1.99)	0.60 (0.24–1.48)	1.29 (0.51–3.31)

OR, odds ratio; CI, confidence interval.

*Multivariable models are adjusted for age, body mass index, high blood pressure, diabetes, dyslipidemia, smoking, and occupation.

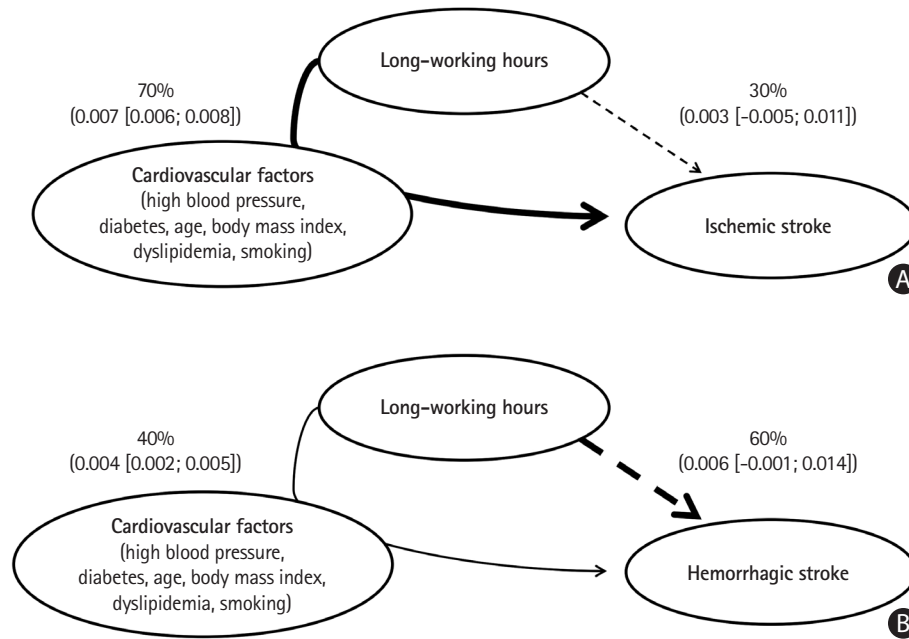


Figure 1. Direct and indirect effect of long working hours on (A) ischemic stroke and (B) hemorrhagic stroke through cardiovascular factors for males.

at baseline, while 1,507 were excluded for their own medical history of stroke. A flow diagram is available in Supplementary Figure 2. There were 463 ischemic stroke cases and 183 hemorrhagic stroke cases during the follow-up period. A full description of the population and the results of the models is provided in Supplementary Table 2. In the male subgroup, only hemorrhagic stroke was associated with LWH for durations of exposure between 5–10 years and 10–15 years, with adjusted odds ratios of 2.75 (1.38–5.49) and 2.36 (1.11–5.02), respectively (Table 1). No significant association with LWH was found in the female subgroup. Age and high blood pressure were associated with both stroke subtypes and both sex subgroups. Results were similar in the multiple imputation models (Supplementary Table 3). All structural equation models were well or very well identified. The total effect of LWH on the risk of ischemic stroke and hemorrhagic stroke was significant in the male subgroup (Figure 1), 70% of the total effect being indirect for ischemic stroke, whereas 60% of the total effect was direct for hemorrhagic stroke, though this was close to significance. The total effect was not significant in the female subgroup, in contrast to the male subgroup for both ischemic and hemorrhagic stroke.

This study explores the pathways of the modest but robust effect of LWH on the risk of ischemic and hemorrhagic stroke, confirming a previously raised hypothesis of differential pathways.³ In the male subgroup, there was a predominance of the indirect effect through cardiovascular risk factors for ischemic stroke contrary to hemorrhagic stroke.

This result is consistent with other studies in the literature,

which have found that exposure to LWH increases harmful health behaviors,⁷⁻⁹ known risk factors for stroke and cardiovascular diseases in general. However, it also shows that direct effects, possibly through stress-related, pro-inflammatory, or hypercoagulability mechanisms, may play a key factor,¹⁰ though its role as a potential trigger still needs to be explored.

The differences between sexes could be related to the lower level of exposure in the female subgroup and related to hormonal status, which was not considered, in addition to possible difference in tasks outside work. Future studies will have to test these hypotheses by focusing on highly exposed women. Furthermore, the weaker effect of LWH on stroke for the ≥15 years of LWH exposure group may be caused by their higher cardiovascular risk factors frequency (Supplementary Tables 4 and 5).

Several limitations should be discussed. All cardiovascular risk factors, as well as exposure to LWH, were assessed at the inclusion, even though working conditions and health behaviors may change over time, and not all cardiovascular factors could be explored. However, we looked at lifetime exposure to LWH, any potential changes in exposures might lead to underestimating associations. Moreover, though there was an update of the cohort's data, stroke remains a rare event, leading to a low number of events and statistical power in some subgroups, especially women.

There are important implications to these findings. Multilevel prevention seems relevant, and interventions focusing on both working conditions at the organizational level and cardiovascular risk factors at the individual level are warranted. Further

research with longitudinal assessment of mediators, better inclusion of other cardiovascular and work-related factors, and focus on women is needed.

Supplementary materials

Supplementary materials related to this article can be found online at <https://doi.org/10.5853/jos.2024.02586>.

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Conflicts of interest

The authors have no financial conflicts of interest.

Author contribution

Conceptualization: MF, AD, YR. Study design: MF, AD. Methodology: MF, AD. Statistical analysis: MF, ERF. Writing—original draft: MF. Writing—review & editing: GS, JL, AL, FP, AS, YR. Approval of final manuscript: all authors.

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The data of the CONSTANCES cohort are protected by our national regulatory agency ("Commission nationale de l'informatique et des libertés", n°910486). The CONSTANCES cohort is "an open epidemiological laboratory," access to and data is available on request (http://www.constances.fr/index_EN.php#propose). Access to some confidential data, on which is based this work, has been made possible within a secure environment offered by CASD – Centre d'accès sécurisé aux données (Ref. 10.34724/CASD).

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Supplementary Table 1. Algorithms used to detect diabetes, high blood pressure, and dyslipidemia status using data from the CONSTANCES cohort and the National Health Data System (Système National des Données de Santé, SNDS)

	Health examination variables*	SNDS variables	Confirmation criteria (if either)
Diabetes	<ul style="list-style-type: none"> - Personal history of type 1 or 2 diabetes - Blood sugar level from blood tests 	<ul style="list-style-type: none"> - Medication dispensation type based on the Anatomical Therapeutic Chemical Classification System (ATC) 	<ul style="list-style-type: none"> - Personal history of type 1 or 2 diabetes reported - Blood sugar level ≥ 7 mmol/L - Medication dispensation of an ATC A10 drug (except A10BX06) in the 6 months before inclusion
High blood pressure	<ul style="list-style-type: none"> - Personal history of high blood pressure - Blood pressure from physical examination 	<ul style="list-style-type: none"> - Medication dispensation type based on ATC classification 	<ul style="list-style-type: none"> - Personal history of high blood pressure reported - Systolic pressure ≥ 140 mm Hg or diastolic pressure ≥ 90 mm Hg - Medication dispensation of specified ATC drugs[†] in the 6 months before inclusion
Dyslipidemia	<ul style="list-style-type: none"> - Personal history of hypercholesterolemia or hypertriglyceridemia - Blood cholesterol and triglyceride levels 	<ul style="list-style-type: none"> - Medication dispensation type based on ATC classification 	<ul style="list-style-type: none"> - Personal history of hypercholesterolemia or hypertriglyceridemia reported - Fasting cholesterol level ≥ 6.61 mmol/L or triglyceride level ≥ 1.7 mmol/L - Medication dispensation of an ATC C10 drug in the 6 months before inclusion

*Variables from the health examination with a health professional; [†]ATC codes for high blood pressure: C03EA, C02AB02, C02AC01, C02AC02, C02AC05, C02AC06, C02CA01, C02CA06, C02DC01, C02LA01, C03AA01, C03AA03, C03BA04, C03BA10, C03BA11, C03BX03, C03CA01, C03CA02, C03CA03, C03DA01, C03DB01, C03EA01, C03EA04, C07AA02, C07AA03, C07AA05, C07AA06, C07AA12, C07AA15, C07AA16, C07AA23, C07AB02, C07AB03, C07AB04, C07AB05, C07AB07, C07AB08, C07AB12, C07AG01, C07BA02, C07BB02, C07BB03, C07BB07, C07BB12, C07CA03, C07DA06, C07FB02, C07FB03, C08CA01, C08CA02, C08CA03, C08CA04, C08CA05, C08CA08, C08CA09, C08CA11, C08CA13, C08CX01, C08DA01, C08DB01, C08GA02, C09AA01, C09AA02, C09AA03, C09AA04, C09AA05, C09AA06, C09AA07, C09AA08, C09AA09, C09AA10, C09AA13, C09AA15, C09AA16, C09BA01, C09BA02, C09BA03, C09BA04, C09BA05, C09BA06, C09BA07, C09BA09, C09BA15, C09BB02, C09BB04, C09BB10, C09BX02, C09CA01, C09CA02, C09CA03, C09CA04, C09CA06, C09CA07, C09CA08, C09DA01, C09DA02, C09DA03, C09DA04, C09DA06, C09DA07, C09DA08, C09DB01, C09DB02, C09DB04, C09XA02, C09XA52, C10BX03.

Supplementary Table 2. Description and univariate tests of the population included according to stroke subtypes

	Male				Female					
	Total (n=81,446)	No stroke (n=81,033)	Ischemic stroke (n=312)	Hemorrhagic stroke (n=101)	P	Total (n=93,479)	No stroke (n=93,246)	Ischemic stroke (n=151)	Hemorrhagic stroke (n=82)	P
Age (yr)	47.4±12.8	47.3±12.8	58.3±9.28	57.5±10.7	<0.001	46.6±12.8	46.6±12.8	57.1±11.1	54.8±11.9	<0.001
Occupation					0.456					0.008
High-skilled white-collar jobs	19,575 (26.2)	19,483 (26.2)	71 (25.1)	21 (23.9)		28,919 (33.7)	28,843 (33.7)	55 (41.0)	21 (28.4)	
Self-employed/chief executive officer/professional jobs	33,481 (44.8)	33,316 (44.8)	124 (43.8)	41 (46.6)		24,116 (28.1)	24,075 (28.2)	24 (17.9)	17 (23.0)	
Low-skilled white-collar jobs	10,361 (13.9)	10,318 (13.9)	33 (11.7)	10 (11.4)		29,722 (34.7)	29,644 (34.7)	49 (36.6)	29 (39.2)	
Blue-collar jobs	11,357 (15.2)	11,286 (15.2)	55 (19.4)	16 (18.2)		2,944 (3.44)	2,931 (3.43)	6 (4.48)	7 (9.46)	
Body mass index					0.020					<0.001
<25 kg/m ²	39,618 (49.4)	39,450 (49.4)	127 (41.1)	41 (41.4)		59,315 (64.4)	59,196 (64.4)	69 (46.3)	50 (61.0)	
25–30 kg/m ²	30,753 (38.3)	30,574 (38.3)	134 (43.4)	45 (45.5)		21,812 (23.7)	21,745 (23.7)	46 (23.7)	21 (25.6)	
≥30 kg/m ²	9,879 (12.3)	9,818 (12.3)	48 (15.5)	13 (13.1)		11,018 (11.9)	10,973 (11.9)	34 (22.8)	11 (13.4)	
Familial history of cardiovascular diseases					0.684					0.480
No	75,363 (93.8)	74,983 (93.8)	285 (92.8)	95 (95.0)		85,315 (92.7)	85,111 (92.7)	132 (91.0)	72 (90.0)	
Yes	4,961 (6.18)	4,934 (6.17)	22 (7.17)	5 (5.00)		6,714 (7.30)	6,693 (7.29)	13 (8.97)	8 (10.0)	
Smoking					<0.001					<0.001
Not smoker	33,125 (41.2)	32,987 (41.2)	98 (31.7)	40 (40.0)		46,096 (50.0)	45,983 (50.0)	74 (50.3)	39 (48.8)	
Current/former smoker <30 pack-years	42,972 (53.4)	42,751 (53.4)	169 (54.7)	52 (52.0)		44,030 (47.8)	43,933 (47.8)	64 (43.5)	33 (41.2)	
Current/former smoker ≥30 pack-years	4,349 (5.41)	4,299 (5.37)	42 (13.6)	8 (8.00)		2,002 (2.17)	1,985 (2.16)	9 (6.12)	8 (10.0)	
Diabetes status					<0.001					0.086
No	77,274 (95.0)	76,902 (95.1)	284 (91.0)	88 (87.1)		90,901 (97.4)	90,679 (97.4)	144 (95.4)	78 (95.1)	
Yes	4,044 (4.97)	4,003 (4.95)	28 (8.97)	13 (12.9)		2,451 (2.63)	2,440 (2.62)	7 (4.64)	4 (4.88)	
High blood pressure status					<0.001					<0.001
No	50,783 (62.4)	50,637 (62.6)	113 (36.2)	33 (32.7)		72,757 (77.9)	72,650 (78.0)	67 (44.4)	40 (48.8)	
Yes	30,548 (37.6)	30,281 (37.4)	199 (63.8)	68 (67.3)		20,600 (22.1)	20,474 (22.0)	84 (55.6)	42 (51.2)	
Dyslipidemia status					<0.001					<0.001
No	50,875 (62.6)	50,672 (62.6)	155 (49.7)	48 (47.5)		69,849 (74.8)	69,714 (74.9)	88 (58.3)	47 (57.3)	
Yes	30,452 (37.4)	30,242 (37.4)	157 (50.3)	53 (52.5)		23,499 (25.2)	23,401 (25.1)	63 (41.7)	35 (42.7)	
Long working hours exposure					<0.001					0.584
<5 years	55,829 (73.0)	55,582 (73.0)	190 (65.1)	57 (62.0)		75,783 (85.8)	75,591 (85.8)	129 (89.6)	63 (82.9)	
5–10 years	6,275 (8.20)	6,245 (8.21)	19 (6.51)	11 (12.0)		5,208 (5.89)	5,194 (5.89)	8 (5.56)	6 (7.89)	
10–15 years	4,451 (5.82)	4,423 (5.81)	19 (6.51)	9 (9.78)		2,819 (3.19)	2,816 (3.19)	1 (0.69)	2 (2.63)	
≥ 15 years	9,937 (13.0)	9,858 (13.0)	64 (21.9)	15 (16.3)		4,559 (5.16)	4,548 (5.16)	6 (4.17)	5 (6.58)	

Values are presented as mean±standard deviation or n (%).

Supplementary Table 3. Multivariable analysis according to stroke subtypes with imputation for missing data by multivariate imputation by chained equations

	Male		Female	
	Ischemic stroke	Hemorrhagic stroke	Ischemic stroke	Hemorrhagic stroke
	Adjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)
Age (yr)	1.08 (1.06–1.09)	1.07 (1.04–1.09)	1.06 (1.04–1.08)	1.04 (1.01–1.06)
Body mass index				
25–30 kg/m ² (vs. <25 kg/m ²)	0.84 (0.66–1.09)	0.84 (0.54–1.31)	1.29 (0.88–1.89)	0.76 (0.45–1.29)
≥30 kg/m ² (vs. <25 kg/m ²)	0.74 (0.52–1.06)	0.55 (0.28–1.08)	1.69 (1.09–2.62)	0.63 (0.31–1.26)
High blood pressure status				
Yes (vs. No)	1.53 (1.18–1.98)	2.01 (1.26–3.20)	2.17 (1.51–3.12)	2.36 (1.44–3.89)
Diabetes status				
Yes (vs. No)	0.88 (0.59–1.32)	1.48 (0.80–2.75)	0.81 (0.37–1.77)	1.09 (0.38–3.08)
Dyslipidemia status				
Yes (vs. No)	1.08 (0.85–1.37)	1.23 (0.81–1.87)	0.97 (0.68–1.37)	1.26 (0.80–2.04)
Familial history of cardiovascular diseases				
Yes (vs. No)	1.08 (0.70–1.67)	0.75 (0.30–1.84)	1.05 (0.59–1.88)	1.23 (0.59–2.56)
Smoking				
<30 pack-years (vs. 0 pack-years)	1.11 (0.87–1.43)	0.83 (0.54–1.25)	1.04 (0.74–1.47)	0.94 (0.59–1.49)
≥30 pack-years (vs. 0 pack-years)	1.55 (1.06–2.25)	0.67 (0.31–1.47)	1.69 (0.84–3.40)	2.94 (1.36–6.37)
Occupation				
Self-employed/chief executive officer/professional (vs. High-skilled white-collar)	1.07 (0.79–1.45)	1.19 (0.70–2.03)	0.67 (0.42–1.07)	1.04 (0.54–2.02)
Low-skilled white-collar (vs. High-skilled white-collar)	1.24 (0.81–1.89)	1.29 (0.61–2.74)	0.88 (0.60–1.29)	1.38 (0.77–2.46)
Blue-collar (vs. High-skilled white-collar)	1.44 (1.00–2.07)	1.55 (0.82–2.92)	0.88 (0.38–2.05)	2.76 (1.17–6.56)
Long working hours exposure				
5–10 years (vs. <5 years)	1.26 (0.78–2.02)	2.36 (1.23–4.54)	1.29 (0.63–2.64)	1.81 (0.77–4.28)
10–15 years (vs. <5 years)	1.34 (0.83–2.02)	2.14 (1.06–4.32)	0.25 (0.04–1.74)	0.88 (0.21–3.60)
≥15 years (vs. <5 years)	1.22 (0.91–1.64)	0.99 (0.55–1.77)	0.59 (0.26–1.34)	1.05 (0.41–2.71)

OR, odds ratio; CI, confidence interval.

*Multivariable models are adjusted for age, body mass index, high blood pressure, diabetes, dyslipidemia, smoking, and occupation.

Supplementary Table 4. Sensitivity analysis of cardiovascular risk factors in the LWH exposure subgroups

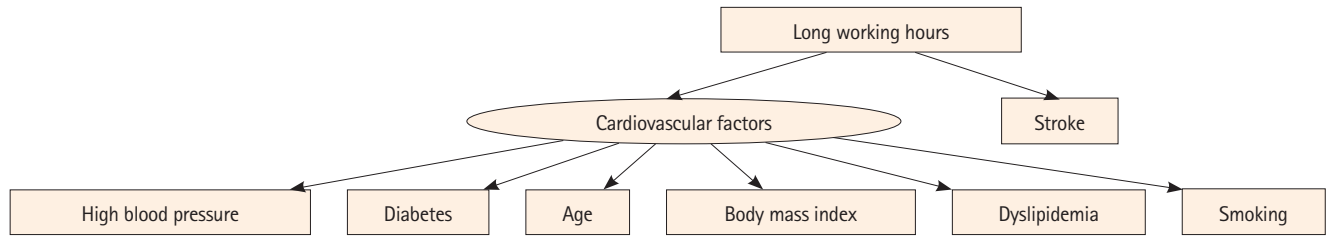
	Total (n=164,861)	LWH <5 years (n=131,612)	LWH 5–10 years (n=11,483)	LWH 10–15 years (n=7,270)	LWH ≥15 years (n=14,496)	P
Age (yr)	46.9±12.8	46.4±13.0	42.2±11.7	46.5±10.9	54.8±9.4	<0.001
Occupation						<0.001
High-skilled white-collar jobs	46,989 (30.6)	39,275 (31.9)	2,700 (25.3)	1,716 (25.3)	3,298 (24.7)	
Self-employed/chief executive officer/professional jobs	54,044 (35.2)	37,487 (30.5)	5,341 (50.0)	3,594 (53.0)	7,622 (57.1)	
Low-skilled white-collar jobs	39,017 (25.4)	34,842 (28.3)	1,817 (17.0)	971 (14.3)	1,387 (10.4)	
Blue-collar jobs	13,698 (8.91)	11,333 (9.22)	814 (7.63)	499 (7.36)	1,052 (7.87)	
Body mass index						<0.001
<25 kg/m ²	93,491 (57.5)	76,553 (59.0)	6,655 (58.8)	3,833 (53.5)	6,450 (45.1)	
25–30 kg/m ²	49,483 (30.4)	38,251 (29.5)	3,357 (29.6)	2,370 (33.1)	5,505 (38.5)	
≥30 kg/m ²	19,559 (12.0)	14,928 (11.5)	1,312 (11.6)	967 (13.5)	2,352 (16.4)	
Familial history of cardiovascular diseases						0.037
No	151,544 (93.2)	121,066 (93.3)	10,534 (93.2)	6,662 (92.7)	13,282 (92.8)	
Yes	11,006 (6.77)	8,682 (6.69)	770 (6.81)	523 (7.28)	1,031 (7.20)	
Smoking						<0.001
Not smoker	75,118 (46.1)	61,892 (47.6)	4,756 (41.9)	2,938 (40.8)	5,532 (38.6)	
Current/former smoker <30 pack-years	81,863 (50.3)	64,037 (49.3)	6,226 (54.8)	3,936 (54.6)	7,664 (53.5)	
Current/former smoker ≥30 pack-years	5,904 (3.62)	4,048 (3.11)	381 (3.35)	333 (4.62)	1,142 (7.96)	
Diabetes status						<0.001
No	158,609 (96.3)	126,975 (96.6)	11,113 (96.9)	6,984 (96.2)	13,537 (93.5)	
Yes	6,035 (3.67)	4,461 (3.39)	356 (3.10)	278 (3.83)	940 (6.49)	
High blood pressure status						<0.001
No	116,691 (70.9)	94,401 (71.8)	8,805 (76.8)	5,215 (71.8)	8,270 (57.1)	
Yes	47,967 (29.1)	37,040 (28.2)	2,666 (23.2)	2,047 (28.2)	6,214 (42.9)	
Dyslipidemia status						<0.001
No	114,003 (69.2)	92,370 (70.3)	8,291 (72.3)	4,940 (68.0)	8,402 (58.0)	
Yes	50,645 (30.8)	39,069 (29.7)	3,180 (27.7)	2,323 (32.0)	6,073 (42.0)	

Values are presented as mean±standard deviation or n (%).
LWH, long working hours.

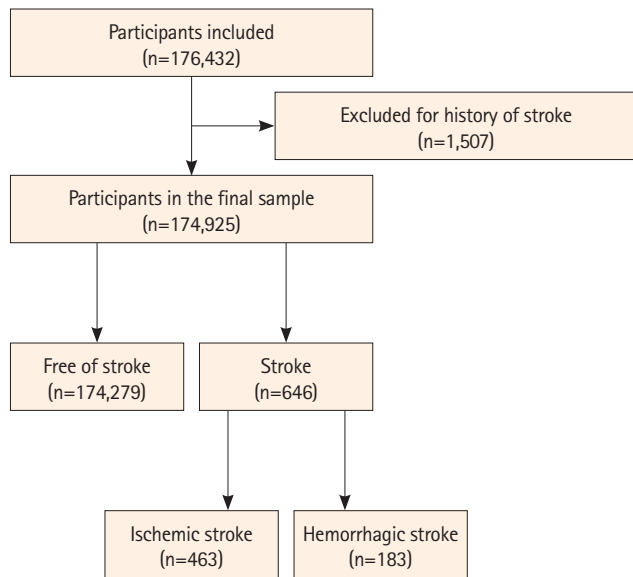
Supplementary Table 5. Sensitivity analysis of cardiovascular risk factors in the LWH exposure subgroups

LWH exposure subgroup	Male		Female	
	Ischemic stroke Crude OR (95% CI)	Hemorrhagic stroke Crude OR (95% CI)	Ischemic stroke Crude OR (95% CI)	Hemorrhagic stroke Crude OR (95% CI)
5–10 years (vs. <5 years)	0.89 (0.55–1.43)	1.72 (0.90–3.28)	0.90 (0.44–1.84)	1.39 (0.60–3.20)
10–15 years (vs. <5 years)	1.26 (0.78–2.02)	1.98 (0.98–4.01)	0.21 (0.03–1.49)	0.85 (0.21–3.48)
≥15 years (vs. <5 years)	1.90 (1.43–2.52)	1.48 (0.84–2.52)	0.77 (0.34–1.75)	1.32 (0.53–3.28)

LWH, long working hours; OR, odds ratio; CI, confidence interval.



Supplementary Figure 1. Conceptual models used for the structural equation model analyses. Latent variables are in ellipses and observed variables in rectangles.



Supplementary Figure 2. Flow diagram of the studied population.