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Long weekly working hours and ischaemic heart disease

a follow-up study among 145 861 randomly selected workers in Denmark

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Harald Hannerz,[1] Ann Dyreborg Larsen,[1] Anne Helene Garde[1,2]

ABSTRACT

Objectives The aim of the present study was to test if incidences of ischaemic heart disease (IHD) and usage of antihypertensive drugs are independent of weekly working hours (WWH) among full-time employees in Denmark.

Design and participants Data on WWH from participants of the Danish labour force surveys, 1999–2013, were linked on an individual level to national registers with data on socioeconomic status (SES), industry, emigrations, redeemed prescriptions, hospital contacts and deaths. Participants were followed until the end of 2014 (on average 7.7 years). Poisson regression was used to model incidence rates as a function of WWH. The analyses were controlled for calendar time, time passed since start of follow-up, employment in the healthcare industry, age, sex, SES and night work.

Results In total, we found 3635 cases of IHD and 20 648 cases of antihypertensive drug usage. The rate ratio of IHD was 0.95 (95% CI 0.85 to 1.06) for 41–48 compared with 32–40 WWH and 1.07 (0.94 to 1.21) for >48 compared with 32–40 WWH. The corresponding rate ratios for antihypertensive drug usage were 0.99 (0.95 to 1.04) and 1.02 (0.97 to 1.08). No statistically significant interactions between WWH and sex, SES and night work, respectively, were found.

Conclusion In this Danish sample, we did not find any statistically significant association between WWH and IHD or antihypertensive drug usage.

Strengths and limitations of this study

► This is the most well-powered single study ever on the prospective association between weekly working hours (WWH) and ischaemic heart disease.

► The participants were culled from the target population of all full-time employees in Denmark, by means of a random selection process.

► Hospital contacts, redeemed prescriptions, deaths and emigrations were determined through national register which cover the entire target population.

► The statistical analyses were completely blinded and described in a peer-reviewed protocol before linkage between exposure and outcome.

► The data on WWH were self-reported and the response rate decreased from 70% in 2002 to 53% in 2013.

INTRODUCTION

An advantage of long weekly working hours (WWH) is that they may generate an extra income and by that reduce the risk or intensity of economic distress, which is a known risk factor for hypertension[1] as well as ischaemic heart disease (IHD).[2] From this viewpoint, we would expect long WWH to be associated with a decreased risk of IHD.

Long WWH are, however, also associated with short sleep,[3–5] which in turn is linked to an increased risk for both hypertension[6] and IHD.[7] It is moreover possible that other IHD-related lifestyle factors, for example, physical exercise,[8] smoking habits[9] and marital status[10] are influenced by long WWH.

The question is if the beneficial effects of long WWH outweigh the detrimental effects or vice versa. A recent meta-analysis[11] suggests that they tend to cancel each other out. The meta-analysis, which combined individual participant data from 20 cohorts in Australia, Europe and USA estimated the following rate ratios for coronary heart disease (CHD) as a function of WWH: 1.02 (95% CI 0.91 to 1.15) for 41–48 WWH, 1.07 (95% CI 0.92 to 1.24) for 49–54 WWH and 1.08 (95% CI 0.94 to 1.23) for >55 or more WWH, compared with 35–40 WWH. The cases in the European cohorts (39% of all cases) were based on registered hospital treatment or death due to IHD, while the cases in the cohorts from USA and Australia (61% of all cases) were based on self-reported heart troubles. These rate ratios provide quite clear and convincing evidence against the hypothesis of a general important effect of WWH on the risk of IHD. However, since cases to a large extent were based on self-reported heart troubles without further specification and the study was performed

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without a pre-published study protocol, some uncertainty remains.

It should also be noted that the lack of a general effect does not exclude the possibility of beneficial as well as detrimental effects among subgroups of the workforce. It has, for example, been suggested that the association between WWH and IHD depends on socioeconomic status (SES)[11 12] and sex.[13]

The present study concerns the relationship between WWH and IHD among employees in the general population of Denmark.

The statistical analyses were conducted in accordance with a detailed study protocol[14] which was written, peer-reviewed and published before the outcome data were linked the exposure data of the study. The protocol defined all hypothesis and statistical methods for two studies. One study concerned the association between WWH and risk of IHD or antihypertensive drug usage (reported here) while the other concerned the association between night-time work and risk of IHD or antihypertensive drug usage (results to be reported elsewhere).

The study protocol[14] contains the following copyright and licence information:

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The hypotheses as well as other relevant details from the study protocol[14] will be repeated in the method section of the present paper.

AIMS AND HYPOTHESES

The aim of the current study was to test the following series of hypotheses:

1. The incidence of IHD and the incidence of antihypertensive drug usage among full-time employees in Denmark are prospectively independent of WWH as well as interaction between WWH and SES, sex and night work, respectively.
  1.1. The incidence of IHD is prospectively independent of WWH as well as interaction between WWH and SES, sex and night work, respectively.
    1.1.1. The prospective association between WWH and incidence IHD is independent of SES.
    1.1.2. The prospective association between WWH and incidence of IHD is independent of gender.

1.1.3. The prospective association between WWH and incidence of IHD is independent of night-time work.
1.1.4. The incidence of IHD is prospectively independent of WWH when we disregard interaction effects.
  1.2. The incidence of antihypertensive drug usage is prospectively independent of WWH as well as interaction between WWH and SES, sex and night work, respectively.
    1.2.1. The prospective association between WWH and incidence of antihypertensive drug usage is independent of SES.
    1.2.2. The prospective association between WWH and incidence of antihypertensive drug usage is independent of sex.
    1.2.3. The prospective association between WWH and incidence of antihypertensive drug usage is independent of night-time work.
    1.2.4. The incidence of antihypertensive drug usage is prospectively independent of WWH when we disregard interaction effects.

The overall significance level for the effects of WWH was set to 0.05 and the multiple testing problems were solved by the following strategy:

► Hypothesis 1 would be rejected if either of its two second-level null-hypotheses (hypothesis 1.1 or 1.2) was rejected.
► At the second level (hypothesis 1.1 or 1.2), a null-hypothesis would be rejected if the p value of its statistical test was ≤0.025.
► At the third level, a null-hypothesis would be rejected if (1) its associated second-level null-hypothesis was rejected and (2) the p value of its statistical test was ≤0.025.

The statuses of the outcomes were declared in our study protocol[14] as follows: 'Hospital treatment or death due to IHD is the primary outcome of the study, and a statically significant association with this outcome would afford direct statistical evidence of an association with IHD.

Hypertension plays an important role in the aetiology of IHD[15] and relative rates of antihypertensive drug usage have been shown to be highly correlated with relative rates of IHD among occupational groups in Denmark.[16 17] We will therefore regard results obtained for antihypertensive drug usage as indirect statistical evidence of an association with IHD if they are statistically significant and show a similar pattern to the results obtained for hospital treatment or death due to IHD'.

METHODS
Data material
The data material of the project is described in our study protocol[14] as follows: 'The data base of the project [consisted] of interview data from the Danish Labour Force Survey (LFS) 1999–2013 which [were] linked at an individual level to data from The Central Person

Register,[18] The Employment Classification Module,[19] The National Patient Register,[20] The Cause of Death Register[21] and The National Prescription Register.[22] The linkage [was] based on the participants' personal identification numbers. The Danish LFS has been conducted since 1994, in accordance with EU directives which apply to all member states of the European Union. It is based on random samples of 15–74 year old people in the Danish population. The samples are drawn quarterly and the participants are invited to be interviewed four times over a period of one and a half year. The structured interviews, which are done by telephone, cover various aspects of labour market participation including specifications on WWH and work schedules.[23] […]

The Central Person Register contains information on sex and dates of birth, death and migrations for every person who is or has been an inhabitant of Denmark sometime between 1968 and present time. A person's SES, occupation and industry are registered annually in The Employment Classification Module since 1975. The National Hospital Register has existed since 1977 and contains data from all public hospitals in Denmark (more than 99% of all admissions). From 1977 to 1994, the register only included inpatients but from 1995 it also covers outpatients and emergency ward visits. Since 1994, the diagnoses are coded according to ICD-10 (International Classification of Diseases, 10th revision).[24] The National Prescription Register covers all redeemed prescriptions at pharmacies in Denmark since 1995 and the products are coded in accordance with the Anatomical Therapeutic Chemical (ATC) Classification System'.

Weekly working hours

'The labour force surveys gather person based information on WWH, calculated by adding the hours worked in secondary jobs to the ones worked in a primary job. The participants are asked first how many hours they usually work and then how many hours they worked during the reference week (a predetermined work week, which occurred 1–4 weeks prior to the interview). They are also asked if and to what extent they work at night. The questions used to gather this information have changed slightly with time. Before 2001 there was no mention of whether meal breaks should be counted as working hours. During 2001–2006 all participants were instructed to exclude meal breaks when they counted their work hours. As of 2007 the time used for meal breaks were to be counted if the person got paid while eating and excluded otherwise.'[14] From 2001, the average of the actual WWH during the 4 weeks preceding the interview was used as substitute for usual WWH among participant whose working hours varied a lot. In the time period 2001–2006, weeks in which the participant was absent due to for example, holidays, vacation or sick leave were to be disregarded when this average was calculated, but from 2007 all of the 4 weeks were to be included in the calculation.

According to article 6 of the EU Working Time Directive[25] : 'Member States shall take the measures necessary to ensure that, in keeping with the need to protect the safety and health of workers: (a) the period of weekly working time is limited by means of laws, regulations or administrative provisions or by collective agreements or agreements between the two sides of industry; (b) the average working time for each 7 day period, including overtime, does not exceed 48 hours'.

As done in the studies of Kleppa et al,[26] Hannerz and Albertsen (2014)[16] and Larsen et al,[27] the present study treated the workers' usual WWH as a categorical variable, with 32–40 WWH as a reference, 41–48 WWH to represent overtime work which lies within the limits of the European Working Time Directive and 49–100 WWH to represent overtime work beyond the threshold of the directive.

The categorisation facilitates interpretation of the results in relation to the EU Working Time Directive in a Danish context, in accordance with the following arguments:

1. If a rate ratio is statistically significantly high among workers with 41–48 WWH, then it might be of practical importance, since it suggests that the 48 hours threshold of the EU Working Time Directive may need to be lowered to protect against IHD from long working hours.
2. If a rate ratio is statistically significantly low among workers with more than 48 WWH then it might be of practical importance, since it suggests that the 48 hours threshold of the EU Working Time Directive either is unnecessary or unnecessarily low (when it comes to protecting employees against IHD from long working hours).
3. If a rate ratio is statistically significantly high among workers with more than 48 WWH but not among employees with 41–48 WWH, then the results do not indicate any need to change the threshold of the Working Time Directive. The elevated rate ratio may, however, be of practical importance from a public health perspective, since it identifies a group of people who might be in need of health promotion.

Another advantage of treating the working hours as a categorical variable rather than a continuous variable in a log-linear regression is that it allows the association to be u-shaped.

Clinical endpoints

'The primary endpoint of the present project is hospital treatment or death with IHD as the principal diagnosis or cause of death, respectively. The case definition includes the following ICD-10 codes: I20 angina pectoris, I21 acute myocardial infarction, I22 subsequent myocardial infarction, I23 certain current complications following acute myocardial infarction, I24 other acute IHDs, I25 chronic IHD. The secondary endpoint is redemption of a prescription for antihypertensive drugs. The following ATC-codes are included: C02 antihypertensive, C03 diuretics, C07

alpha-blockers and beta-blockers, C08 calcium channel blockers and C09 ACE-inhibitors and angiotensin-II antagonists'.[14]

For circulatory disease as a principal diagnosis, 73.4% of the recorded cases in the National Patient Register have been estimated to be accurately coded.[28] In regards to IHD diagnoses, data show that the validity of myocardial infarction has risen from 92% in 1979–1980[29] to almost 100% in 1996–2009.[30] Even when including earlier versions of ICD codes the Danish administrative registers have demonstrated high accuracy in coding practices.[31]

Follow-up and inclusion criteria

'The participants were followed from the beginning of the calendar year which succeeded the one of their baseline interview. The follow-up ended at the time the participant [became a case], [emigrated], [died] or the study period [ended] (31 December 2014), whichever came first.'[14]

The analysis of IHD included participants of the LFS in the time period 1999–2013. The analysis of antihypertensive drug usage included participants of the LFS in the time period 2000–2013.

'To be eligible for inclusion, they should be between 21 and 59 years old at the start of the follow-up period and employed with>=32 WWH at the time of the interview. People who received hospital treatment for IHD during the calendar year of the interview [were] excluded from the IHD analysis. People who redeemed a prescription for antihypertensive drugs during the calendar year of the interview [were] excluded from the antihypertensive drug analysis.'[14]

Primary analysis

'We [used] Poisson regression to analyse incidence rates of IHD and antihypertensive drug usage, respectively, as a function of WWH (32–40; 41–48; >48 hours/week), night work (Yes vs No), sex, age (10 year classes), calendar time (2000–2004; 2005–2009; 2010–2014), time passed since start of follow-up (0–4 years; 5–9 years; >=10 years), employment in the healthcare industry (Yes vs No) and SES (Low; Medium; High; Unknown). Age, calendar time and time passed since start of follow-up [were] treated as dynamic (time-varying) variables. The remaining variables [were] fixed at baseline (the calendar year of the interview). The logarithm of person years at risk was used as offset. People who participated in more than one interview were classified in accordance with the responses they gave in their first interview. Later interviews were disregarded.'[14]

The data were split by calendar year. Time-dependent variables were updated first of January each year and were thereafter held constant throughout the rest of the calendar year. The analyses were implemented in the GENMOD procedure of SAS V.9.4.

'Information on occupation and industry [were retrieved] from The Employment Classification Module, and [refers] to the status during the calendar year of the baseline interview. Industries were coded in accordance

with the classification DB93[32] in 1999–2002, DB03[33] in 2002–2007 and DB07[34] in the calendar years 2008–2013. Occupations were coded in accordance with DISCO-88 (the Danish version of the International Standard Classification of Occupations, ISCO-88)[35] in the calendar years 1999–2009 and DISCO-08 (the Danish version of ISCO-08)[36] in the calendar years 2010–2013.'[14]

Employment in the healthcare industry has been linked to referral and prescription bias,[37–39] and this problem was addressed by the inclusion of 'the variable "Employment in the healthcare industry", [which was coded] as "Yes" if the three-digit industrial code of DB93 or DB03 [equalled] 851 or the two-digit code of DB07 [equalled] 86'.[14]

The SES was based on the three class version of the European Socioeconomic Classification (ESeC). It was retrieved from the DISCO code in the Employment Classification Module with an algorithm that is given in our study protocol.[14]

Data about night-time work was obtained through the LFS. Participants who responded either with 'Yes, regularly' or 'Yes, occasionally' to a question about night time work was defined as exposed while the ones who responded with 'No' was defined as unexposed to night work. Further information about this variable is given in our study protocol.[14]

The first regression model contained the covariates sex, age, night work, calendar time, time passed since start of follow-up, employment in the healthcare industry and SES. The second model contained the covariates of model 1 plus WWH. The third model contained the covariates of model 2 plus interaction between SES and WWH. The fourth model contained the covariates of model 2 plus interaction between sex and WWH. The fifth model contained the covariates of model 2 plus interaction between night work and WWH. The sixth model contained the covariates of model 2 plus interaction between WWH and SES, sex and night work, respectively.

The parameters were estimated by use of the maximum likelihood method and the p values of the various hypotheses were based on likelihood ratio tests. The overall hypotheses (which state that the incidence is prospectively independent of WWH as well as interaction between WWH and SES, sex and night work, respectively) were tested by comparing model 6 to model 1. The hypotheses (1.1.4 and 1.2.4) which state that the incidence is prospectively independent of WWH when we disregard interaction effects were tested by comparing model 2 to model 1. The test for interaction between SES and WWH (hypothesis 1.1.1 and 1.2.1) compared model 3 to model 2. The test for interaction between sex and WWH (hypothesis 1.1.2 and 1.2.2) compared model 4 to model 2. The test for interaction between night work and WWH (hypothesis 1.1.3 and 1.2.3) compared model 5 to model 2.

Parameter estimates were used to obtain rate ratios and 95% confidence as a function of WWH, with and without stratification by SES, sex and night work. Rate ratios by

SES were based on the parameter estimates of model 3, rate ratios by sex were based on the parameter estimates of model 4, rate ratios by night work were based on the parameter estimates of model 5 and rate ratios, without stratification by SES, sex or night work, were based on the parameter estimates of model 2.

We also performed the following sensitivity analyses, as defined by our study protocol.

Sensitivity analysis 1

'Since the questions used to obtain information about WWH were revised in 2001 and then again in 2007, we [performed] a sensitivity analysis with the results stratified by calendar period of interview (1999–2000, 2001–2006, 2007–2013). The end point, covariates and statistical model of the sensitivity analysis [were] the same as the ones used to test [hypothesis] 1.1.4.'[14]

Sensitivity analysis 2

'To ascertain that an observed instance of hospital treatment during the follow-up (was) a new episode rather than a revisit in a course of treatment that was initiated before baseline, the primary analysis [excluded] all workers who were treated for IHD sometime during the calendar year preceding baseline. It [did], however, not exclude all former cases of IHD, and it [was] possible that the estimates of the primary analysis [would] be affected by non-excluded workers who were treated for IHD more than 1 year earlier than baseline. We [addressed] this issue with a sensitivity analysis, which [excluded] all workers who received hospital treatment for IHD one or more times during a 5 year period prior to baseline. The analysis [included] only those who were at least 20 years old and lived in Denmark throughout the 5 year period of interest. In all other respects, the design (was) the same as the one used to test [hypothesis] 1.1.4.'[14]

Sensitivity analysis 3

'The actual working hours, that is, the hours worked during the reference week, constitute a well-defined quantity with minimal recall bias. The usual working hours are less well-defined and the way they are understood and remembered might vary between individuals. In spite of this drawback, we chose to base our analysis on the workers' usual rather than their actual working hours. We did so because some of the participants, by chance, would work less than usual during the reference week due to, for example, holidays, vacation or sickness absence while others would work more than usual due to, for example, a deadline or a temporary staff shortage. Since the usual working hours might be associated with recall bias, we [performed] a sensitivity analysis in which we only included participants who belonged to the same category according to their actual working hours as they did according to their usual working hours. In all other respects, the design [was] the same as the one used to test [hypothesis] 1.1.4.'[14]

Patient and public involvement

The study was based on historical data. Patients and public were not involved in the design and conduct of the present study. The study participants will be able to read about the results at http://www.nfa.dk/.

RESULTS

The inclusion criteria were fulfilled by 145 861 persons for the analyses of IHD and by 125 367 persons for the analyses of redeemed prescriptions for antihypertensive drugs. In total, we found 3635 cases of IHD in 1 126 767 person years at risk and 20 648 cases of antihypertensive drug usage in 834 551 person years at risk. Flowcharts for the inclusion procedures are given in figures 1 and 2.

We did not find any statistically significant association between WWH and IHD nor between WWH and antihypertensive drug usage. The p values for each of the tested hypotheses were all above 0.11 (table 1).

In the model where only main effects were included, the rate ratio of IHD was 0.95 (95% CI 0.85 to 1.06) for 41–48 compared with 32–40 WWH and 1.07 (95% CI 0.94 to 1.21) for >48 compared with 32–40 WWH. The corresponding rate ratios for antihypertensive drug usage were 0.99 (95% CI 0.95 to 1.04) and 1.02 (95% CI 0.97 to 1.08).

Rate ratios are stratified by sex, SES, night work status and calendar year of interview in tables 2 and 3.

In the second sensitivity analysis, which excluded all workers who received hospital treatment for IHD one or more times during a 5-year period prior to baseline, the rate ratios of IHD were 0.96 (95% CI 0.86 to 1.08) for 41–48 compared with 32–40 WWH and 1.09 (95% CI 0.96 to 1.24) for >48 compared with 32–40 WWH.

In the third sensitivity analysis, which only included workers whose working hours during the reference week belonged to the same working hour category as their usual working hours, the rate ratios of IHD were 0.93 (95% CI 0.80 to 1.07) for 41–48 compared with 32–40 WWH and 1.00 (95% CI 0.86 to 1.18) for >48 compared with 32–40 WWH.

The numbers of participants stratified by working hour category and year of interview, age, sex, SES, night-time work (yes/no) and healthcare industry (yes/no), respectively, are shown in table 4.

DISCUSSION

The present study did not support the hypothesis of a general effect of long WWH on IHD and it did not find any statistically significant interactions with sex, SES or night-time work in a random sample of employees in Denmark.

Strengths, weaknesses and limitations

With 145 861 persons, 3635 cases of IHD and 20 648 cases of antihypertensive drug usage, this is the most well-powered single study ever on the association between WWH and incident IHD/antihypertensive drug usage.
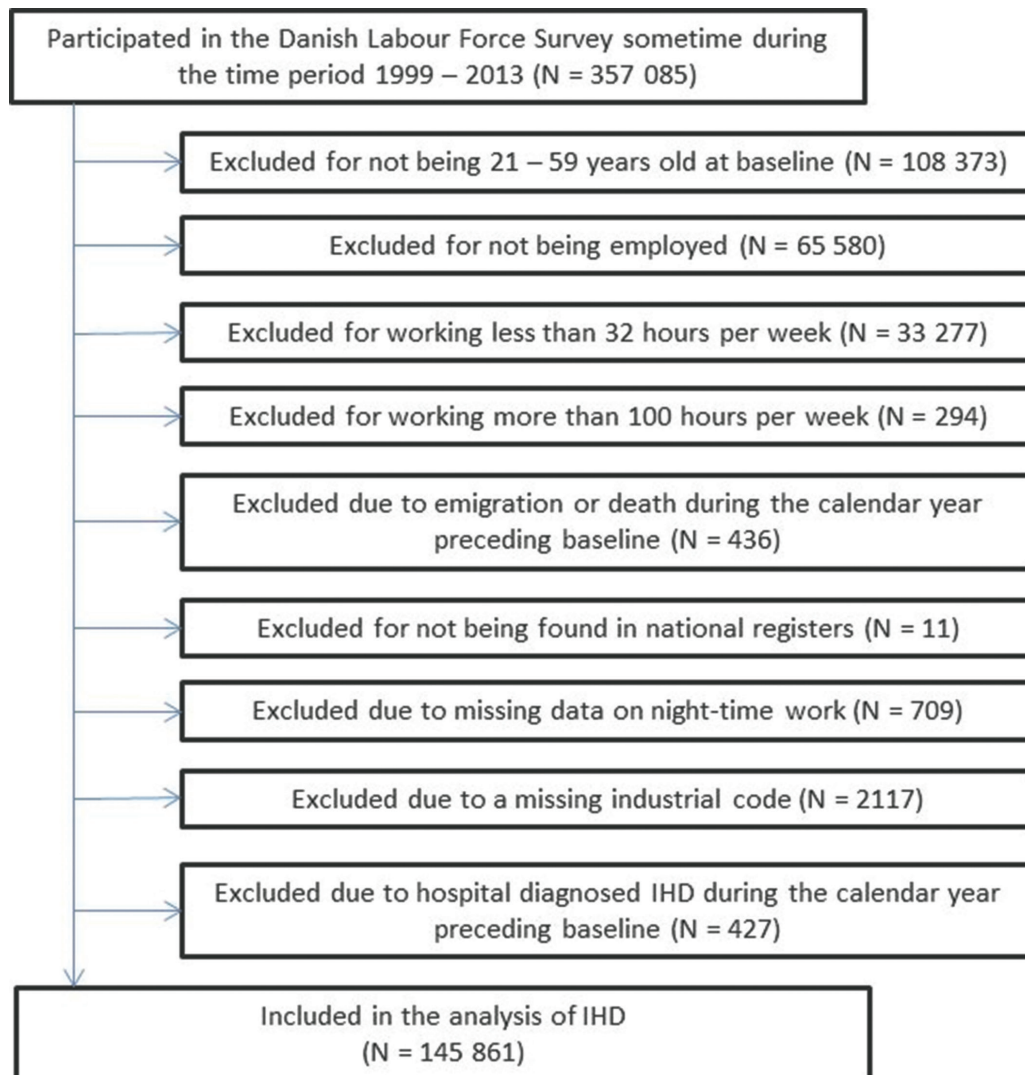
Figure 1 Flowchart for the inclusion and exclusion from the analysis of IHD. IHD, ischaemic heart disease.

Further, the interview surveys were conducted among randomly selected employees, which increases the external validity. Based on the personal identification number a linkage to the Danish health, death and migration registers meant marginal loss to follow-up. All diagnoses included in the used patient register are coded by a professional healthcare worker, which excludes risk of bias due to self-report. The study was further strengthened by its prepublished study protocol, in which all statistical methods and hypotheses were completely defined and peer-reviewed before the analysts were allowed to link the exposure data to the outcome data. Since the study protocol was followed, it guarantees that the study is free from within-study selection bias.

Some limitations must also be addressed. In the main analysis, WWH was only assessed from the first interview and therefore any alterations in work schedules during the follow-up period were ignored. However, the conducted sensitivity test revealed no differences in risk estimates when we only included participants with stable WWH. Further, WWH were self-reported and thereby

open to recall bias. It should also be noted that workers with cardiovascular health problems may be less likely to enter or stay in jobs with long working hours. Hence, the so-called healthy worker effect may have biased rate ratios downward. The rate ratios for IHD were, however, very close to unity also in the sensitivity analysis which only included workers without IHD diagnosis during a 5-year period prior to baseline.

As requested by a reviewer, we performed a posthoc analysis, which estimated the rate ratio for IHD without exclusion of prevalent cases at 0.95 (95% CI 0.86 to 1.06) for 41–48 and 1.06 (0.94–1.20) for >48 compared with 32–40 WWH. The analysis was controlled for the same covariates and used the same follow-up period as the primary analysis. Since the rate ratios obtained in this posthoc analysis were very close to the ones obtained in the primary analysis, we do not believe that the null finding of the present study was due to the decision to exclude participants diagnosed with IHD in the year prior to the follow-up period.
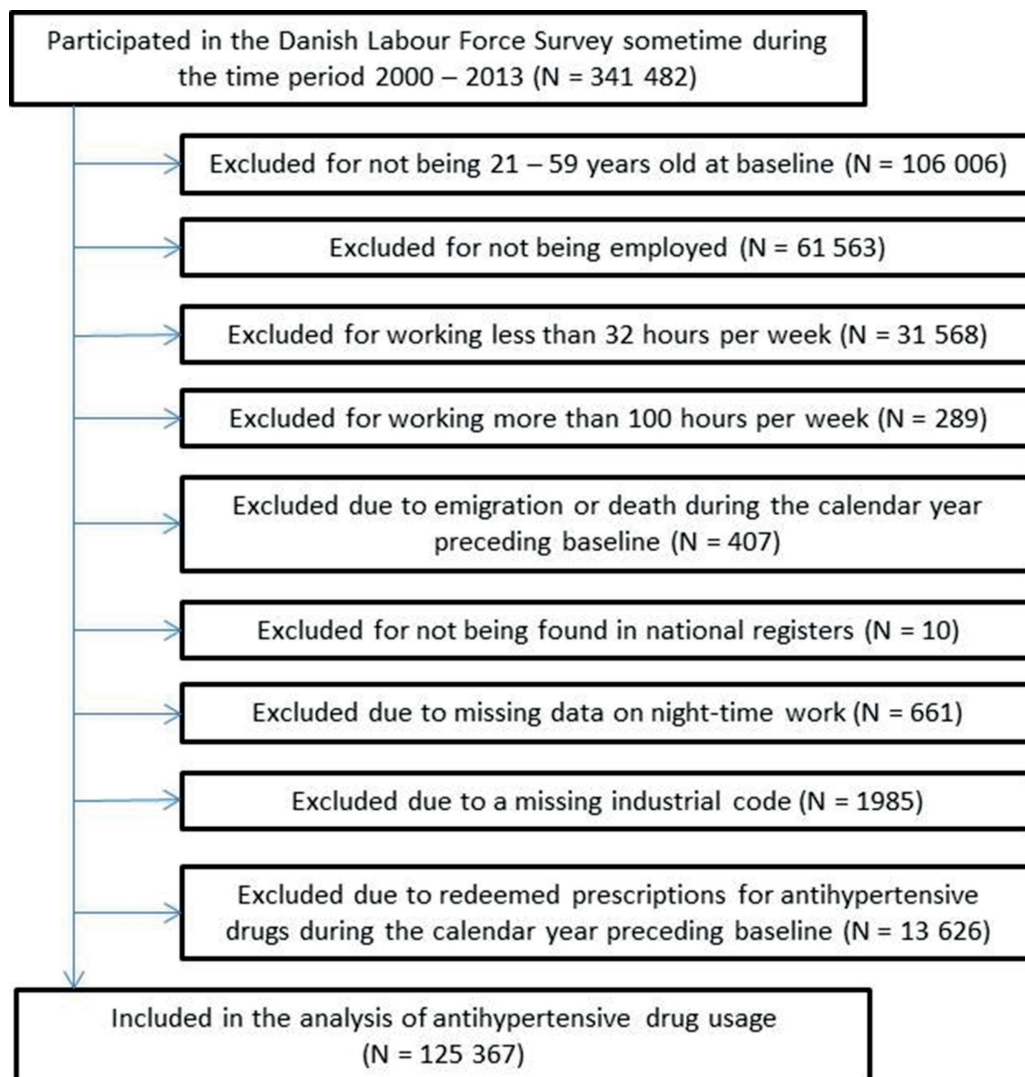
Figure 2 Flowchart for the inclusion and exclusion from the analysis of antihypertensive drug usage.

When we analyse hospital discharge data, there is always a possibility of referral or detection bias. Mild forms of IHD might go undetected by the workers as well as by their general practitioners. It is, moreover, possible that the probability of awareness of symptoms as well as the inclination to seek healthcare for a minor IHD depends on

Table 1	P values for each of the tested hypotheses		
Hypothesis		**P value for hospitalisation or death due to IHD**	**P value for antihypertensive drug usage**
The incidence is prospectively independent of weekly working hours as well as interaction between weekly working hours and socioeconomic status, sex and night work, respectively*		0.1638	0.8807
The incidence is prospectively independent of interaction between weekly working hours and socioeconomic status†		0.1527	0.9861
The incidence is prospectively independent of interaction between weekly working hours and sex†		0.5528	0.7080
The incidence is prospectively independent of interaction between weekly working hours and night work†		0.5658	0.1149
The incidence is prospectively independent of weekly working hours when we disregard interaction effects†		0.3242	0.6668

*Overall hypothesis.
†Subhypothesis.
IHD, ischaemic heart disease.

Table 2 Rate ratio with 95% CI IHD, as a function of weekly working hours among employees in Denmark 2000–2014, with and without stratification by sex, socioeconomic status night work status and calendar year of interview, respectively

Population	Weekly working hours	Person years	Cases	Rate ratio	95% CI
All workers	>48	71 258	284	1.07	0.94 to 1.21
	41–48	124 106	380	0.95	0.85 to 1.06
	32–40	931 403	2971	1.00	–
Male workers	>48	55 968	256	1.10	0.96 to 1.26
	41–48	77 153	294	0.97	0.86 to 1.10
	32–40	459 262	2027	1.00	–
Female workers	>48	15 290	28	0.88	0.61 to 1.29
	41–48	46 953	86	0.90	0.72 to 1.12
	32–40	472 141	944	1.00	–
Workers with a high socioeconomic status	>48	26 597	99	1.04	0.84 to 1.29
	41–48	44 809	129	0.96	0.79 to 1.16
	32–40	238 046	591	1.00	–
Workers with a medium socioeconomic status	>48	10 487	35	0.93	0.66 to 1.31
	41–48	20 801	70	1.07	0.83 to 1.37
	32–40	189 350	497	1.00	–
Workers with a low socioeconomic status	>48	22 486	115	1.27	1.05 to 1.53
	41–48	46 095	138	0.85	0.71 to 1.01
	32–40	421 053	1636	1.00	–
Workers with unknown socioeconomic status	>48	11 689	35	0.84	0.59 to 1.19
	41–48	12 401	43	1.14	0.82 to 1.58
	32–40	82 954	247	1.00	–
Workers with night-time work	>48	21 262	97	1.22	0.97 to 1.52
	41–48	17 677	59	0.98	0.74 to 1.29
	32–40	108 410	378	1.00	–
Workers without night-time work	>48	49 997	187	1.01	0.87 to 1.18
	41–48	106 429	321	0.95	0.84 to 1.06
	32–40	822 994	2593	1.00	–
Workers interviewed 1999–2000	>48	20 837	88	1.08	0.86 to 1.35
	41–48	36 010	87	0.72	0.58 to 0.90
	32–40	283 012	954	1.00	–
Workers interviewed 2001–2006	>48	34 230	141	1.14	0.95 to 1.36
	41–48	61 746	203	1.04	0.89 to 1.21
	32–40	348 992	1117	1.00	–
Workers interviewed 2007–2013	>48	16 192	55	0.93	0.71 to 1.23
	41–48	26 350	90	1.08	0.87 to 1.35
	32–40	299 399	900	1.00	–

IHD, ischaemic heart disease.

the person's WWH. As suggested by one of the reviewers, we addressed this issue in a posthoc analysis in which the case definition was restricted to acute myocardial infarction (ICD-10: I21). The rate ratios for acute myocardial infarction were estimated at 0.96 (95% CI 0.80 to 1.14) for 41–48 and 0.98 (0.80–1.20) for >48 compared with 32–40 WWH. The statistical model was otherwise the same as the one used in the primary analysis. We note that the rate ratios of the posthoc analysis were closer to unity than the ones acquired in the primary analysis. We therefore do not believe that the null-finding of the present study was due to referral or detection bias.

The low response rate, which decreased from 70% in 2002 to 53% in 2013, may have caused selection bias due to differential participation. However, this is only a problem if participation is related to exposure, for

Table 3 Rate ratio with 95% CI for incident use of antihypertensive drugs, as a function of weekly working hours among employees in Denmark 2001–2014, with and without stratification by sex, socioeconomic status and night work status, respectively

Population	Weekly working hours	Person years	Cases	Rate ratio	95% CI
All workers	>48	55 221	1350	1.02	0.97 to 1.08
	41–48	99 090	2339	0.99	0.95 to 1.04
	32–40	680 240	16 959	1.00	–
Male workers	>48	43 998	1033	1.02	0.95 to 1.09
	41–48	63 324	1399	1.01	0.95 to 1.07
	32–40	341 977	8059	1.00	–
Female workers	>48	11 223	317	1.05	0.93 to 1.17
	41–48	35 766	940	0.98	0.91 to 1.05
	32–40	338 263	8900	1.00	–
Workers with a high socioeconomic status	>48	20 040	474	1.04	0.94 to 1.14
	41–48	36 225	778	1.00	0.93 to 1.08
	32–40	179 021	3771	1.00	–
Workers with a medium socio economic status	>48	7849	189	1.03	0.89 to 1.20
	41–48	16 424	384	1.02	0.92 to 1.14
	32–40	137 163	3448	1.00	–
Workers with a low socioeconomic status	>48	17 407	453	1.03	0.93 to 1.13
	41–48	35 858	939	0.98	0.91 to 1.05
	32–40	297 368	8107	1.00	–
Workers with unknown socioeconomic status	>48	9925	234	0.99	0.86 to 1.14
	41–48	10 583	238	1.00	0.87 to 1.14
	32–40	66 688	1633	1.00	–
Workers with night-time work	>48	16 254	434	1.12	1.01 to 1.24
	41–48	14 723	333	0.98	0.87 to 1.10
	32–40	77 666	1953	1.00	–
Workers without night-time work	>48	38 967	916	0.99	0.92 to 1.06
	41–48	84 368	2006	1.00	0.95 to 1.05
	32–40	602 574	15 006	1.00	–

example, if persons with long WWH were more (or less) likely to not participate. This can result in an underestimation (or overestimation) of the association between WWH and IHD and antihypertensive drug usage. As with most surveys, the direction of the possible differential participation is not known.

In the analysis of antihypertensive drug usage, we included all types of antihypertensive drugs in the case definition. Here, it needs to be mentioned that diuretics may be prescribed for treatment of hypertension and for chronic kidney disease[40] and that beta blockers and calcium channel blockers may be prescribed for migraine.[41] It is therefore possible that the estimations of rate ratios for antihypertensive drug usage were slightly biased either towards or away from unity.

Another limitation of the study is that the surveys did not include any information on sleep patterns or income. As previously mentioned, one of the main theoretical reasons for a detrimental effect of a long work week is that it has been linked to short sleep, while one of the main theoretical reasons for a beneficial effect is its association with an increased income. Hence, it would have been of interest to study effect modification by income and sleeping habits.

It should also be noted that the present study concerns tendencies in the general working population of Denmark, and that the results therefore cannot be generalised to patient populations; that something is safe for an average worker does not mean that it also is safe for workers who are treated for hypertension or other types of circulatory disease.[42 43]

Previous research

There are convincing prospective studies which support the hypothesis of a negative association between WWH and hypertension,[44–46] but there is also an equally convincing study which points in the opposite direction.[47]

Table 4 Number of participants stratified by working hour category and year of interview, age, sex, SES, night-time work (yes/no) and healthcare industry (yes/no), respectively

	Included in the analysis of ischaemic heart disease							Included in the analysis of antihypertensive drug usage						
		Weekly working time (hours per week)							Weekly working time (hours per week)					
	Total	32–40		41–48		>48		Total	32–40		41–48		>48	
	N	N	%	N	%	N	%	N	N	%	N	%	N	%
Total	145 861	122 718	84.1	14 498	9.9	8645	5.9	125 367	104 816	83.6	12 978	10.4	7573	6.0
Year of interview														
1999	16 404	13 945	85.0	1497	9.1	962	5.9							
2000	8144	6429	78.9	1118	13.7	597	7.3	15 558	12 263	78.8	2154	13.8	1141	7.3
2001	8083	6453	79.8	1059	13.1	571	7.1	7670	6119	79.8	1021	13.3	530	6.9
2002	7772	6196	79.7	1002	12.9	574	7.4	7272	5795	79.7	933	12.8	544	7.5
2003	6877	5452	79.3	899	13.1	526	7.6	6386	5055	79.2	836	13.1	495	7.8
2004	7137	5580	78.2	986	13.8	571	8.0	6626	5168	78.0	914	13.8	544	8.2
2005	7077	5389	76.1	1102	15.6	586	8.3	6505	4941	76.0	1019	15.7	545	8.4
2006	6785	5047	74.4	1106	16.3	632	9.3	6189	4592	74.2	1015	16.4	582	9.4
2007	19 782	17 103	86.5	1665	8.4	1014	5.1	17 817	15 396	86.4	1509	8.5	912	5.1
2008	12 407	10 785	86.9	1007	8.1	615	5.0	10 674	9298	87.1	858	8.0	518	4.9
2009	9017	7992	88.6	631	7.0	394	4.4	7928	7031	88.7	557	7.0	340	4.3
2010	8994	8046	89.5	602	6.7	346	3.8	8125	7277	89.6	543	6.7	305	3.8
2011	9178	8151	88.8	607	6.6	420	4.6	8214	7298	88.8	540	6.6	376	4.6
2012	9186	8168	88.9	608	6.6	410	4.5	8280	7375	89.1	544	6.6	361	4.4
2013	9018	7982	88.5	609	6.8	427	4.7	8123	7208	88.7	535	6.6	380	4.7
Age (years)														
21–29	22 379	19 057	85.2	2192	9.8	1130	5.0	20 515	17 320	84.4	2126	10.4	1069	5.2
30–39	39 721	33 363	84.0	4099	10.3	2259	5.7	36 405	30 423	83.6	3883	10.7	2099	5.8
40–49	42 968	35 797	83.3	4380	10.2	2791	6.5	37 527	31 064	82.8	3942	10.5	2521	6.7
50–59	40 793	34 501	84.6	3827	9.4	2465	6.0	30 920	26 009	84.1	3027	9.8	1884	6.1
Sex														
Men	77 278	61 663	79.8	8927	11.6	6688	8.7	66 874	52 892	79.1	8091	12.1	5891	8.8
Women	68 583	61 055	89	5571	8.1	1957	2.9	58 493	51 924	88.8	4887	8.4	1682	2.9
SES														
High	43 755	35 179	80.4	5305	12.1	3271	7.5	38 261	30 671	80.2	4775	12.5	2815	7.4
Medium	27 644	24 170	87.4	2292	8.3	1182	4.3	23 463	20 420	87	2037	8.7	1006	4.3

Continued

Table 4 Continued

	Included in the analysis of ischaemic heart disease						Included in the analysis of antihypertensive drug usage					
	Weekly working time (hours per week)						Weekly working time (hours per week)					
	Total	32–40		41–48		>48	Total	32–40		41–48		>48
	N	N	%	N	%	N	%	N	N	%	N	%	N	%
Low	60201	52113	86.6	5391	9	2697	4.5	50765	43623	85.9	4763	9.4	2379	4.7
Unknown	14261	11256	78.9	1510	10.6	1495	10.5	12878	10102	78.4	1403	10.9	1373	10.7
Night work													
Yes	18658	14034	75.2	2067	11.1	2557	13.7	16070	11930	74.2	1910	11.9	2230	13.9
No	127203	108684	85.4	12431	9.8	6088	4.8	109297	92886	85	11068	10.1	5343	4.9
Healthcare worker													
Yes	9009	8055	89.4	618	6.9	336	3.7	7745	6942	89.6	539	7.0	264	3.4
No	136852	114663	83.8	13880	10.1	8309	6.1	117622	97874	83.2	12439	10.6	7309	6.2

SES, socioeconomic status.

Virtanen et al[48] estimated the rate ratio for CHD at 1.80 (95% CI 1.42 to 2.29) for 'long' compared with 'normal' working hours, in a meta-analysis which included 12 studies (five from Japan, five from Europe and two from USA). The meta-analysis included studies on the subject regardless of whether the information on working hours and CHD was obtained through registers or self-reports. It also allowed studies in which the outcome was defined as circulatory diseases without further specification. Some of the studies were based on WWH, some were based on daily working hours and some were based on overtime work (Yes vs No). The cut-offs for long WWH varied from >40 to >65 while the cut-offs for long daily working hours varied from >9 to >11 hours. Seven of the studies had a case-control design, four had a prospective cohort design and one was cross-sectional. The design-specific estimated rate ratios were 2.43 (95% CI 1.81 to 3.26), 1.39 (95% CI 1.12 to 1.72) and 1.29 (95% CI 0.98 to 1.70) for the case-control, prospective cohort and cross-sectional studies, respectively. The rate ratio was 2.07 (95% CI 1.51 to 2.85) among the studies which only included men and 1.43 (95% CI 1.05 to 1.93) among the studies which also included women.

A drawback with the meta-analysis by Virtanen et al[48] is that it only included published studies and that it did not require that the statistical analyses of the studies were blinded, which means that their results may have been distorted by publication and within study selection bias. A larger meta-analysis on WWH and risk of CHD by Kivimäki et al,[11] included both published and unpublished data, thus limiting the risk of publication bias. The study by Kivimäki et al also eliminated recall bias by restricting the inclusion criteria to prospective cohort studies. Their results did not lend support to the hypothesis of a general important association between WWH and IHD; a trend test resulted in a p value at 0.18 and the most significant contrast (≥55 compared with 35–40 WWH) resulted in a p value at 0.27 (Rate ratio=1.08, 95% CI 0.94 to 1.23). One of several subanalyses suggested, however, an SES-dependent association between long WWH (≥55 vs 35–40) and CHD. The estimated rate ratios were 2.18 (95% CI 1.25 to 3.81) among workers with low SES, 1.22 (95% CI 0.77 to 1.95) among workers with intermediate SES and 0.87 (95% CI 0.55 to 1.38) among workers with high SES.

The largest single study ever on the relationship between WWH and mortality was performed by O'Reilly and Rosato.[12] It was based on the 2001 Census returns for the whole enumerated population of Northern Ireland and included 414 949 people who worked at least 35 hours/ week. The participants were divided into the categories 35–40, 41–48, 49–54 and ≥55 WWH and were followed up for 8.7 years through linkage with a cause of death register. The study did not find any general effect of long working hours on all-cause mortality. They found, however, an interaction effect between SES and WWH among male workers (=0.004); the risk increased with WWH among men with a low SES while it decreased with WWH among men with a high SES. The increased/

decreased risk was, however only manifest among those with ≥55 WWH. A similar pattern was observed with regard to mortality due to IHD, where the rate ratio for the contrast ≥55 vs 35–40 WWH among men in routine occupations was estimated at 1.53 (95% CI 1.08 to 2.12). A drawback with the study by O'Reilly and Rosato[12] is that it only regarded hours worked in the person's main job. This may cause bias as the status among participants with extra jobs and thereby longer WWH could be misclassified as 'normal working hours'.

The findings of the present study do not support the hypothesis of a general important effect of WWH on IHD, which is in line with the findings presented by O'Reilly and Rosato[12] and by Kivimäki et al.[11]

The hypothesis of an interaction effect between WWH and SES was not confirmed by the present study, but the SES-specific rate ratios for the contrast (>48 vs 32–40 WWH) suggest that long work weeks might be associated with a slightly elevated risk of IHD among workers with a low SES. Although not statistically significant according to the criteria of the present study, this warrants attention, since similar results were observed first by O'Reilly and Rosato[12] and then by Kivimäki et al.[11] A possible explanation for an increased risk in this group is that drivers are included and their work has been associated with long working hours,[49] an unhealthy lifestyle and an elevated risk of IHD.[50]

Some large Scandinavian cohort studies have demonstrated a very clear and important relationship between income and the risk of IHD[51] and stroke[52]; the higher the income, the lower the risk. These findings held good for both genders also after control for many potential confounders. The relationship between income and IHD was adjusted for 'age, cohort of investigation, tobacco, alcohol, systolic blood pressure, cholesterol, body mass index, physical activity in leisure time and diabetes mellitus'[51] while the relationship between income and stroke was adjusted for 'age, marital status, foreign born, educational level, occupational class, job control and working full time'.[52] Since an increased number of working hours normally leads to an increased income, one might expect long WWH to be associated with a decreased risk of IHD. The null-finding of the present study is therefore interesting because it implies that beneficial effects from an increased income tend to be offset by detrimental effects from other long working hour related factors, for example, short sleep and a reduced time for restitution between work shifts.

Implications for practice

Long WWH were overall not related to increased rates of IHD in this random sample of employees in Denmark. Thus with the current level of working hours duration, there appears to be no increased risk of IHD due to long WWH in the general, healthy population. However, this general effect does not rule out the possibility of a harmful effect among unhealthy subpopulations, for example, previous patients with IHD. Further, secondary

analyses indicate that there may be an increased risk of IHD among workers with a low SES and very long working hours. Although not statistically significant according to the conservative approach of the present study, this warrants further attention and from a precautionary principle special attention should be given to this group. The EU Working Time Directive requires that an employee's usual WWH should be ≤48. Since no increased risk of IHD was observed among workers with moderate overtime work (41–48 WWH) in any of the examined subgroups, the present study does not indicate any need for further regulations. Furthermore, there may be different reasons for working long hours in different countries. In Denmark, those working long hours may be more likely to be healthy since most employees can support a family based on a 40 hours per week salary.

Finally, it should be noted that the authors' interpretation of the presented methods and results are not shared by all researchers in the field. We therefore recommend the reader to also read the article's prepublication history, in which one of our reviewers provides an alternative interpretation of the methods and results of the study.

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