Informal caregiving, stress-related disease, and sickness absence; and the modifying effect of work life

PhD thesis by
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This thesis has been submitted to the Graduate School of Health and Medical Sciences, University of Copenhagen on December 22, 2017
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Acknowledgements

The work presented in this thesis was carried out from 2015 to 2017 at the Section of Social Medicine (now Section of Epidemiology), Department of Public Health, University of Copenhagen. The project is part of a larger grant from the Danish Work Environment Research Foundation (grant number 12-2013-03) exploring work-family interactions and health consequences.

I wish to thank my main supervisor, Professor Naja Hulvej Rod for being a good mentor in the scientific discipline of epidemiology, and for her flexibility when I decided to move back to Aarhus. I also wish to thank my co-supervisor Theis Lange and Nadya Dich, and the Psychosocial Epidemiology research group for good academic discussions. I addition, I would like to thank my co-authors for the collaboration on the scientific papers included in this thesis. I would like to thank Adam Hulman and Omar Silverman for making it enjoyable to come to the office at the Section of Epidemiology, at Aarhus University, and for many good discussions during lunch at the Math’s canteen. Lastly, I will thank Anne for being very supportive during the final months of my PhD.
List of scientific papers

This thesis is based on four scientific papers, which has been published or submitted for publication in international peer-reviewed journals.

Study 1:


Study 2:


Study 3:


Study 4:

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English summary

Informal caregiving, which is defined as unpaid caregiving for a sick, disabled, or elderly family member or other closely related person, is common in working age. Informal caregiving may be associated with positive feelings, such as a sense of personal accomplishment and gratification. However, informal caregiving may also be perceived as stressful and burdensome for the caregiver, and may be associated with a higher risk of depression, burnout, and sickness absence. In line with this, studies have shown an altered physiological stress response in informal caregivers compared with non-caregivers, with the most consistent findings on the stress hormone cortisol. In line with this, a blunted cortisol awakening response and flattened diurnal cortisol slope, have been suggested to be markers of chronic stress and may be associated with a higher risk of type 2 diabetes and cardiovascular disease. Accordingly, several studies have shown that informal caregiving may be associated with a higher risk of cardiovascular disease, but according to a literature search, no previous studies have investigated the association between informal caregiving and risk of type 2 diabetes. Furthermore, no previous studies have addressed the association between informal caregiving and long-term sickness absence, which is a marker of health status among employees that may be associated with serious illness in the absentee.

Previous research on the negative health consequences of informal caregiving in general has some limitations. There is a scarcity of studies, which have investigated the potential modifying effect of work life and gender on the associations between informal caregiving and health consequences. Thus, work-family conflicts from being jointly exposed to informal caregiving and paid work may exacerbate the health consequences from having one of these exposures in its own. Furthermore, it has been shown that women providing informal care experience a greater caregiving burden than men, since women tend to take the role as primary caregiver; and informal caregiving may therefore have greater health consequences for women than men. In addition, most previous studies on informal caregiving have not addressed the impact of various aspects of informal caregiving on health consequences. Thus, the
relationship with the care recipient, weekly hours of caregiving as an indicator of intensity, and the
duration of caregiving, may all have an effect on the burden of informal caregiving.

The overall objective of this thesis was to investigate the effect of informal caregiving on the
physiological stress response, stress-related disease, and long-term sickness absence; and to investigate
how work life and gender modify these effects. Data from four large cohort studies were used: The Finnish
Whitehall II cohort study from the UK. Information on informal caregiving, work life, and covariates, were
gathered from questionnaires. The physiological stress response was measured in diurnal cortisol levels,
which were gathered from saliva samples. Data on stress-related diseases were gathered from registers,
clinical test, and self-reports, and data on long-term sickness absence were gathered from national and
company registers.

Results supported an effect of informal caregiving on the physiological stress response, in a
dose response manner, with many weekly hours of caregiving being associated with a blunted cortisol
awakening response, in men. Furthermore, the blunted cortisol awakening response among men was more
pronounced in caregivers in paid work compared to those outside the labor market. The relationship
between informal caregiving and the physiological stress response was less consistent in women.

Investigating the effect of informal caregiving on the risk of stress-related disease, there was no association
between informal caregiving and the risk of type 2 diabetes. However, low social support at work was
associated with a higher risk of type 2 diabetes, especially among informal caregivers. Many weekly hours
of caregiving was associated with a higher risk of cardiovascular disease, which was especially pronounced
among long-term caregivers. Investigating sickness absence, results showed that informal caregiving was
associated with a higher risk of long-term sickness absence in women, but not in men. High job strain was
also associated with a higher risk of long-term sickness absence in women, but job strain did not modify the
effect of informal caregiving on the risk of long-term sickness absence.
To conclude, caregiving for a sick, disabled or elderly family member or other closely related person may be have negative health consequences for caregivers in paid work; especially among those who provide many weekly hours of caregiving for several years. Social support at work from supervisors and coworkers may be one potential aspect of work life that may alleviate some of the health consequences from informal caregiving. Gender differences in the investigated associations were observed with regard to the physiological stress response and long-term sickness absence. Men providing care had a blunted cortisol awakening response, which may be a marker of chronic stress, whereas women did not. On the other hand, women providing care had a higher risk of long-term sickness absence, whereas men did not. Despite cultural and welfare state differences in the four included cohort studies from Finland, France, Sweden, and the UK, similar tendencies across these cohorts were found. It should be acknowledged that results from studies on type 2 diabetes, cardiovascular disease, and long-term sickness absence should not be generalized to people with unstable work situations or people outside the labor market.
Danish summary


Tidligere studier af de negative helbredsmaessige konsekvenser forbundet med uformel pleje har nogle generelle begrænsninger. Der er således en mangel på studier, som har undersøgt den potentielle effektmodifikation fra arbejdsliv og køn, på sammenhængen mellem uformel pleje og helbredsmål. Konflikt mellem arbejds- og familieliv der kan opstå ved uformel pleje og lønnet arbejde, kan således forværre helbredsmaessige konsekvenser, set i forhold til helbredsmaessige konsekvenser ved at have en af disse eksponeringer for sig selv. Endvidere har undersøgelser vist, at kvinder, der yder uformel pleje, oplever en større plejebyrde end mænd, da kvinder har tendens til at tage rollen som primær plejegiver, og uformel pleje kan derfor være forbundet med større helbredsmaessige konsekvenser for kvinder. Derudover har de fleste tidligere studier ikke undersøgt effekten af forskellige aspekter af uformel pleje på helbredsmaessige
konsekvenser. Således kan forholdet til plejemodtageren, ugentlige plejetimer som en indikator for intensitet, samt varigheden af pleje alle have en virkning på byrden ved uformel pleje.


Det kan konkluderes at pleje for et sygt, handicappet eller ældre familiemedlem eller anden nærtstående person kan have negative helbredsmæssige konsekvenser for plejegivere i lønnet arbejde, samt hos plejegivere der yder mange ugentlige timers pleje i flere år. Social støtte på arbejdspladsen kan være et aspekt af arbejdslivet, som kan være medvirkende til at sænke de helbredsmæssige konsekvenser ved uformel pleje. Resultaterne viste kønsforskelle i de undersøgte sammenhænge med hensyn til det fysiologiske stressrespons og langtidssygefravær. Mænd, der ydede pleje, havde et sænket kortisol respons om morgenen, hvilket kan være en markør for kronisk stress, mens kvinder ikke havde et sænket respons. På den anden side havde kvinder, der ydede pleje, en højere risiko for langtidssygefravær, mens dette ikke kunne genfindes hos mænd. På trods af kulturelle og sociale forskelle i de fire inkluderede kohortstudier fra Finland, Frankrig, Sverige og Storbritannien blev der fundet tilsvarende tendenser i disse kohorter. Til sidst bør det understreges, at resultater fra undersøgelserne vedrørende type 2 diabetes, hjerte-karsygdomme og langtidssygefravær ikke bør generaliseres til personer med ustabile arbejdsforhold eller personer uden for arbejdsmarkedet.
Introduction

Caregiving for chronically ill and elderly people entails a large burden for the formal health care services. Informal caregiving, which is defined as unpaid care for a sick, disabled, or elderly family member or other closely related person (1) saves the formal health care services great expenses annually (2). It is estimated that 34.3% of the population in 20 European countries provide any type of informal care for a family member, and 7.6% provide intensive care categorized as ≥11 hours of care a week (3), with the highest prevalence of informal caregivers among women (3). Due to a growing population of elderly (4) and therefore potentially also a growing population of people living with disabilities, it is anticipated that the formal health care services will be under even more pressure in the coming years (5). Therefore, informal care is expected to play an increasing role in relieving the formal health care system of the caregiving burden (6).

Informal caregiving may be associated with positive feelings (7). In a recent meta-analysis, four key domains on positive aspects of informal caregiving were identified: sense of personal accomplishment and gratification, feelings of mutuality in a dyadic relationship, an increase of family cohesion and functionality, and a sense of personal growth and purpose in life (8). However, informal caregiving may also be perceived as stressful and burdensome for the caregiver (9–11). In a large study among informal caregivers, it was found that 46% experienced emotional stress, 32% experienced physical strain, 18% experienced economical strain, and 22% felt that their health had gotten worse as a result of caregiving (10). In addition, several studies have shown worse quality of life in informal caregivers compared with non-caregivers (12–14), and other studies have shown that informal caregiving may lead to burnout and depression (15–17). Potential health consequences of informal caregiving may be due to a chronic activation of the physiological stress response system. Thus, whether or not you perceive caregiving for a family member as gratifying or an emotional burden, it may cause an altered stress response, which may have a long-term negative health consequences (18).
The primary endocrine systems involved in the physiological stress response are the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis (19). The key mediators of the sympathetic nervous system are epinephrine and norepinephrine, whereas activation of the HPA-axis affects the release of cortisol (18). A recent systematic review has brought together findings from different empirical studies on the associations between informal caregiving for family members with dementia and markers of the physiological stress response. It was concluded that the most consistent associations with informal caregiving is seen with cortisol levels, whereas the associations between informal caregiving and other physiological markers of stress, such as epinephrine and norepinephrine, were less consistent. In general the findings support elevated cortisol levels in informal caregivers compared with non-caregivers (20).

Both elevated and flattened cortisol slopes has been shown to increase the risk of stress-related diseases such as type 2 diabetes and cardiovascular disease (CVD) (21–23). No previous studies have investigated the effect of informal caregiving on type 2 diabetes, but a great number of studies have shown that informal caregiving is associated with higher risk of CVD (24–31). Nonetheless, findings on the health consequences of informal caregiving are inconclusive as several other studies have found a protective effect of informal caregiving on mortality risk (32–36), while one study found higher mortality risk among caregivers with high perceived caregiver strain compared with low strain caregivers (37). However, mortality is a comprehensive health outcome, which may be linked to a vast amount of other underlying factors affecting mortality risk, and addressing more specific health outcomes may be more appropriate when trying to establish the causal link between informal caregiving and potential health consequences (33).

Most previous research on the potential health consequences of informal caregiving do not address specific aspects of caregiving (20). Thus, it is likely that the relationship with the care recipient, caregiving intensity, and duration of caregiving may have an impact on the physiological stress response,
and ultimately an impact on the health of the caregiver (20,27,38). Furthermore, most previous studies on informal caregiving have not thoroughly addressed the contribution of work life on health consequences of informal caregiving. Thus, meta-analyses by the individual participant data (IPD) work consortium have shown that long working hours and high job strain (the combination of high job demands and low job control) was associated with a higher risk of type 2 diabetes and CVD (39–43). In line with this, another meta-analysis found that high job strain was associated with higher risk of recurrent events of CHD (44); and in the INTERHEART study it was found that both stress at work and stress at home was associated with a higher risk of acute myocardial infarction (45). Looking at broader health consequences in the working population, long-term sickness absence has often been used as a marker of health status in research (46), since long-term sickness absence spells is a marker of serious illness in the absentee (46–48). Furthermore, it is a relevant topic for work places and decision makers, as sickness absence can be directly transferred to expenses for the workplace and society at whole (49).

Based the above findings, suggesting negative health consequences from informal caregiving and work life, and further evidence showing that the combined workload of family life and work life is associated with various negative health consequences (50–57); it is likely that informal caregivers in paid work are at higher risk of long-term health consequences compared with caregivers not in paid work (58). On the other hand, addressing factors which may amend the health consequences from the double burden of informal caregiving and paid work, several studies have shown beneficial health effects associated with having social support (59–63). Thus, social support from coworkers and supervisors may be a focus area for preventing negative health consequences among informal caregivers in paid work.

It has been shown that more women than men provide informal care (3,10), and that women providing care often take part in heavier caregiving tasks than men providing care, and more often take the role as primary caregiver (3,5,64,65). Based on this, women providing care may be more prone to chronic stress from caregiving compared with men providing care. By using data form several European
occupational cohorts with comparable data, it is possible to address the modifying effect of work life and gender on the effect of informal caregiving on various stress-related health consequences; and investigate the impact of specific aspects of informal caregiving on these effects.

**Objectives and hypotheses**

The overall objective of this thesis was to investigate the effect of informal caregiving on the physiological stress, stress-related disease, and long-term sickness absence; and to investigate how work life and gender modify these effects. The objective is expressed in four specific aims:

1. To investigate the effect of informal caregiving on the physiological stress response, stress-related disease and long-term sickness absence.
2. To investigate how paid work and psychosocial work factors modify the effect of informal caregiving on the physiological stress response, stress-related disease and long-term sickness absence.
3. To investigate the effect of various aspects of informal caregiving on the physiological stress response and stress-related disease, including the relationship with the care recipient, caregiving hours as a measure of care intensity, and duration of caregiving.

The specific aims are addressed in four scientific studies, which are presented in this thesis. A simplified causal model of the investigated effects is presented in figure 1, along with established and suggested paths. The overall hypotheses, which were addressed in studies 1-4, is that informal caregivers would have flattened cortisol response and be at higher risk of stress-related disease and long-term sickness absence compared with non-caregivers. More specifically, in study 1 the effect of informal caregiving on cortisol levels was investigated, in study 2 the effect of informal caregiving on risk of type 2 diabetes was
investigated, in study 3 the effect of informal caregiving on risk of CVD was investigated, and in study 4 the effect of informal caregiving on risk of long-term sickness absence was investigated. It was also hypothesized, that the negative health consequences from the joint effects of informal caregiving and work life would exceed the expected effects from the individual effects of each of these exposures (58). This was addressed in studies 1-4. In addition to the main hypotheses, it was hypothesized that spousal caregivers would have worse health consequences than caregivers for recipients not in the household, that many weekly hours of caregiving opposed to few weekly hours of caregiving would entail worse health consequences, and that long-term caregiving would cause worse health consequences compared with short-term caregiving (24,25,27). These hypotheses were addressed in study 1, study 3, and to a lesser degree in study 2 and study 4. Lastly, it was hypothesized that the health consequences from informal caregiving would be worse for women compared with men, due to heavier caregiving burden for women (3,5,64,65). This hypothesis was addressed in study 1 and study 4.

![Figure 1. Simplified causal model of the effects investigated in this thesis](image-url)
Background

Informal caregiving and the physiological stress response

Numerous studies have shown that informal caregiving may be associated with a higher risk of feeling stresses (9–11). However, to investigate the causal link between informal caregiving and negative health consequences, it is essential to investigate the physiological stress response in informal caregivers. Individuals react to outside stressors and perceived stress by activation of the HPA-axis, which is the primary endocrine system involved in the physiological stress response, along with the sympathetic nervous system (19). Cortisol is one of the major stress hormones, which is released from the adrenal glands following activation of the HPA axis (18). Cortisol levels vary throughout the day, with a relatively high level at awakening, a steep increase until around 30 minutes from awakening called the cortisol awakening response (CAR), followed by a decrease in the cortisol levels until nadir around midnight (66).

Hyper-activation of the HPA-axis, with an immediate increase in the cortisol response, can be seen in acute stressful circumstances, such as giving a public performance (67). However, cortisol levels has also been suggested to be a marker of chronic stress (68,69). Some studies find elevated diurnal cortisol levels as a marker of chronic stress, while others find low levels of cortisol in specific chronically stressful circumstances such as post-traumatic stress disorder (69). However although inconclusive, it has been suggested that a flattened cortisol response may be associated with chronic stress, depression, and burnout, irrespectively of the overall diurnal cortisol level (68,69). In line with this, some studies have shown that low socioeconomic status, which may be related to high risk of chronic stress, is associated with flattened cortisol response (70,71). In addition, flattened cortisol slopes have been suggested to be associated with difficulties in unwinding before bedtime and general poor health status (66).

Caregivers for family members with dementia is a group commonly studied in the informal caregiving literature. Due to many years of caregiving with changing demands caused by the cognitive decline in the care recipient, dementia may have great impact on the wellbeing of spousal caregivers.
A recent systematic review have brought together findings from studies on informal caregivers for dementia patients, and associations with various physiological stress responses (20). The majority of the included studies have used cortisol as a stress response, and results have revealed abnormal HPA-axis activity with elevated diurnal cortisol levels for caregivers compared to non-caregivers (20). Some studies included in the review have found flattened CAR for caregivers compared with non-caregivers (77,78), indicating that informal care may be associated with chronic stress. Another indicator of physiological stress which was included in the systematic review is allostatic load (20), which comprise an array of multiple biological markers of stress, such as blood pressure, body mass index (BMI), cholesterol, insulin, and glucose (79). However, based on the few studies included in the review, it was concluded that caution should be used in comparing these measures across studies, given that the score will be affected by the nature and number of biomarkers measured, as well as the method of assessment (20). Thus, based on the systematic review, the most consistent findings on the association between informal caregiving and physiological stress response, is seen in the studies which have applied cortisol as a marker of the physiological stress responses (20); although the studies included are rather small and incomparable in the methods applied to analyze cortisol levels. Furthermore, a limitation in the included studies is that they have not addressed differences in cortisol levels, according to relationship with the care recipient, intensity and duration of caregiving. These limitations were addressed in study 1, investigating the effect of various aspects of informal caregiving on cortisol levels, as a marker of the physiological stress response.

**Informal caregiving and stress-related disease**

Chronic stress may have cardiometabolic health consequences, which may lead to diseases such as type 2 diabetes and CVD (18,21–23); presently defined as stress-related diseases. Thus, it has been shown that high cortisol levels decrease insulin production and increase glucose production, and the physiological stress response is therefore assumed to play a role in the development of type 2 diabetes (22).
Furthermore, chronic stress is suspected to increase the risk of CVD, mainly by acceleration of the atherosclerotic process (18). In line with this, it has been shown that a flattened cortisol slope is associated with a higher risk of type 2 diabetes and CVD (21,23). Based on this evidence, it is imperative to investigate the effect of informal caregiving on the risk of these stress-related diseases, in uncovering the long-term health consequences from informal caregiving.

Addressing the risk of stress-related disease, a longitudinal study on nurses providing informal caregiving, found that caregiving for ≥9 hours weekly was associated with a higher risk of coronary heart disease (CHD) compared with non-caregivers, but only for spousal caregivers (24). Also, a cross-sectional study found that spousal caregiving was associated with a higher risk of an elevated Framingham stroke risk score, but not a higher risk of an elevated Framingham CHD risk score (26). Another longitudinal study among civil servants found a higher risk of CVD in informal caregivers providing care for a parent, spouse or child, compared with non-caregivers (27). In a more recent study, informal caregiving was only associated with CHD in caregivers reporting being in poor health (25). Additionally, several studies have found higher risk of markers of CVD such as hypertension in informal caregivers compared with non-caregivers (28–31). Although not conclusive, the findings above show a rather well established association between informal caregiving and the risk of CVD (24–31). According to a literature search, no previous studies has investigated the effect of informal caregiving on the risk of type 2 diabetes. However, this association is important to investigate due to the proposed causal link between the physiological stress response and the development of type 2 diabetes (22). Based on this, the effect of informal caregiving on the risk of type 2 diabetes was investigated in study 2.

Informal caregiving: care recipient, intensity and duration

Investigating the effect of informal caregiving on health consequences, it should be considered that there are various aspects of providing care, which may have an impact of the burden of caregiving, e.g. the care
recipient, the intensity of caregiving, and the duration of caregiving (20,24,27). Providing care for a child, spouse, parent or other closely related person may not necessarily encompass the same caregiving burden. Thus, it has previously been suggested that caregiving for a spouse may be associated with worse health consequences than caregiving for a parent (24); a likely explanation being that the caregiver live in the same household as the spouse, whereas living together with parents is less common among people in the working age. In line with this, it has been shown that caregiving for a spouse is particularly time-intensive (10). Furthermore, it has been suggested that many weekly hours of caregiving as a measure of caregiving intensity, is associated with worse health consequences compared with fewer hours of caregiving (15,24,80–82). In addition, it has been shown that caregivers for individuals in the same household have a poorer health status than caregivers for individuals outside the household (83). This finding is likely due to the constant emotional stress of living together with a disabled spouse (83), but it could also be due to a shared unhealthy lifestyle with the care recipient.

Another aspect of informal caregiving that may influence the perceived burden is the duration of caregiving. Thus, being in an emotional, physical, socially and economically stressful situation over a long duration may lead to chronic stress (20). In line with this, studies have shown exacerbated risk of hypertension and CVD in long-term caregivers compared with current caregivers using non-caregivers as the reference (27,30), but no exacerbated risk of depression for long-term caregivers (16). Long-term caregivers may not only be burdened by the long duration of caregiving, but it has been shown that these caregivers are also the caregivers with most weekly hours of caregiving (10). These various aspects of informal caregiving have not previously been investigated in studies investigating the association between informal caregiving and cortisol levels as a marker of the physiological stress response. Based on these limitations, the effect of these various aspects of informal caregiving on cortisol levels was investigated in study 1. Furthermore, based on the rather well established association between informal caregiving and the risk of CVD, the potential dose-response relationship between weekly hours of caregiving and the risk
of CVD was investigated in study 3. Additionally, in study 3 the effect of the duration of informal caregiving on the risk of CVD was investigated.

**Informal caregiving and gender**

Although the gender division among informal caregivers has become less weighted in recent years (5) informal caregiving is still more common among women compared to men (3,5,10). In a study with data from 20 European countries it was found the 55% of caregivers were women (3). Looking at the physiological stress responses it has been shown that women have higher evening cortisol than men (84), indicating that women may have more difficulties relaxing before nighttime (85); a likely explanation being that women may take more responsibility for household chores (86). In line with this, it has been shown that women who provide care often take part in heavier caregiving tasks than men providing care, and more often take the role as primary caregiver (3,5,64,65). Based on this, informal caregiving may have greater health consequences for women than men, justifying that certain research questions on stress from informal caregiving should be addressed for men and women separately. In addition, it has been suggested that women experience additional psychological job constraint when they combine work and long-lasting caregiving demands (87). Based on this, gender differences in the effect of informal caregiving on the physiological stress response was investigated in study 1, and gender differences in the effect of informal caregiving on the risk of long-term sickness absence was investigated in study 4.

**Multiple roles from informal caregiving and paid work**

Work life may be a stressor that may have an additional impact on the health consequences from informal caregiving. According to the *role strain theory* proposed by William J. Goode (58), having multiple roles from e.g. informal caregiving responsibilities and paid work may increase the mental strain in the individual. The role strain theory is built on the assumption that not all individuals in a society may have the
resources to conform with certain role requirements (58). Goode states that individuals are likely to face a wide, distracting, and sometimes conflicting array of role obligations. Furthermore, he states that if individuals conform fully or adequately in one direction, fulfillment will be difficult in another. Role strain, defined as difficulty in meeting given role demands is therefore considered normal (58). Having its departure in the role strain theory, role overload and role conflict has been proposed as being two separate entities of role strain. Role overload referring to the constraints by time and role conflict referring to the different and conflicting role expectations (88).

The role accumulation theory by Sam D. Sieber on the other hand, raises the question whether multiplicity of roles creates more strain than gratification (88). He states that positive aspects of role accumulation may be classified into four types: “(1) role privileges, (2) overall status security, (3) resources for status enhancement and role performance, and (4) enrichment of the personality and ego gratification.” The role accumulation theory is not meant to deny the occurrence of role conflict and overload, but to broaden to view of societal roles as being sources of role strain (88).

Looking at evidence for these two theories in the informal caregiving literature, role overload may be a natural consequence of spending many hours weekly on caregiving besides having a full-time job; and role conflict may arise when caregiving responsibilities gets in the way of doing your job satisfactory or vice versa. In line with this, many studies have shown negative health consequences from having conflicts between family life and work life, such as psychological strain, burnout, and depression (50–54,89,90). Furthermore, many studies have investigated lifestyle and health consequences among informal caregivers in paid work (16,24,27,30,36,83,91,92). However, few studies have investigated how work life modify the effect of informal caregiving on lifestyle and negative health consequences (81,93). One study among civil servants, found that informal caregivers with low decision latitude (94) (part of the job strain model) were more likely to increase alcohol consumption following onset of caregiving, and another study found that the risk of high allostatic load from many weekly hours of caregiving was exacerbated by having high job
Addressing caregiving for ill family members, one study based on employees in a large financial company, found that caregiving was associated with higher absenteeism due to these caregiving responsibilities (95). A study on lifestyle factors have shown that informal caregivers influenced by negative psychosocial work factors were more likely to increase alcohol consumption and less likely to quit smoking, compared with non-caregivers influenced by the same psychosocial work factors (93). A qualitative study found that informal caregiving responsibilities diminished productivity, and led to missed opportunities for promotion, and that work had an effect on the quality of care and the relationship with the patient (96). Furthermore, in a recent national survey of informal caregivers in the U.S., 52% reported that informal caregiving had interfered with their employment, and these caregivers were more likely to report higher levels of emotional stress associated with caregiving demands, compared to caregivers who did not experience that informal caregiving had interfered with their employment (97). They also found that 40% had quit their job because of caregiving responsibilities, highlighting the difficulties with combining informal caregiving and paid work (97). This finding is partly supported in another recent study, which found that full-time employed people who provided care to a family member in the household (but not outside) were more likely to quit working than non-caregivers (98).

There is also support for the role accumulation theory within the informal caregiving literature. Thus, in a systematic review it has been shown that informal caregiving may lead to a sense of personal accomplishment and personal growth (8). However, the review does not specifically address these issues among caregivers in paid work. Taking work life into consideration, a qualitative study found that employed caregivers had higher perceived well-being than unemployed caregivers (99), signifying the benefits of from joint caregiving responsibilities and paid work. However, the employed caregivers were more likely to be younger and share caregiving responsibilities with others, suggesting that the unemployed caregivers may have had a greater caregiver burden. Finally, in another study among civil servants, it was found that informal caregivers with few caregiving hours had lower allostatic load compared with non-caregivers, irrespectively of perceived job strain (81).
Based on the findings above, there is evidence supporting both the role strain and the role accumulation theory (58,88), within the informal caregiving literature. However, presently it was hypothesized that multiple roles from informal caregiving and paid work would be more detrimental for health than gratifying, thus supporting the role strain theory (58). The modifying effect of work life, on the effect of informal caregiving on negative health consequences, was investigated in study 1-4.

**Informal caregiving and sickness absence**

Investigating health consequences among informal caregivers in paid work it is relevant to investigate the effect on sickness absence, as it has been shown to be a valid marker of health status among employees (46). Numerous prospective studies have found that psychosocial work factors such as high job demands, low job control, discrimination, role conflict/clarity, emotional demands and low social support is associated with higher risk of sickness absence (100–104). Furthermore, including the interplay with family life, several prospective studies have shown that high combined demands from work and family life also predict the onset of sickness absence (50–53). However, according to a literature search only one study has investigated the effect of informal caregiving on sickness absence. However, the study have investigated the risk of sickness absence in caregivers for ill family members, without addressing whether care was provided on a regular basis (95). Furthermore, the study looked at absence from work due to these caregiving responsibilities and not absence from work due to own illness. Addressing this limitation, long-term sickness absence may be a valid measure of health consequences for the caregiver (46–48), as sickness absence for several consecutive days usually require a certificate from a general practitioner. Based on the above, there is a lack of evidence on the effect of informal caregiving on sickness absence. Thus, the effect of informal caregiving on the risk of long-term sickness absence was investigated in study 4.
Informal caregiving and social support

Investigating the health consequences among informal caregivers in paid work, it is important to uncover how the labor market may contribute with diminishing these health consequences. Thus, social support at work may be one component, which may have a positive effect on the health of informal caregivers. Numerous studies in the general population have shown beneficial health effects associated with having social support from family, peers, supervisors and coworkers (59–63). Two different models on these health effects has been proposed (105); the stress buffer model proposing that support is related to well-being for persons under stress, and the main-effect model, proposing that social support have a beneficial effect on health irrespectively of whether the person is under stress (105). Evidence point to a buffering effect when the social support measure assesses the perceived availability of interpersonal resources that are responsive to the needs elicited by stressful events. Evidence for a main effect model has been found when the support measure assesses a person's degree of integration in a large social network (105). Thus, being in a large social network may represent a feeling of stability for the caregiver but may not necessarily help one directly in the face of stress (105). On the other hand, having family, coworkers or a supervisor that have an understanding of the impact of caregiving responsibilities, may be a valuable buffer against chronic stress. Based on this, the effect modification from social support at work, on the effect of informal caregiving on the risk of type 2 diabetes, was investigated in study 2.
## Methods

### Overview of studies included in the thesis

#### Table 1. Overview of the four studies included in the thesis

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Study population</th>
<th>Informal caregiving and modifiers in work life (questionnaire data)</th>
<th>Health outcomes</th>
<th>Confounders</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cross-sectional</td>
<td>Whitehall II</td>
<td>Informal caregiving Do you provide care for one of the following: Spouse, parent, friend, other relative. Weekly hours of caregiving. Caregiving in previous phase. Work exposure In paid work (yes/no)</td>
<td>Salivary cortisol Measured on a weekday at wakeup, 30 minutes, 2.5 hours, 8 hours, 12 hours, bedtime.</td>
<td>Age, Married/cohabiting, ethnicity, work status, household income, wakeup</td>
<td>Cortisol awakening response analyzed in a regression model and cortisol slope in a linear mixed model. Stratified by gender.</td>
</tr>
<tr>
<td>2</td>
<td>Prospective: 10 years follow-up</td>
<td>GAZEL SLOSH Whitehall II</td>
<td>Informal caregiving GAZEL: Do you provide regular care for an aged person (&gt;65 years)? SLOSH &amp; Whitehall II: Do you provide care for an aged or disabled relative? Weekly hours of caregiving in SLOSH and Whitehall II. Work exposure High job strain (yes/no): Combination of high job demands and low job control. High social support (yes/no): Combination of high support from supervisor and coworkers</td>
<td>Type 2 diabetes Self reported in GAZEL, Self-reported and from hospital admissions in SLOSH, Self-reported, diabetes medication, and oral glucose tolerance test in Whitehall II. (data was gathered from study waves and not time-to-event)</td>
<td>Age, sex, married/cohabiting, occupational grade, follow-up time</td>
<td>Logistic regression. Random-effects meta-analysis.</td>
</tr>
<tr>
<td>3</td>
<td>Prospective: 10 years follow-up</td>
<td>SLOSH Whitehall II</td>
<td>Informal caregiving SLOSH &amp; Whitehall II: Do you provide care for an aged or disabled relative? Weekly hours of caregiving in both cohorts. Caregiving in subsequent phase in Whitehall II. Work exposure Weekly work hours in SLOSH. Workhours on a normal weekday in Whitehall II (multiplied by five).</td>
<td>Cardiovascular disease Diagnoses coronary heart disease (ICD-10 codes I20-I25) and stroke (ICD-10 codes I60-I63). From national registers.</td>
<td>Age, sex, married/cohabiting, children, occupational grade</td>
<td>Cox proportional hazard model. Random-effects meta-analysis.</td>
</tr>
<tr>
<td>4</td>
<td>Prospective: Two years follow-up</td>
<td>FPS GAZEL Whitehall II</td>
<td>Informal caregiving FPS: Do you provide care for a sick, disabled, or aged relative? GAZEL: Do you provide regular care for an aged person (&gt;65 years)? Whitehall II: Do you provide care for an aged or disabled relative? Weekly hours of caregiving in FPS and Whitehall II. Work exposure High job strain (yes/no): Combination of high job demands and low job control.</td>
<td>Long-term sickness absence First and second event of long-term sickness absence (&gt;14 consecutive days). From national and company registers.</td>
<td>Age, married/cohabiting, children, occupational grade, death of relative/divorce, longstanding illness, previous long-term sickness absence</td>
<td>Cox proportional hazard model with recurrent events. Random-effects meta-analysis. Stratified by gender.</td>
</tr>
</tbody>
</table>
Cohort studies

In this thesis, questionnaire and register-based data from four occupational cohort studies from Finland, France, Sweden, and the UK were used, to investigate the research questions. All individuals included have given consent to participate in the cohort studies, and the cohort studies have been approved by the respective committees on research ethics. The cohorts are based on self-administered questionnaires on the work environment, private life, and health related outcomes. Due to personal identification numbers, this data can be linked to national registers on sickness absence, medical prescriptions, hospital admission, and mortality registers. A brief overview of the included cohort studies is presented in following section.

_Finnish Public Sector Study, Finland_

The Finnish Public Sector Study (FPS) is an open cohort. It was established in 1997 and comprises public employees in 10 towns and 21 hospitals (106). The eligible population of 151,618 included those who had been employed for a minimum of 6 months at the participating organizations between 1991 and 2005. A nested cohort including a total of 66,418 participants includes questionnaires on psychosocial work and domestic factors, along with health outcomes, which is sent out every fourth year (106).

_GAZEL, France_

The GAZ and Electricité (GAZEL) Cohort Study includes employees of the French national gas and electricity company (107). The company employs around 150,000 workers from both urban and rural areas from all regions of France. The cohort was established in 1989 and includes 20,624 blue- and white-collar workers, with 15,010 men and 5,614 women. The entry age was 40-50 and 35-50 for men and women respectively. The GAZEL cohort study have an annual response rate of approximately 75%. Participants answer annual questionnaires with socioeconomic, behavioral, and health questions.

_Swedish Longitudinal Occupational Survey of Health, Sweden_

The Swedish Longitudinal Survey of Health (SLOSH) is an open cohort, which comprises individuals representative of the Swedish working population in 2003 and 2005 (108). SLOSH includes questionnaires
on work organization, work environment and health. SLOSH was established in 2006 with 9,214 participants, and it is a follow-up study from the Swedish Work Environment Survey (SWES) (109). Self-administered questionnaires have been sent every second year; one addressed to gainfully employed people working at least 30% of full time, and another addressed to those not gainfully employed, i.e. working less than 30% of full time and those outside the labor market.

Whitehall II, the UK

The Whitehall II cohort was established in 1985 and includes 10,308 British civil servants from 20 London-based departments, age 35-55 years at entry (110). The population encompass white-collar workers from cleric and office support grades, middle-ranking executive grades, and senior administrative grade, with wide differences in salary. Participants are invited to clinical visits at 5-year intervals, and in the phases in between, postal questionnaires are sent out. The response rate at each phase is between 79% and 92%.

Informal caregiving

Informal caregiving was the main exposure in this thesis, with information from questionnaires in all four cohorts. However, with some differences in the detail of information. All cohorts have a question with yes/no response on whether they provide informal caregiving, and in the respective cohorts the questions reads as follows: In FPS the question is: “Do you provide care for a sick, disabled or elderly family member?”, in GAZEL the question is: “Do you provide regular care for an aged person (>65 years)?”, and in both SLOSH and Whitehall II the question is: “Do you provide regular care for an aged or disabled relative?”. In FPS, SLOSH, and Whitehall II there is additional information on weekly hours of caregiving. Furthermore, in FPS and Whitehall II there is information on the relationship with the care recipient (Spouse, parent, child, other relative, or friend). Lastly, in Whitehall II there is information on informal caregiving from several consecutive phases, which made it possible to investigate the impact of long-term
Psychosocial work factors

In this section, the psychosocial work factors included in study 2-4 is presented. These encompass job strain, weekly work hours, and social support at work.

To assess perceived stress at work, the job strain model was applied (94), which has been widely applied in work-stress research (41–43,111–113). The job strain model is based on a series of questions on job demands and job control. In FPS and GAZEL, information on job strain came from the Job Content Questionnaire, and in SLOSH and Whitehall II, information came from the Demand-Control Questionnaire. These questionnaires have slight differences in the wording of statements, but have been validated for harmonization (114). Each question concerning job demands and job control is scored on a 4-point Likert scale (1=Strongly disagree, 2=Disagree, 3=Agree, 4=Strongly agree). Job demands was based on five questions in GAZEL, and four questions in the other cohorts, and include statements such as: “My job requires working very hard”. A score above the median of the cohort specific study population was considered as high job demands and below the cut-off is considered as low job demands (114). Job control encompass two sub-scales, skill discretion and decision authority. Skill discretion was assessed with four items in all cohorts and includes statements such as: “My job requires that I learn new things”. Decision authority was assessed with two items and includes statements, such as: “I have a lot to say about what happens on my job”. A score below the median of the cohort specific study population was considered as low job control and above the cut-off was considered as high job control (114). Job strain was defined as the combination of high job demands and low control. The three other combinations derived from these binary variables was considered as no high job strain (94). In GAZEL, the Job Content Questionnaire was...
sent out one year prior to baseline in study 2 and study 4 and this is therefore used as a proxy to assess job strain at baseline.

Information on work hours was available in SLOSH and Whitehall II. In SLOSH, participants were asked how many hours they worked on a normal week, and in Whitehall II, participants were asked how many hours they worked on a normal workday. To harmonize these measures, work hours in Whitehall II was multiplied by five, based on the assumption that employees in the civil service work five days a week. Weekly work hours were categorized as <35 hours, 35-40 hours (reference), 41-54 hours, and ≥55 hours per week, which is in line with studies by the IPD-work consortium (39,115).

Social support at work was included as a potential stress-buffer in study 2, on the effect of informal caregiving on the risk of type 2 diabetes. Social support encompassed social support from supervisors and coworkers. In GAZEL, Social support from supervisors was assessed with the statement: “My superior is concerned about the well-being of those under him/her” in SLOSH with the question: “Does your manager show that he/she cares about you?”, and in Whitehall II with the question: “How often is your immediate superior willing to listen to your problems?” In GAZEL, coworker support was assessed with the statement: “The colleagues with whom I work show an interest in me”, in SLOSH with the statement: “My colleagues are there for me”, and in Whitehall II with the question: “How often do you get help and support from your colleagues?” Both types of work support were scored on a 4-point Likert scale (1=never, 2=seldom, 3=sometimes, 4=often). A score of three or four on both the supervisor and coworker support question was defined as high social support at work (reference category), and all other combinations were defined as low social support at work.
Outcome measures

In the following section, the health outcome investigated in this thesis is presented. These included cortisol, type 2 diabetes, CVD, and long-term sickness absence.

Cortisol

Cortisol measures were available in Whitehall II. Briefly explained, participants were requested to provide six saliva samples in salivettes over the course of a normal weekday at waking, 30 minutes from awakening, 2.5 hours from awakening, 8 hours from awakening, 12 hours from awakening, and bedtime. Participants were instructed not to brush teeth or eat or drink anything for 15 min before sample collection. An instruction booklet was used to record information on the day of sampling including date of collection, wake time, time each sample was taken, and stressful events. Salivettes were centrifuged at 3000 rounds per minute for 5 minutes, resulting in a clear supernatant of low viscosity. Salivary cortisol levels were measured using a commercial immunoassay with chemiluminescence detection (CLIA; IBLHamburg, Hamburg, Germany). The lower concentration limit of this assay is 0.44 nmol/liter; intra- and inter assay coefficients of variance were below 8%. Any sample over 50 nmol/liter was reanalyzed (116). The CAR and diurnal cortisol slopes were analyzed, since they have been suggested to be more meaningfully related to stress exposure compared to other analytic approaches (66). The CAR was calculated by subtracting the cortisol measure at awakening from the cortisol measure at 30 minutes from awakening. Cortisol slopes were calculated using time points from the 30 min peak until nadir at bedtime (66).

Analyses were restricted to wakeup samples that were collected within 10 minutes of waking and with a peak response no later than 45 minutes from awakening, because of a reduced CAR in those with longer delays (117). Furthermore, participants with cortisol values outside ±3 SD of the mean were considered outliers and were removed from analyses (66). Also, in line with recommendations, participants who woke up before 4am or after 11am were removed from analyses, due to irregular CAR (118).
Type 2 diabetes

In assessment of incident type 2 diabetes, individuals <30 of age were excluded to minimize the risk of including incidents of type 1 diabetes (119). The best available data was applied in each cohort to assess incidents of type 2 diabetes. In GAZEL, only self-reported incidences of type 2 diabetes were available, which was based on the statement: “Here is a list of health problems. Enter here the ones you have or have had over 12 months”. In SLOSH, self-reported information was supplemented by information from hospital admissions on type 2 diabetes. The question in the SLOSH was: “Do you have or have had any of the following long-term or serious illnesses or complains the past two years?” In Whitehall II, both information on type 2 diabetes from Oral Glucose Tolerance Test, self-reported diabetes medication, along with self-reported information was available, with self-report information based on the question: “Has a doctor ever told you that you have diabetes?” A total of 10 years follow-up was available in GAZEL and Whitehall II, and six years follow-up was available in SLOSH. Individuals were censored at death.

Cardiovascular disease

Diagnoses of CVD was applied with data from SLOSH and Whitehall II. CVD was defined according to the 10th edition of the International Classification of Disease (120). CVD encompassed diagnoses CHD (ICD-10 codes I20-I25) and stroke (ICD-10 codes I60-I63). Individuals with a CVD diagnosis at baseline were excluded from the study. Incident CVD was assessed with six years follow-up in SLOSH and 10 years follow-up in Whitehall II. Individuals were censored at death from other causes.

Long-term sickness absence

Data on long-term sickness absence came from FPS, GAZEL, and Whitehall II. In GAZEL, information came from a company register and in FPS and Whitehall II, information came from national registers. Long-term sickness absence was chosen as the outcome, since it has been shown to be a valid measure of health among employees, as opposed to shorter spells, which may represent a coping behavior to avoid serious illness (46–48). There is no clear definition of long-term sickness absence in the previous research.
literature. This is partly accounted for by different sick-pay systems in the investigated countries. Presently, a cut-off at >14 consecutive days was applied to define long-term sickness absence, as shorter spells were self-reported in some instances. Thus, by only including register-based sickness absence any reporting bias was prevented. Two years of follow-up was applied, to allow the burden of informal caregiving showing its long-term health consequences. Time at risk included time until an event of long-term sickness absence or until censoring due to retirement/disability pension/incapacity benefit, death. Short-term sickness absence spells were included in time-at-risk of long-term sickness absence, based on the argument that one would still be at risk of long-term sickness absence during shorter spells. To account for recurrent events of long-term sickness absence the Prentice, Williams and Peterson Total Time (PWP-TT) model was applied(121). In PWP-TT, multiple events are ordered by stratification, based on the prior number of events. Here, all participants are at risk of an event in the first stratum, but only those with a prior event are at risk for a recurrent event (121). Analyses were truncated at two spells of long-term sickness absence during follow-up, due to few participants with a greater number of long-term sickness absence spells.

Potential confounding and mediating variables

Potential confounding factors were identified based on current knowledge on factors associated with informal caregiving, work life and the investigated health outcomes. These variables were presented in directed acyclic graphs in the scientific papers (122), to get a graphical overview of the temporality of variables included in the analytical models. In this section, confounders including in all four studies will be presented. Further, information about confounding variables included in the studies can be found in the scientific papers and in the online appendices.

Informal caregiving is more common in older working age compared with younger working age, and is also associated with the investigated health outcomes (9,36,123,124), and age is therefore a potential confounder. Informal caregiving is also more common among individuals who are married or
cohabiting since having a spouse increased the risk of becoming informal caregiving, and being married or cohabiting is associated with an unhealthy lifestyle (125,126), which is a risk factor for the investigated outcomes. Socioeconomic status may be associated with informal caregiving (127), and there is a social gradient in health, showing that people from lower socioeconomic groups have worse health status than people from higher socioeconomic groups (128). In the present thesis, household income was used as an indicator of socioeconomic status in study 1, and occupational grade was used as an indicator of socioeconomic status in studies 2-4. Lifestyle factors such as smoking, obesity, and alcohol consumption, and physical inactivity may be a consequence of caregiving stress (91,93,95), and lifestyle factors were therefore only adjusted for in sensitivity analyses.

**Statistical analyses**

Random-effects meta-analysis was applied in IPD meta-analyses in study 2-4. A random-effects meta-analysis is a sort of multilevel analysis, which account for the clustering of participants within cohort studies, and weights cohort specific estimates in a joint model (129). Random-effects as opposed to fixed-effect take into account that the true effect size between the included cohort studies may vary; e.g., welfare state differences may result in variance on associations between informal caregiving and the investigated health outcomes. Inconsistency between cohort-specific estimates was assessed with the $I^2$, which describes the percentage of total variation across studies that is due to heterogeneity rather than chance (130). As a guideline, an $I^2$ of 25%, 50%, and 75% constitute low, moderate and high between-study heterogeneity, respectively. The random-effects meta-analysis and $I^2$ was analyzed with the *ipdmetan* package for STATA, which is a prefix that can be combined with a variety of different statistical models. Thus, in study 2 and study 4, proportional hazard models were applied and presented as hazard ratios (HR) with 95% confidence intervals (CI). In study 2, a logistic regression model was applied and presented as Odds Ratios (OR) with 95%CI. In study 1, a linear regression model was applied for analyzing the CAR and a multilevel linear model with random slopes and random intercept was applied for analyzing the cortisol
slope. In this model, measurement time was used as a level 1 identifier and person was used as a level 2 identifier. More negative slopes suggest a more rapid decline in cortisol levels, whereas slope values closer to zero reflect flatter diurnal slopes. Because of right-skewed distributions of cortisol levels, data for analyzing cortisol slopes were log transformed. Data on cortisol is presented as difference in β-coefficients between exposed and unexposed, with 95%CI.

In all studies, statistical interaction between informal caregiving (Exposure1) and work factors (Exposure2) in relation to our outcome if interest was investigated. For these analyses, joint models with four exclusive groups were created: (1=No exposure1, No exposure2; 2=No exposure1, Exposure2; 3=Exposure1, No exposure2; 4=Exposure1, Exposure2). According to the STROBE guidelines, both multiplicative and additive effect modification were analyzed in study 2-4, and additive effect modification in study 1. Multiplicative effect modification was assessed by including a product term between the two binary exposures explained above, and additive effect modification was assessed with the Synergy Index (SI), which can be interpreted as the additional risk from double exposure when effect modification is present, relative to the risk from double exposure when there is no effect modification (131).

Several sensitivity analyses were carried out to test the robustness of results in the four included studies. Most additional analyses can be seen in the scientific papers and online appendices. However, a few additional analyses not included in the scientific papers, were also carried out. In study 3, multiple imputation with chained equation was carried out to investigate bias from excluding individuals with missing data (132), and in study 3, the main effect of informal caregiving on the risk of CVD was also analyzed. In study 2 and study 3, ethnicity was included as a potential confounder on data from Whitehall II, and in study 2 and study 4, the GAZEL cohort was excluded from analyses due to potential misclassification of informal caregiving.
Results

Informal caregiving and the physiological stress response

In study 1, the effect of various aspects of informal caregiving on cortisol were investigated, along with the modifying effect of work life. A total of 3,727 participants from the Whitehall II cohort study were included in analyses, with 286 (10%) men and 128 (13%) women providing informal caregiving.

As seen in table 2, providing care was associated with a blunted CAR ($\beta$: -1.39 % CI: -2.74;-0.04 (nmol/L)) in men, but not for women ($\beta$: 1.33 % CI: -0.86;3.51 (nmol/L)), ($P_{Interaction}=0.03$). Among men providing caregiving there were also a dose-response relationship between weekly hours of caregiving and the CAR, indicating that more hours of care were associated with a blunted CAR ($P_{trend}=0.03$). Also among men, results showed that short-term caregiving was associated with a blunted CAR ($\beta$: -3.27; 95% CI: -5.35;-1.19 (nmol/L)), which was not seen with long-term caregiving ($\beta$: -0.87; 95% CI: -2.74;-1.00 (nmol/L)). There were no associations between the various aspects of informal caregiving investigated and cortisol slopes, and further details on these results is therefore only presented in the scientific paper.

Joint models of informal caregiving and paid work and the associations with the CAR and cortisol slope are presented in table 3 and 4. These results showed that providing care was associated with a blunted CAR among men in paid work ($\beta$: -3.23; 95% CI: -5.73;-0.72 (nmol/L)), ($P_{Interaction}=0.07$). Among women, there was an interaction showing that women provided informal care and were also in paid work had the steepest cortisol slope among the four exposure groups ($P_{Interaction}=0.01$). Post hoc analyses investigating the prevalence of spousal caregivers among those in paid work revealed that there was an overrepresentation of spousal caregivers who had retired compared with spousal caregivers in paid work ($p=0.002$).
Table 2. Various aspects of informal caregiving and the association with differences in cortisol awakening response

<table>
<thead>
<tr>
<th></th>
<th>Men (n=2,772)</th>
<th>Women (n=955)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number (%)</td>
<td>Difference in CAR (nmol/L), β (95%CI)</td>
</tr>
<tr>
<td>Informal caregiving</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caregivers</td>
<td>286 (10%)</td>
<td>-1.39 (-2.74;-0.04)</td>
</tr>
<tr>
<td>Non-caregivers</td>
<td>2,486 (90%)</td>
<td>0</td>
</tr>
<tr>
<td>Care recipient:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spouse</td>
<td>89 (3%)</td>
<td>-1.96 (-4.32;0.39)</td>
</tr>
<tr>
<td>Other family member</td>
<td>197 (7%)</td>
<td>-1.32 (-2.94;0.30)</td>
</tr>
<tr>
<td>or friend</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-caregivers</td>
<td>2,486 (90%)</td>
<td>0</td>
</tr>
<tr>
<td>Weekly caregiving</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hours:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;100 hours</td>
<td>33 (1%)</td>
<td>-2.38 (-6.15;1.40)</td>
</tr>
<tr>
<td>20-100 hours</td>
<td>40 (1%)</td>
<td>-3.17 (-6.60;0.25)</td>
</tr>
<tr>
<td>9-20 hours</td>
<td>60 (2%)</td>
<td>-1.46 (-4.27;1.35)</td>
</tr>
<tr>
<td>1-8 hours</td>
<td>128 (5%)</td>
<td>-0.37 (-2.36;1.63)</td>
</tr>
<tr>
<td>Non-caregivers</td>
<td>2,485 (91%)</td>
<td>0</td>
</tr>
<tr>
<td>Test for trend</td>
<td>p=0.03</td>
<td></td>
</tr>
<tr>
<td>Duration of caregiving:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-term caregiving</td>
<td>142 (5%)</td>
<td>-0.87 (-2.74;1.00)</td>
</tr>
<tr>
<td>Short-term caregiving</td>
<td>115 (4%)</td>
<td>-3.27 (-5.35;-1.19)</td>
</tr>
<tr>
<td>Non-caregivers</td>
<td>2,421 (90%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: CAR=Cortisol Awakening Response. Multiple adjusted: Age, ethnicity, married/cohabiting, paid work, income category, and wakeup time. For difference in the CAR, a negative β represents a blunted response.
Table 3. Joint effects of informal caregiving and paid work on differences in cortisol awakening response

<table>
<thead>
<tr>
<th></th>
<th>Men (n=2,772)</th>
<th></th>
<th>Women (n=955)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number (%)</td>
<td>Difference in CAR</td>
<td>Number (%)</td>
<td>Difference in CAR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(nmol/L) β (95%CI)</td>
<td></td>
<td>(nmol/L) β (95%CI)</td>
</tr>
<tr>
<td>Caregiving, in paid work</td>
<td>86 (3%)</td>
<td>-3.23 (-5.73;-0.72)</td>
<td>30 (3%)</td>
<td>-0.27 (-4.79;4.26)</td>
</tr>
<tr>
<td>Caregiving, not in paid work</td>
<td>200 (7%)</td>
<td>-0.71 (-2.33;0.91)</td>
<td>98 (10%)</td>
<td>1.41 (-1.16;3.98)</td>
</tr>
<tr>
<td>Non-caregivers, in paid work</td>
<td>805 (29%)</td>
<td>0.23 (-0.86;1.31)</td>
<td>206 (22%)</td>
<td>-1.79 (-3.97;0.40)</td>
</tr>
<tr>
<td>Non-caregivers, not in paid work</td>
<td>1,681 (61%)</td>
<td>0</td>
<td>621 (65%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: CAR=Cortisol awakening response. Multiple adjusted: Age, ethnicity, married/cohabiting, paid work, income category, and wakeup time. Additive effect modification: men p=0.07, women p=0.97. For difference in the CAR, a negative β represents a blunted response.

Table 4. Joint effects of informal caregiving and paid work on differences in cortisol slopes

<table>
<thead>
<tr>
<th></th>
<th>Men (n=2,772)</th>
<th></th>
<th>Women (n=955)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number (%)</td>
<td>Difference in slope</td>
<td>Number (%)</td>
<td>Difference in slope</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(log nmol/L/hour) β (95%CI)</td>
<td></td>
<td>(log nmol/L/hour) β (95%CI)</td>
</tr>
<tr>
<td>Caregiving, in paid work</td>
<td>86 (3%)</td>
<td>0.004 (-0.003;0.009)</td>
<td>30 (3%)</td>
<td>-0.014 (-0.036;0.009)</td>
</tr>
<tr>
<td>Caregiving, not in paid work</td>
<td>200 (7%)</td>
<td>0.000 (-0.008;0.009)</td>
<td>98 (10%)</td>
<td>0.009 (-0.003;0.022)</td>
</tr>
<tr>
<td>Non-caregivers, in paid work</td>
<td>805 (29%)</td>
<td>0.002 (-0.008;0.018)</td>
<td>206 (22%)</td>
<td>0.014 (0.004;0.025)</td>
</tr>
<tr>
<td>Non-caregivers, not in paid work</td>
<td>1,681 (61%)</td>
<td>0</td>
<td>621 (65%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Multiple adjusted: Age, ethnicity, married/cohabiting, paid work, income category, and wakeup time. Additive effect modification: men p=0.84, women p=0.01. For the difference in cortisol slope, a negative β represents a steeper slope.
Informal caregiving, work life, and risk of stress-related disease

Informal caregiving, psychosocial work factors, and risk of type 2 diabetes

In study 2, the effect of informal caregiving on the risk of type 2 diabetes was investigated, along with the modifying effect of job strain and social support at work. A total of 21,243 participants from GAZEL, SLOSH, and Whitehall II were included. Of these, 1,058 incident cases of type 2 diabetes were registered during 10 years follow-up. The associations between informal caregiving, job strain, and social support at work on the risk of type 2 diabetes, can be seen in figure 2-4.

Figure 2. Association between informal caregiving type 2 diabetes. Adjusted for age, sex, married/cohabiting, occupational grade, and follow-up time

Figure 3. Association between job strain and type 2 diabetes. Adjusted for age, sex, married/cohabiting, occupational grade, and follow-up time

Figure 4. Association between social support at work and type 2 diabetes. Adjusted for age, sex, married/cohabiting, occupational grade, and follow-up time
Analyses on the effect modification by job strain and social support at work, on the association between informal caregiving and risk of type 2 diabetes can be seen in table 5. As seen there was an effect modification by social support, showing that the joint effect of informal caregiving and low social support exceeded the expected risk of type 2 diabetes, from the individual effects of informal caregiving and low social support \( (P_{\text{Interaction}}=0.04) \). In sensitivity analyses investigating potential misclassification of informal caregiving, the association between informal caregiving and risk of type 2 diabetes attenuated slightly when removing the GAZEL cohort study from analyses \( (OR=1.07, 95\% CI:0.82;1.40) \), \( (I^2=0\%) \). In another sensitivity analysis using Whitehall II data, the associations between informal caregiving and risk of type 2 diabetes were additional adjusted for ethnicity (white/non-white). In analysis adjusted for age, sex, married/cohabiting, occupational grade, and follow-up time the odds ratio for the association between informal caregiving and risk of type 2 diabetes was \( (OR=0.97, 95\% CI:0.71;1.31) \). With further adjustment for ethnicity the odds ratio was \( (OR=1.03, 95\% CI:0.76;1.40) \).

Table 5. The joint association between informal caregiving, psychosocial work factors and incident type 2 diabetes during 10 years follow-up

<table>
<thead>
<tr>
<th>Informal caregiving and job strain</th>
<th>OR (95% CI)</th>
<th>( I^2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caregiving, high job strain</td>
<td>1.18 (0.82;1.68)</td>
<td>0%</td>
</tr>
<tr>
<td>No caregiving, high job strain</td>
<td>1.05 (0.83;1.33)</td>
<td>30%</td>
</tr>
<tr>
<td>Caregiving, no high job strain</td>
<td>1.13 (0.92;1.39)</td>
<td>0%</td>
</tr>
<tr>
<td>No caregiving, no high job strain</td>
<td>1</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Informal caregiving and social support at work</th>
<th>OR (95% CI)</th>
<th>( I^2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caregiving, low social support</td>
<td>1.40 (1.08;1.82)</td>
<td>0%</td>
</tr>
<tr>
<td>No caregiving, low social support</td>
<td>1.11 (0.93;1.32)</td>
<td>9%</td>
</tr>
<tr>
<td>Caregiving, high social support</td>
<td>0.93 (0.72;1.20)</td>
<td>0%</td>
</tr>
<tr>
<td>No caregiving, high social support</td>
<td>1</td>
<td>-</td>
</tr>
</tbody>
</table>

Abbreviations: OR= Odds ratio. Adjusted for age, sex, married/cohabiting, occupational grade, and follow-up time. Multiplicative effect modification: job strain \( p=0.78 \), social support \( p=0.04 \). Additive effect modification: job strain synergy index=1, social support synergy index=10.
Weekly hours of caregiving, weekly work hours, and risk of cardiovascular disease

In study 3, data from SLOSH and Whitehall II was applied to investigate to associations between weekly hours of informal caregiving, weekly work hours, and the risk of CVD. The study population included 1,396 informal caregivers who were who were also in paid work. A total of 59 participants developed CVD in 10,410 person-years at risk, with 50 cases of coronary heart disease and 9 cases of stroke. The associations between weekly hours of informal caregiving, paid work, and risk of CVD can be seen in table 6, along with sensitivity analyses applying multiple imputation on eligible participants with missing information exposures and confounders. In the multiple imputation analyses there were 2,171 participants; with 109 cases of CVD during 15,764 person-years at risk. In general, estimates attenuated in multiple imputation analyses, but associations between many weekly hours of caregiving and risk of CVD was robust when including participants with missing information.

Table 6. Associations between weekly caregiving, work hours and cardiovascular disease during 10 years follow-up in informal caregivers from SLOSH and the Whitehall II study

<table>
<thead>
<tr>
<th>Caregiving hours</th>
<th>Cases/participants*</th>
<th>Main analysis, HR (95%CI)</th>
<th>I²</th>
<th>Multiple imputation, HR (95%CI)</th>
<th>I²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=1,396)</td>
<td></td>
<td></td>
<td>(n=2,171)</td>
<td></td>
</tr>
<tr>
<td>&gt;20 hours</td>
<td>9/169</td>
<td>2.63 (1.20;5.76)</td>
<td>0%</td>
<td>2.09 (1.15;3.82)</td>
<td>0%</td>
</tr>
<tr>
<td>9-20 hours</td>
<td>15/227</td>
<td>3.31 (0.53;20.5)</td>
<td>85%</td>
<td>2.18 (0.65;7.39)</td>
<td>74%</td>
</tr>
<tr>
<td>1-8 hours</td>
<td>35/1000</td>
<td>1</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Work hours</td>
<td>Cases/participants</td>
<td>Multiple-adjusted* HR (95%CI)</td>
<td>I²</td>
<td>Multiple imputation, HR (95%CI)</td>
<td>I²</td>
</tr>
<tr>
<td>≥55 hours</td>
<td>14/149</td>
<td>2.23 (1.14;4.35)</td>
<td>0%</td>
<td>1.53 (0.54;4.35)</td>
<td>41%</td>
</tr>
<tr>
<td>41-54 hours</td>
<td>13/481</td>
<td>0.67 (0.34;1.33)</td>
<td>0%</td>
<td>0.77 (0.41;1.46)</td>
<td>0%</td>
</tr>
<tr>
<td>35-40 hours</td>
<td>28/590</td>
<td>1</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>&lt;35 hours</td>
<td>4/176</td>
<td>0.64 (0.19;2.10)</td>
<td>0%</td>
<td>0.96 (0.35;2.64)</td>
<td>21%</td>
</tr>
</tbody>
</table>

*For main analysis. Abbreviations: HR= Hazard ratio. Adjusted for age, sex, children, marital status, occupational grade, along with caregiving hours adjusted for work hours and vice versa.
As seen in table 7, there was no effect modification from weekly work hours, on the association between weekly hours of caregiving and the risk of CVD ($P_{\text{interaction}}=0.26$). However, caregivers providing $>8$ hours of care weekly and working $\leq 40$ hours weekly were at higher risk of CVD than those providing $\leq 8$ hours of care weekly and working $\leq 40$ hours weekly ($HR=3.23$, 95%CI:1.25;8.37). In table 7, estimates attenuated in multiple imputation analyses, but the confidence intervals narrowed and the heterogeneity between studies were lowered.

Table 7. Joint associations between weekly caregiving and work hours and cardiovascular disease during 10 years follow-up in 1,396 informal caregivers from SLOSH and the Whitehall II study

<table>
<thead>
<tr>
<th>Cases/participants*</th>
<th>Main analysis, HR (95%CI), (n=1,396)</th>
<th>$I^2$</th>
<th>Multiple imputation, HR (95%CI), (n=2,171)</th>
<th>$I^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;8 hours caregiving, &gt;40 hours work</td>
<td>7/134</td>
<td>2.87 (0.45;18.3)</td>
<td>65%</td>
<td>1.60 (0.46;5.49)</td>
</tr>
<tr>
<td>&gt;8 hours caregiving, $\leq 40$ hours work</td>
<td>18/264</td>
<td>3.23 (1.25;8.37)</td>
<td>24%</td>
<td>3.12 (1.66;5.88)</td>
</tr>
<tr>
<td>1-8 hours caregiving, &gt;40 hours work</td>
<td>20/496</td>
<td>1.34 (0.67;2.68)</td>
<td>0%</td>
<td>1.07 (0.53;2.18)</td>
</tr>
<tr>
<td>1-8 hours caregiving, $\leq 40$ hours work</td>
<td>15/504</td>
<td>1</td>
<td>-</td>
<td>1</td>
</tr>
</tbody>
</table>

*For main analysis. Abbreviations: HR= Hazard Ratio. Adjusted for age, sex, children, marital status, and occupational grade. Multiplicative effect modification, $p=0.26$. Additive effect modification, synergy index=0.73.

In a sensitivity analyses on 16,620 individuals, of whom were 1,575 caregivers and 15,045 were non-caregivers, there were 654 cases of CVD during 123.477 years of follow-up; with a non-significant tendency, that informal caregiving was associated with a higher risk of CVD compared with non-caregiving (Figure 5). In other sensitivity analyses using Whitehall II data, the associations between weekly caregiving hours and risk of CVD were adjusted for ethnicity (white/non-white). With adjustment for age, sex, marital status, children, and occupational grade, those with 9-20 and >20 weekly hours of caregiving had a hazard ratio of ($HR=1.34$, 95%CI:0.57;3.12) and ($HR=2.13$, 95%CI:0.91;5.02) respectively, compared to those with 1-8 weekly hours of caregiving. After also adjusting for ethnicity, those with 9-20 and >20 weekly hours of
Informal caregiving, job strain, and risk of long-term sickness absence

In study 4, the effect of informal caregiving and job strain on the risk of long-term sickness absence was investigated. A total of 26,800 participants from GAZEL, FPS, and Whitehall II were included. There were 5,946 spells of long-term sickness absence during 46,794 person-years. A total of 12% of men and 21% of women had at least one spell of long-term sickness absence within a two-year period. The association between informal caregiving and long-term sickness absence can be seen in figure 6a and 6b; and the associations between high job strain and long-term sickness absence can be seen in figure 7a and 7b. In sensitivity analyses investigating potential misclassification of informal caregiving, the association between informal caregiving and long-term sickness absence attenuated when removing the GAZEL cohort from analyses, with (HR=0.96, 95%CI:0.76;1.23),(I^2=17%) for men and (HR=1.09, 95%CI:0.86;1.38),(I^2=37%) for women.
A. Men

<table>
<thead>
<tr>
<th>Study</th>
<th>Haz. Ratio (95% CI)</th>
<th>%</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>GAZEL</td>
<td>1.05 (0.88, 1.25)</td>
<td>60.35</td>
<td>60.35</td>
</tr>
<tr>
<td>FPS</td>
<td>0.89 (0.69, 1.14)</td>
<td>28.77</td>
<td>28.77</td>
</tr>
<tr>
<td>Whitehall II</td>
<td>1.16 (0.77, 1.74)</td>
<td>10.89</td>
<td>10.89</td>
</tr>
<tr>
<td>Overall (I-squared = 0.0%, p = 0.431)</td>
<td>1.01 (0.88, 1.16)</td>
<td>100.00</td>
<td>100.00</td>
</tr>
</tbody>
</table>

B. Women

<table>
<thead>
<tr>
<th>Study</th>
<th>Haz. Ratio (95% CI)</th>
<th>%</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>GAZEL</td>
<td>1.08 (0.92, 1.28)</td>
<td>25.28</td>
<td>25.28</td>
</tr>
<tr>
<td>FPS</td>
<td>1.16 (1.05, 1.28)</td>
<td>71.25</td>
<td>71.25</td>
</tr>
<tr>
<td>Whitehall II</td>
<td>0.87 (0.55, 1.36)</td>
<td>3.47</td>
<td>3.47</td>
</tr>
<tr>
<td>Overall (I-squared = 0.0%, p = 0.383)</td>
<td>1.13 (1.04, 1.23)</td>
<td>100.00</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Figure 6. Association between informal caregiving and long-term sickness absence. Adjusted for age, married/cohabiting, children, occupational grade, previous long-term sickness absence, and longstanding illness.

A. Men

<table>
<thead>
<tr>
<th>Study</th>
<th>Haz. Ratio (95% CI)</th>
<th>%</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>GAZEL</td>
<td>1.10 (0.88, 1.38)</td>
<td>39.61</td>
<td>39.61</td>
</tr>
<tr>
<td>FPS</td>
<td>1.21 (0.97, 1.51)</td>
<td>40.17</td>
<td>40.17</td>
</tr>
<tr>
<td>Whitehall II</td>
<td>0.87 (0.62, 1.22)</td>
<td>20.21</td>
<td>20.21</td>
</tr>
<tr>
<td>Overall (I-squared = 19.7%, p = 0.288)</td>
<td>1.09 (0.93, 1.28)</td>
<td>100.00</td>
<td>100.00</td>
</tr>
</tbody>
</table>

B. Women

<table>
<thead>
<tr>
<th>Study</th>
<th>Haz. Ratio (95% CI)</th>
<th>%</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>GAZEL</td>
<td>0.98 (0.81, 1.17)</td>
<td>18.97</td>
<td>18.97</td>
</tr>
<tr>
<td>FPS</td>
<td>1.12 (1.02, 1.23)</td>
<td>75.81</td>
<td>75.81</td>
</tr>
<tr>
<td>Whitehall II</td>
<td>0.99 (0.70, 1.41)</td>
<td>5.22</td>
<td>5.22</td>
</tr>
<tr>
<td>Overall (I-squared = 0.0%, p = 0.373)</td>
<td>1.08 (1.00, 1.17)</td>
<td>100.00</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Figure 7. Association between job strain and long-term sickness absence. Adjusted for age, married/cohabiting, children, occupational grade, death of relative and/or divorce, previous long-term sickness absence, and longstanding.
In Table 8, it is seen that women exposed to informal caregiving and high job strain were at higher risk of long-term sickness absence than non-caregiving women with no high job strain were (HR=1.22, 95% CI:1.04;1.43). However, there was no effect modification by job strain, on the association between informal caregiving and long-term sickness absence. Among men, double exposure to informal caregiving and high job strain was not associated with a higher risk of long-term sickness absence compared with non-caregivers with no high job strain.

Table 8. Joint associations between informal caregiving and job strain on the risk of long-term sickness absence; using data from FPS, GAZEL, and the Whitehall II cohort study

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th></th>
<th>Women</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95%CI)</td>
<td>I²</td>
<td>HR (95%CI)</td>
<td>I²</td>
</tr>
<tr>
<td>Caregiving, high job strain</td>
<td>0.95 (0.69;1.30)</td>
<td>0%</td>
<td>1.22 (1.04;1.43)</td>
<td>0%</td>
</tr>
<tr>
<td>No caregiving, high job strain</td>
<td>1.13 (0.95;1.35)</td>
<td>13%</td>
<td>1.10 (1.01;1.20)</td>
<td>0%</td>
</tr>
<tr>
<td>Caregiving, no high job strain</td>
<td>1.06 (0.92;1.22)</td>
<td>0%</td>
<td>1.17 (1.04;1.31)</td>
<td>12%</td>
</tr>
<tr>
<td>No caregiving, no high job strain</td>
<td>1</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
</tbody>
</table>

Abbreviations: HR= Hazard Ratio. Adjusted for age, married/cohabiting, children, occupational grade, death of relative and/or divorce, previous long-term sickness absence, and longstanding illness. Multiplicative effect modification: men p=0.17, women p=0.65. Additive effect modification: men synergy index=-0.26, women synergy index=0.81.
Discussion

In the following section, the main findings of the thesis in relation to the study hypotheses and previous knowledge will be addressed; and the internal and external validity of the included studies will be evaluated.

Main findings in relation to hypotheses and previous knowledge

*Informal caregiving, work life, and the physiological stress response*

In the present thesis, salivary cortisol was applied as a measure of the physiological stress response. The main hypothesis in study 1 was that informal caregivers would have blunted CAR and flattened cortisol slope compared with non-caregivers, since a flattened cortisol response has been shown to be associated with chronic stress, depression and burnout. There was partly support for this hypothesis, with men providing care having a blunted CAR compared with non-caregivers, but this association was not found among women. A recent systematic review on dementia caregiving and the physiological stress response have included 31 studies using various approaches of analyzing cortisol data. The review in general support elevated diurnal cortisol response among caregivers compared with non-caregivers (20), but does not conclude whether the diurnal cortisol slopes of informal caregivers are flattened. However, some studies included in the review found a blunted CAR among informal caregivers compared with non-caregivers, as a results of a higher cortisol level at wakeup among caregivers (77,78). Furthermore, another study included in the review, found both elevated cortisol levels at wakeup and at the peak response in caregivers compared with non-caregivers. However, this study did not calculate the difference in cortisol at wakeup and at the 30 minutes peak response, which is how the CAR is measured (133). In the present thesis, the blunted CAR observed among men providing care was not a result of elevated cortisol levels at wakeup. In addition to results on the CAR, there was no evidence for flattened cortisol slopes among neither men nor women providing care.
Other hypotheses investigated in study 1, were that a flattened cortisol response would be most pronounced among informal caregivers with many weekly hours of caregiving, among spousal caregivers opposed to other recipients, and among those providing long-term caregiving. In support of this, there was a dose-response relationship in men providing care (but not women) showing that more weekly hours of caregiving were associated with a blunted CAR. There was no support for the hypothesis that long-term caregivers would have a flattened cortisol response. However, a blunted CAR was evident among men providing short-term caregiving, suggesting that short-term caregivers may be in a state of chronic stress, whereas long-term caregivers may have learned to cope with the caregiving responsibilities. In addition, there was no support for the hypothesis that caregiving for a spouse would be associated with flattened cortisol response compared with caregiving for other family members or friends. No previous studies have investigated the associations regarding the relationship with the care recipient and cortisol levels as a physiological marker of stress. However, some studies have compared caregiving for different groups of care recipients in relation to other health consequences. In the Nurses’ Health Study it was found that caregiving for a spouse was associated with a higher risk of CHD compared with non-caregiving, but caregiving for parents or other family members was not associated with a higher risk of CHD compared with non-caregiving (24). In a recent Japanese study, there was not a higher risk of non-fatal CHD for informal caregivers with either parent, parent in law, or other care recipients compared with non-caregivers (92). Also, in a recent study including informal caregivers in the U.S., there was no increased risk of emotional difficulty, physical difficulty, and work productivity loss in spousal caregivers compared with caregivers for other recipients (9). However, not surprisingly, they found that spousal caregivers experienced higher financial difficulties compared with other informal caregivers. Probably due to a decrease in the household income from having a spouse with a disability (9).

A secondary hypothesis in study 1, was that a flattened cortisol response would be most pronounced among informal caregivers in paid work, based on the role strain from having this double burden (58). This hypothesis was supported among men, showing that caregivers in paid work had a
noticeable blunted CAR. In contrast to the hypothesis, an effect modification was found among women, showing that women in paid work, who provided care had the steepest cortisol slope, compared with the other exposure groups. This finding was surprising since a steeper slope indicate that it may be easier to unwind in the evening, and steeper cortisol slopes has therefore also been associated with better health status (66). This result could be caused by a healthy caregiver effect, with women carrying the double burden of informal caregiving and paid work being the most resilient caregivers (134), whereas more burdened and less resilient caregivers quit their job to commit to their caregiving responsibilities (97). However, it has also been shown that caregivers for family members in the household are more likely to quit working compared with caregivers for relatives living outside the household (97,98). Thus, with previous findings suggesting that caregiving in the same household is more burdensome than caregiving outside the household (83), there could be an overrepresentation of caregivers for family outside the household among caregivers in paid work. This could be an explanation for the general lack of support for the hypothesized negative effects from the joint burden of informal caregiving and paid work (58). To investigate this issue, a post hoc analysis revealed that in the population in study 1 on cortisol, there was an overrepresentation of spousal caregivers who had retired compared with spousal caregivers in paid work. Thus, with spousal caregiving being more likely to be in the same household compared with caregiving for other recipients, the suggestion that there is an overrepresentation of caregivers for family members outside the household among caregivers in paid work, seems to be supported by this additional analysis.

Informal caregiving, work life, and stress-related disease

Informal caregiving, psychosocial work factors, and the risk of type 2 diabetes

Based on a proposed causal link between the physiological stress response and the risk of type 2 diabetes (22), it was hypothesized in study 2 that informal caregivers would be at higher risk of type 2 diabetes than non-caregivers; and that job strain and social support at work would modify this effect. The effect of informal caregiving on the risk of type 2 diabetes was not supported in this thesis, and neither was informal
caring a risk factor for type 2 diabetes in those with high job strain. However, it was found that low
social support was associated with a higher risk factor of type 2 diabetes, and informal caregivers with low
social support were at particularly high risk of type 2 diabetes, which as partly in line with the hypothesis.

No previous studies have investigated the risk of type 2 diabetes in informal caregivers, and
comparison with other studies should therefore be broadened to other health outcomes. In the systematic
review on informal caregiving and the physiological stress response, the general conclusion was that
informal caregiving was associated with overall elevated cortisol levels during the day. Since elevated
cortisol has been shown to decrease insulin production and increase glucose production (22), which are
mechanisms, involved in the development of type 2 diabetes, it was anticipated that an association
between informal caregiving and risk of type 2 diabetes would be seen in the present thesis. However, it
should be acknowledged that there might be various other mechanisms linking physiological stress with the
risk of type 2 diabetes. Furthermore, in study 1, which seems to be the largest study, which have
investigating the association between informal caregiving and cortisol levels, there did not seem to be
elevated cortisol levels among informal caregivers, thus blurring the potential causal link between informal
caregiving stress and the risk of type 2 diabetes. However, lifestyle may be another mediating factor, linking
informal caregiving with the risk of type 2 diabetes. Thus, in a previous study, lower frequency of sports
activities was associated with time spent on caregiving and providing nursing care (91). In addition, it has
been shown that caregivers with low decision latitude (part of the job strain model) may be more likely to
increase alcohol consumption compared with non-caregivers, and caregivers with high job demands are
less likely to quit smoking compared with non-caregivers (93). However, uncertainty about the temporality
of onset of informal caregiving and an unhealthy lifestyle remains, as another study have found higher BMI
among informal caregivers compared with non-caregivers without distinguishing between cause and effect
(127). Furthermore, in the present thesis, adjustment for lifestyle factors such as BMI and smoking had
little impact on results, suggesting that lifestyle was neither a strong confounder nor mediator.
Results in this thesis showing that low social support at work is associated with higher risk of type 2 diabetes is a novel finding. As with informal caregiving, an unhealthy lifestyle should be considered as a factor playing a role in the causal link between low social support and the risk of type 2 diabetes. Thus, a previous study on Whitehall II, have showed that becoming a caregiver was associated with a higher change of quitting smoking if caregivers had high social support at work (93). Thus, with smoking being a strong risk factor for type 2 diabetes (41), this may partly explain the finding. However, it should be acknowledged that in the previous study, high social support was not a protective factor against other risk factors for type 2 diabetes (93), such as high alcohol intake or reduced physical exercise (41).

This was the first study to investigate the effect of informal caregiving on the risk of type 2 diabetes. It is therefore strongly recommended that more research be carried out, before drawing conclusions on the association between informal caregiving and the risk of type 2 diabetes, as there may be several paths, which may causally link informal caregiving with the risk of type 2 diabetes.

**Weekly hours of informal caregiving, weekly work hours, and the risk of CVD**

In study 3, the main hypothesis was that informal caregivers with many weekly hours of caregiving would be at higher risk of CVD compared with caregivers with few weekly hours of caregiving. Furthermore, it was hypothesized that those with many weekly hours of caregiving and long working hours would have the most pronounced risk of CVD. Results partly supported this hypothesis, as many weekly hours of caregiving was associated with a higher risk of CVD compared with having few hours of caregiving, irrespectively of weekly work hours. This finding is in line with findings from previous studies showing negative health consequences from many weekly hours of caregiving (15,24,27,80–82,92). Looking specifically at the risk of CVD, three previous studies have shown that informal caregivers with many hours of caregiving were at higher risk of CVD (24,27,92). In the Nurses’ Health Study from the U.S., caregiving for an ill or disabled spouse for ≥9 hours weekly was associated with a higher risk of CHD, but only among spousal caregivers (24). In the Health and Retirement Study, also from the U.S., spousal caregiving ≥14 hours weekly was
associated with a higher risk of CVD (27). Lastly, in a recent Japanese study, a pronounced risk of non-fatal CHD was seen among those providing 20-69 hours of care weekly (92). On the other hand, in a study from the UK, there was no higher risk of CHD in those with >5 hours caregiving weekly compared to those providing fewer hours of care (25). However, the latter study applied a crude measure of weekly hours of caregiving. Thus, results are not conclusive, but an increasing amount of research point towards a higher risk of CVD and negative health consequences in general, among caregivers with many weekly hours of caregiving (15,24,27,80–82,92). These findings are not surprising, since many weekly hours of caregiving may be associated with spousal caregiving, caregiving in the household, and severe disease in the care recipient (10,135), which are all aspects of informal caregiving that may exacerbate the negative health consequences of informal caregiving (20,24,83).

Results from study 3 builds on previous research, which have shown associations between informal caregiving and risk of CVD (24–31). In study 3, the main effect of informal caregiving on the risk of CVD was not investigated, since the purpose of the study was to investigate the dose-response relationship between weekly hours of caregiving and CVD. However, in a post hoc analysis in this thesis, the association between informal caregiving and risk of CVD was investigated, showing a non-statistical significant tendency of an association between informal caregiving and risk of CVD. In a recent study from Japan there was also no association between informal caregiving and the risk of non-fatal CHD (92). However, due to cultural differences the study population is not likely to be generalized to a western population. Furthermore, CHD was based on self-report, which may lead to non-differential misclassification and a blurred effect of informal caregiving on the risk of CHD (136). Therefore, the rather well established association between informal caregiving and risk of CVD in western countries is little affected by these results.

Based on a hypothesis that long-term caregiving is especially detrimental for health, a sensitivity analyses was carried out in study 3, showing that many weekly hours of caregiving was only a risk
factor for CVD in long-term caregivers but not in short-term caregivers. Relating this to previous knowledge, several studies based on the Health and Retirement Study from the U.S. have investigated the association between long-term informal caregiving and health consequences (16,27,30). In these studies, long-term caregiving was defined as informal caregiving in two consecutive waves, as in the present thesis. However, it should be noted that non-caregivers in the Health and Retirement Study included those who provided care for 14 hours or less (16,27,30). In the Health and Retirement Study, an exacerbated risk of hypertension and CVD was found in long-term caregivers compared with non-caregivers (27,30), and both current and long-term caregiving was associated with a higher risk of depression (16). Findings from this thesis support these previous findings, by showing that long-term caregivers with many weekly hours of caregiving were at higher risk of CVD compared with short-term caregivers. Based on these findings, it seems that long-term caregiving may be especially detrimental for cardiovascular health in informal caregivers.

Informal caregiving, work life, and long-term sickness absence

In study 4 it was hypothesized that informal caregivers would be at higher risk of long-term sickness absence compared with those who were unexposed. Furthermore, it was hypothesized that the effect of informal caregiving on the risk of long-term sickness absence would be modified by job strain. In addition, it was hypothesized that the risk of long-term sickness absence among informal caregivers would be highest among women. There was partly support for these hypotheses in the present thesis. Among women, both informal caregiving and high job strain were risk factors for long-term sickness absence. However, there was no effect modification by job strain on the association between informal caregiving and the risk of long-term sickness absence. Among men, neither informal caregiving nor high job strain were risk factors for long-term sickness absence.
According to a literature search, no previous studies has investigated the risk of long-term sickness absence in informal caregivers compared with non-caregivers. However, numerous studies have shown negative health consequences from informal caregiving, which may potentially lead to sickness absence (6,9−11,20,24–31,72–77,81,137,138). Furthermore, several prospective studies investigating the combined demands from work and family life have shown associations with the risk of sickness absence (50−53). Two of these studies were based on GAZEL, and applied the combined demands from having work stressors and having dependent family members, as a measure of high demands from work and family life (50,52). One of these studies found that high demands from work and family was associated with a higher risk of long-term sickness absence (50), and the other study found that high demands from work and family was associated with a higher risk of sickness absence due to non-psychotic psychiatric disorders (52).

Furthermore, a study from Sweden found that high demands from work and family was associated with a higher risk of sickness absence in women, but not in men (53). Lastly, a Finnish study found that negative spillover from work into family life was associated with a higher risk of sickness absence among both women and men (51). Results from the present thesis partly support these findings by showing that women but not men, with the double burden from informal caregiving and high strain job were at higher risk of long-term sickness absence compared with non-caregivers with low job strain. However, more studies should investigate sickness absence among informal caregivers, since informal caregiving may be associated with higher risk of sickness absence compared to high work and family demands attributed to care for e.g. healthy children.
Internal validity

Selection bias

In longitudinal studies, selection bias may be introduced in selection of the study population and by loss to follow-up (136). In FPS and SLOSH, responders to the baseline questionnaire were older and were more likely to be women than non-responders (139). In GAZEL, responders to the baseline questionnaire were also older, but were more likely to be men than non-responders were. In Whitehall II, responders to the baseline questionnaire were more likely to be men than non-responders. Therefore, besides from Whitehall II, there seems to be an underrepresentation of younger eligible individuals. Informal caregiving is less common in younger working age compared older working age (9,36,123,124). Furthermore, non-participants in large surveys tend to have a worse health profile than participants. Thus, there could potentially be an underrepresentation of non-caregivers in poor health, thus being a source of bias away from the null in analyses on data from FPS, GAZEL, and SLOSH.

In the study 2, there was no follow-up on approximately 1,500 individuals, since information on type 2 diabetes was partly based on self-reported information. However, this missing information was not related to either exposures or covariates, and is therefore unlikely to have biased results. Due to register-based information on CVD and sickness absence, there was full follow-up of participants in study 3 and study 4, aside from individuals who were censored from mortality. In the case of sickness absence, participants could also be censored because of retirement, which could be a competing risk for the risk of long-term sickness absence. Sensitivity analyses were therefore carried out in study 4, in which participants were censored at the age of 58 to account for the competing risk of retiring due to statutory pension age. However, this analysis did not change the conclusions regarding the associations between informal caregiving, job strain and long-term sickness absence.

In study 3 on CVD, there were 775 eligible participants with missing information on either caregiving hours, work hours, marital status, children, or occupational grade. These otherwise eligible
participants with missing information were more likely to be men compared with complete cases. Furthermore, if those with missing information differed concerning certain underlying factors associated with informal caregiving and risk of CVD, the associations in the main analyses may be biased. Based on this, sensitivity analyses applying multiple imputation were carried out, showing that the association between many weekly hours of caregiving and risk of CVD was robust to the missing information.

Information bias

Information bias may be introduced in longitudinal studies if the exposure and/or outcome is misclassified.

Misclassification of the exposure

There were slight differences in the question on informal caregiving, as explained in the methods section. Thus, in GAZEL the question did not included care recipients under the age of 65. Since most participants in GAZEL were in their start fifties at baseline, most people would not be placed in the informal caregiving category if they provided care for a spouse. Consequently, if participants in GAZEL only provided informal care to a spouse or other family member younger than 65 years, they would be placed in the non-caregiving category; thus blurring the effect of informal caregiving on type 2 diabetes and long-term sickness absence. However, excluding GAZEL data from analyses in study 2 and study 4 did not change conclusions regarding the associations between informal caregiving and risk of type 2 diabetes and long-term sickness absence. A further limitation in GAZEL is that information on job strain in year 1999 was used as a proxy for job strain at the baseline in year 2000, since data on job strain was not available at baseline. However, it was assumed that job strain would be consistent in year 1999 and 2000, which does not seem to be a strong assumption, since employees of the French national gas and electricity company have stable work situations due to their civil servant-like status (107).

A general limitation of the data on informal caregiving is that there was no information on the type of caregiving provided, and the severity of the disease of the care recipient. Thus, there may be a
huge difference in the burden of informal caregiving, based on whether providing assistance with e.g. personal care or grocery shopping (10). The type of care provided is also associated with the severity of the disability of the care recipient. Thus, the effect of informal caregiving on negative health consequences would most likely be worse for the group of caregivers providing care for family members with severe disabilities. Thus, findings may be underestimated, by including caregivers who assist with small activities of daily living, which may not entail any physical or emotional burden.

Both job strain and social support is based on questions on how respondent perceive their psychosocial work environment. Based on this, misclassification is not a relevant source of bias for these exposures. Regarding work hours, in Whitehall II participants were asked how many hours they spend working on an average weekday. Thus, misclassification of weekly work hours could occur if participants did not work five days a week, thus blurring the effect of work hours on risk of CVD because of an overestimation of work hours. However, this is unlikely to be a substantial issue given that the civil servants included have regular and stable work situations (110).

Misclassification of the outcome

Cortisol was applied as a measure of the physiological stress response, and was measured from saliva samples, collected by participants. Samples were collected on a single weekday, which should be acknowledged as a limitation, since it has been suggested that cortisol measures from several days may provide a better overall picture of the physiological stress response in the individual participant (140). Furthermore, participants were instructed to write down the time of each cortisol sample, which is essential information in analyzing the CAR (140). Information on the timing of each sample could be subjected to misclassification if participants reported the wrong sampling time in order to comply with the protocol for gathering the cortisol samples (117). In line with this, it has been shown that individuals who were told that they were monitored, reported the timing of the gathered cortisol samples more accurately.
than another group of participants, who did not know that the timing of cortisol samples were monitored (117). In the present thesis, the accuracy of the reported timing of cortisol samples was not monitored. Therefore, if participants had a delayed CAR and miss-reported the timing of the sample to comply with the protocol, it could lead to an erroneous blunted CAR. This delayed CAR could potentially be seen among spousal caregivers, since caregiving responsibilities may have conflicted with complying with the cortisol sample protocol. However, there is no evidence in study 1 that spousal caregiving was associated with a blunted CAR, and the mentioned source of misclassification is therefore unlikely to have biased estimates.

In study 2, various sources of information were applied to establish the diagnosis of type 2 diabetes. In SLOSH, information was partly from registers, and in Whitehall II information was partly ascertained from Oral Glucose Tolerance Test, which is considered the golden standard in diagnosing type 2 diabetes. However, in both GAZEL, SLOSH, and Whitehall II information on diabetes also came from self-administered questionnaires. Thus, misclassification could occur, if participants were unsure whether they had a diabetes diagnosis. This potential misclassification is likely to be greatest in GAZEL, since information on diabetes was solely based on self-report in this cohort. However, it seems unlikely that caregivers would have more misclassification than non-caregivers, thus resulting in non-differential misclassification with bias towards the null. In study 3, misclassification of the outcome is less likely to occur, since diagnosis of CVD was solely gathered from registers.

In study 4, a cutoff of >14 consecutive days of sickness absence was chosen for long-term sickness absence, to ensure that information of sickness absence spells were register-based. Thus, minimizing the risk of misclassification of sickness absence. However, there could potentially be cases where employers allow an emotionally stressed employee to take sick leave in order to provide care for e.g. a terminally ill spouse or parent. This would entail a misclassification of long-term sickness absence, since it is not illness in the caregiver, but illness in the family member that is the cause of the absence spell; thus, making misclassification differential, as it will occur among those who provide informal caregiving. This type
of misclassification would overestimate the association between informal caregiving and long-term sickness absence.

**Confounding**

Confounding concerns the misinterpretation of associations between an exposure and outcome, which may be caused by a third variable that is associated with both the exposure and outcome of interest.

Analysis were adjusted for ethnicity in study 1 on cortisol, since it has been shown that informal caregiving is more common among people from non-white ethnic groups (10,141), and ethnicity also has a differential effect on cortisol levels (142). However, ethnicity may also be associated with risk of type 2 diabetes and CVD (143,144). Thus, analysis investigating the effect of informal caregiving and risk of type 2 diabetes and CVD should ideally also be adjusted for ethnicity. However, information on ethnicity was only available in the Whitehall II cohort. Based on this, sensitivity analyses were carried out, with adjustment for ethnicity using Whitehall II data, on the associations between informal caregiving and the risk of type 2 diabetes and CVD. However, there was also no noteworthy change in estimates from adjusting for ethnicity, and socioeconomic status has been shown to have a much stronger association with diabetes prevalence than ethnicity (145). Furthermore, it should be noted that informal caregiving was not more common among non-white than white people in the Whitehall II cohort.

Study 1 and study 2 on cortisol and type 2 diabetes were not adjusted for whether or not participants had any children, but analyses in study 3 and study 4 on CVD and long-term sickness absence were (146). The reason was that having children is not associated with a higher risk of type 2 diabetes. In study 1, there was no information on children at baseline. However, participants were unlikely to have children living at home, since the mean age of the study population was 66 years. Furthermore, being married or cohabiting, which was adjusted for in all studies, is highly correlated with having children, and may therefore have removed some of the effect of having children on cortisol levels. Based on this, there
does not seem to be noteworthy residual confounding from not adjusting for children in the studies on cortisol and type 2 diabetes.

In study 1 on cortisol, analyses were adjusted for annual household income instead of occupational grade as a measure of socioeconomic status. The reason was that less than 30% of participants were in paid work, and thus, without information on occupational grade at baseline or in the preceding phase. However, it should be noted that low household income could be a result of a spouse becoming ill or disabled, and thus, not be able to contribute to the household income. Based on this, household income may be a plausible mediating factor on the causal link between informal caregiving and cortisol levels, for those providing care inside the household. However, there was no attenuation from adjusting for household income, neither in analyses on the main effect of informal caregiving nor in analyses on care recipients, indicating that household income was neither a mediator nor an important confounder in study 1.

In study 4 on long-term sickness absence, analyses were adjusted for previous spells of long-term sickness absence in the main analysis, since previous sickness absence is a strong risk factor for subsequent spells of sickness absence. However, it has been suggested that bias could be introduced by conditioning on the outcome (147), since this conditioning may introduce dependence between other risk factors, which would bias estimates towards the null (147). Whether this is the case for outcomes such as long-term sickness absence remains to be investigated. However, to account for this potential bias sensitivity analyses were carried out, which were not adjusted for previous spells of long-term sickness absence, and these analyses yielded similar results as the main analyses. Therefore, adjusting for previous long-term sickness absence was not an important confounder in study 4.

The health status of the caregiver could be another potential confounder. Thus, longstanding illness may be a consequence of a shared lifestyle with a spouse, and thus leading to becoming a caregiver for a spouse who is even more ill than the caregiver is. Furthermore, previous illness may increase the risk
of recurrence, or the onset of new diseases, and thus lead to sickness absence spells. In study 4, analyses were adjusted for long-term illness such as CVD, diabetes, cancer, and respiratory diseases based on the above arguments. However, because of the lack of information about the onset of informal caregiving in the present thesis, any illness reported at baseline or before, could potentially also be a consequence of stress from informal caregiving. Thus, in study 3, adjusting for hypertension and previous events of CVD could attenuate the true effect of informal caregiving on the risk of new events of CVD, if these previous events were also a consequence of informal caregiving stress. However, in study 2 on type 2 diabetes, sensitivity analyses were adjusted for family history of diabetes, with no noteworthy impact on results.

Main analyses in all studies were not adjusted for lifestyle factors such as smoking, alcohol consumption, BMI, and physical inactivity, since these lifestyle factors are likely to be a consequence of the burden of informal caregiving (91,93,95), and thus mediating factors on the causal link between informal caregiving and negative health consequences (91). However, it has also been shown that informal caregivers are in worse health to begin with, compared with non-caregivers (83), perhaps due to a shared lifestyle with a care recipient in the household (83). Based on this uncertainty about the temporality of exposure to informal caregiving and an unhealthy lifestyle, sensitivity analyses with adjustment for lifestyle factors were made, in the studies on type 2 diabetes and CVD. In study 2 on type 2 diabetes, there was no change in estimates after adjusting for lifestyle factors, but investigating the effect of weekly hours of informal caregiving on risk of CVD in study 3, there was a slight attenuation of estimates after adjusting for lifestyle factors.
**External validity**

One of the strengths of this thesis is that several large European cohort studies was included. The respective countries have different welfare state systems and the included cohorts has employees from various occupational sectors. Therefore, it may be a strength that findings in general have shown the same tendencies across countries regarding associations between informal caregiving, psychosocial work factors, and negative health consequences.

In the four included countries, there are some differences in long-term care systems for the elderly. In Finland and Sweden, people are eligible for long-term care provided by the state from an assessment of need principle (148,149). In France, people over the age of 60 are eligible for long-term care if they are dependent in carrying out activities of daily living (150). Here, families play a central role in financing and providing care for the dependent elderly, whereas the state and health insurance systems play a minor role in management of long-term care (150). Lastly, in the UK the responsibility of long-term care is placed with the dependent and their families (151). Thus, informal caregiving would be suspected to be on a more voluntary basis in Finland and Sweden, compared with France and the UK, where families are obligated to help their family members. Informal caregiving was also most common in GAZEL, but with similar prevalence in FPS, SLOSH and Whitehall II. There was no obvious pattern in the results on the associations between informal caregiving and negative health consequences, thus indicating that the welfare state arrangements had no impact on the results. In support of this, it has been shown that informal caregiving may result in psychological stress irrespective of the type of welfare state (83).

In Finland, France and the UK employees have the right to receive sick-leave pay if their working inability can be determined by a doctor’s certificate (152–154). However, there are some differences in the social security systems. In Finland, employees are entitled to sick-leave payment for nine days if they have been at their workplace for more than a month, but usually the payment period is longer according to the applicable collective agreement. Following this, employees are eligible for sick leave
allowance (152). In France, employees working for more than a year are entitled to sick pay provided by the employer and social security system, with 90% of total salary for at least 30 days (153). Finally, in the UK statutory sick pay is paid by the employer, if the employee is sick for a period longer than 4 consecutive days but less than 28 weeks (154). Based on this, there are some welfare state differences regarding statutory sick pay, but for long-term sickness absence spells all countries have a social security system that will provide economical support for the absentee (152–154). However, these differences should be taken into consideration when generalizing results to a broader working population, since other western countries may also have variation in the social security systems. Thus, results from the studies on the physiological stress response and stress-related disease may be generalized to a broader population than the study on sickness absence, since these results are not influenced by the same welfare state differences as results on long-term sickness absence.

When generalizing results this thesis, it should be considered that participants were in paid work, and results should therefore not be generalized to people with unstable work situations or people outside the labor market, except for study 1, in which two thirds had retired from the labor market. Foreigners is not that common in the included cohorts, which should be taken into account when generalizing results; as other ethnic groups may have a different culture regarding care for ill or disabled family members, and may have other risk profiles for the investigated health outcomes.
Conclusions

The overall objective of this thesis was to investigate the effect of informal caregiving on the physiological stress, stress-related disease, and long-term sickness absence; and to investigate how work life, and gender modify these effects.

Previous research have shown altered cortisol response in informal caregivers compared with non-caregivers. Study 1 in this thesis added to this knowledge by investigating the associations between various aspects of informal caregiving and cortisol levels, and the modifying effect of work life in data from the UK. Among men, results supported an effect of informal caregiving on the physiological stress response, in a dose response manner, with many weekly hours of caregiving being associated with a blunted cortisol awakening response. Furthermore, the blunted cortisol awakening response among men was most pronounced in caregivers in paid work compared to those outside the labor market. The relationship between informal caregiving and the physiological stress response was less consistent in women. The results for women both providing caregiving and were in paid work, showed an indication of a healthy caregiver effect; with steeper cortisol slopes, which has been associated with better health status.

When interpreting the results, it should be taken into consideration that cortisol samples were gathered on a single day, and may therefore not capture long-term variations in the physiological stress response. Furthermore, it should be acknowledged that the participants came from a homogenous population of civil servants from the UK, of whom two thirds had retired from the labor market, which may limit the generalizability of the results to more heterogeneous populations.

Previous research have shown that informal caregiving is associated with altered physiological stress response and an unhealthy lifestyle, which are risk factors for type 2 diabetes. In study 2, there was no support for a direct effect of informal caregiving on the risk of type 2 diabetes, in analyses using data from France, Sweden, and the UK. However, low social support at work was associated with a higher risk of type 2 diabetes, especially among informal caregivers. This was the first study to have
investigated these associations, and more research is needed before drawing strong conclusions on the lack of association between informal caregiving and type 2 diabetes. Furthermore, the association between social support at work and risk of type 2 diabetes is a novel finding, which requires further research.

From previous research, the association between informal caregiving and CVD is rather well established. Study 3 in the present thesis contributed to this evidence, by showing an association between many weekly hours of caregiving and a higher risk of CVD, using data from Sweden and the UK. This association was especially pronounced among long-term caregivers, which is a novel finding. These findings may be explained with many weekly hours of caregiving and long-term caregiving being most pronounced among caregivers for family members with severe disabilities living in the same household. There was no effect modification by weekly work hours. In a post hoc analysis, there was only a statistically non-significant tendency that informal caregivers had a higher risk of CVD compared with non-caregivers. Thus, in line with some of the previous studies on CVD, it seems that only those providing many weekly hours of caregiving are at higher risk of CVD.

According to a literature search, no previous studies have investigated the association between informal caregiving and risk of long-term sickness absence. Study 4 in this thesis adds knowledge to the informal caregiving literature by showing that informal caregiving was associated with a higher risk of long-term sickness absence in women, but not in men, using data from Finland, France, and the UK. This is a novel finding, which should be taken into consideration by employers and policy makers. However, misclassification of long-term sickness absence in informal caregivers may have biased the association away from the null, since absence could be related to providing care and not illness in the caregiver. High job strain was also associated with a higher risk of long-term sickness absence in women, but job strain did not modify the effect of informal caregiving on risk of long-term sickness absence. These findings were based on data from three countries with different elder care systems, which strengthen the generalizability of the
findings. On the other hand, when generalizing these findings to the broader working population in western countries, welfare state differences regarding sick leave payment should be acknowledged.

In all studies, the informal caregiving category may have included participants who assisted family members in other households with activities of daily living such as cleaning and cooking. Thus, this type of caregiving may not necessarily encompass the emotional burden, which may be seen among spousal caregivers who assist their husband or wife with personal care. Therefore, when generalizing results, it should be acknowledged that a very broad group of informal caregivers was included in this thesis. Despite cultural and welfare state differences in the four included cohort studies from Finland, France, Sweden, and the UK, similar tendencies across these countries were found. It should be acknowledged that results from studies on type 2 diabetes, cardiovascular disease, and long-term sickness absence should not be generalized to people with unstable work situations or people outside the labor market.
Implications

Public health implications

Although findings from the present thesis are inconclusive regarding the health consequences of informal caregiving, there is much scientific evidence showing that informal caregivers may be a population group that requires extra attention from policy makers and employers. Thus, there is likely going to be an increasing number of informal caregivers in the years to come, due to a growing population of elderly (4). An increasing amount of evidence, suggest that special attention should be given to those caregivers who provide caregiving for many hours weekly over a long period of time (15,16,24,27,30,80–82). In line with this, one study have shown that people who provide high intensity caregiving, care inside the household, and spousal caregiving, are more likely to quit the labor market compared with non-caregivers (98), and another study have shown that 40% of informal caregivers reported that they had quit their job or retired early due to caregiving demands (97). Thus, in order to keep informal caregivers in the labor market, policy makers and employers should establish more caregiver-friendly work arrangements, such as the possibility to take time off, individual agreements with supervisors, formal care leave arrangement, and reduction in work hours (155). Previous findings have suggested that especially low educated informal caregivers are unaware of such arrangements in their own work situation (155). In the present thesis, it was shown that social support from supervisors and coworkers might be one focus area in workplaces, which may help alleviate the negative health consequences from informal caregiving.

Research implications

This was the first research to investigate various aspects of informal caregiving such as care recipient, caregiving hours, and duration of caregiving and the association with cortisol levels. Inconclusive findings from the study suggest that more research is needed on these associations. Using repeated measures on informal caregiving and cortisol measures would strengthen conclusions regarding the causal link between
informal caregiving and the physiological stress response (66). Furthermore, it has been suggested that cortisol measured in hair may be a better marker of chronic stress than cortisol measured in saliva, since it may be a valid measure of long-term cortisol production (156). Another marker of the physiological stress response is allostatic load, which is an index representing neuroendocrine, immune, metabolic, and cardiovascular functions related to stress and disease (79). Still, there are only few studies on the association between informal caregiving and allostatic load (81,137,138,157). However, more studies on informal caregiving and allostatic load are warranted, with indexes applying the same biomarkers, in order to compare results across studies.

Findings on the association between informal caregiving, stress-related disease and long-term sickness absence were also inconclusive. Applying mediation analysis may be a statistical approach, which may help getting closer to the causal link between informal caregiving, stress-related disease and long-term sickness absence, through potential mediating factors such as the physiological stress response and lifestyle factors. Large multi-cohort studies offer the opportunity to investigate effect modification by work life, gender and other factors, on the associations between informal caregiving and health consequences. However, multi-cohort studies also create challenges if data from the included cohort studies are not comparable. Furthermore, welfare state differences should always be considered when comparing results from different countries.

In the future, cohort studies gathering information on informal caregiving should get information on the relationship with the care recipient, weekly hours of caregiving, the duration of caregiving, the severity of the recipients disease, and whether caregiving is inside or outside the household, as these are essential elements of the burden of informal caregiving. Furthermore, having this information from multiple questionnaire phases makes it possible to investigate changes over time.
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Appendix
Study 1

Informal caregiving and diurnal patterns of salivary cortisol: results from the Whitehall II cohort study

Submitted for Psychoneuroendocrinology 2017

Informal caregiving and diurnal patterns of salivary cortisol: results from the Whitehall II cohort study

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Abstract

The objective was to investigate the relation between various aspects of informal caregiving and diurnal patterns of salivary cortisol, with special attention to the moderating effect of sex and work status. The study population was composed of 3,727 men and women from the British Whitehall II study. Salivary cortisol was measured six times during a weekday. Aspects of caregiving included the relationship of caregiver to recipient, weekly hours of caregiving, and length of caregiving. Diurnal cortisol profiles were assessed using the cortisol awakening response (CAR) and diurnal cortisol slopes. Results showed that men, but not women, providing informal care had a blunted CAR compared with non-caregivers (P_{interaction}=0.03). Furthermore, we found a dose-response relationship showing that more weekly hours of informal care was associated with a more blunted CAR for men (P_{trend}=0.03). Also, the blunted CAR for men was especially pronounced in those in employment. In women, the steepest cortisol slope was seen among those in paid work who were providing care (P_{interaction}=0.01). To conclude, providing informal care may affect men and women’s cortisol profiles differently. Men, who provided informal care, had a blunted CAR, which has previously been associated with chronic stress and burnout. This association was especially pronounced for men in paid work and among those providing many weekly hours of care.
Introduction

Informal caregiving, defined as unpaid caregiving for a disabled or elderly relative (USLegal, 2017), is becoming increasingly common due to growing numbers of elderly people (WHO, 2012). Recent studies suggest that informal caregiving can be stressful due to the continued physical and emotional burden of caregiving responsibilities for a closely related loved one (Hunt et al., 2015; Wolff et al., 2016). A potential health consequence of chronic stress is dysregulation of the cardiovascular system caused by a cascade of neural and physiological responses including hyper- or hypo-activation of the hypothalamic-pituitary-adrenal (HPA) axis (Dragoş and Tănăsescu, 2010). HPA activity stimulates secretion of the stress hormone cortisol by the adrenal glands (Adam et al., 2006).

Cortisol levels have a natural circadian rhythm, with a high level upon awakening and a rapid increase during the first 30-45 minutes from awakening, called the cortisol awakening response (CAR) (Adam and Kumari, 2009; Stalder et al., 2015). Following the awakening response, cortisol levels decline during the day with a nadir around midnight (Adam and Kumari, 2009). The CAR and cortisol slope components of the diurnal cortisol profile, which are based on repeated cortisol measures during waking hours, have been suggested to characterize response to acute and chronic stressors (Adam and Kumari, 2009). An increased CAR is suspected to be a marker of acute psychological stress, while a blunted CAR may be a marker of chronic stress, depression, and burnout (Leggett et al., 2015; Miller et al., 2007). Accordingly, steep cortisol slopes suggest a more rapid decline in cortisol levels throughout the day, whereas cortisol slopes with values closer to zero reflect flatter diurnal rhythms, indicating that the bedtime cortisol level is heightened or that the person may be in poor health status with difficulties unwinding before nighttime (Adam and Kumari, 2009).

According to a recent systematic review, providing informal caregiving for a family member with dementia is associated with higher cortisol levels throughout the day, although the findings are not completely consistent (Allen et al., 2017). Some of the studies found a higher cortisol level at awakening for
caregivers and blunted CAR (de Vugt et al., 2006; Fonareva et al., 2011) while other studies reported flattened diurnal cortisol slopes (Allen et al., 2017). A limitation in those studies is that they did not investigate specific aspects of informal caregiving, such as the relationship with the care recipient, intensity of caregiving, and duration of caregiving, which may all affect the physiological stress response imposed by informal caregiving (Allen et al., 2017). For example, it has been suggested that caregiving for a spouse may be more detrimental for health compared to caregiving for a parent (Lee et al., 2003) due to the higher intensity of caregiving (Hunt et al., 2015). In line with this, high intensity caregiving may also be associated with providing care for a family member in the household, which is a considerable emotional burden (Hunt et al., 2015). In addition, providing long-term caregiving may be more detrimental for the carer’s health as opposed to short-term caregiving, because of the ongoing burden (Benjamin et al., 2012; Capistrant, 2013). This raises the hypothesis that caregiving for a spouse, providing caregiving for many weekly hours, and long-term caregiving may be associated with particularly blunted CAR and flattened cortisol slopes, as markers of chronic stress (Adam and Kumari, 2009; Leggett et al., 2015; Miller et al., 2007).

Simultaneously providing informal care and being active in the labor market may constitute a double burden (Goode, 1960; Longacre et al., 2016). Previous analyses of data from the British Whitehall II study have shown that the CAR was greater on workdays compared to weekends, suggesting that work-life is associated with acute stressors (Kunz-Ebrecht et al., 2004). However, the study population used in that analysis was a selective population of healthy participants (Kunz-Ebrecht et al., 2004). Thus for informal caregivers, we hypothesize that the long-term burden of caregiving responsibilities and paid work would make individuals more prone to be chronically stressed (Goode, 1960; Longacre et al., 2016), resulting in blunted CAR and flattened cortisol slopes in such populations (Adam and Kumari, 2009; Leggett et al., 2015; Miller et al., 2007).

The objective of the present study was to investigate the association between informal caregiving and diurnal patterns of salivary cortisol, with special focus on the nature of the relationship with
the care recipient, weekly hours of providing caregiving, and length of caregiving. We examined whether this association was more pronounced for caregivers in paid work compared to those who have retired or otherwise not in the labor market. In addition, we investigated whether gender modified the association between informal caregiving and diurnal patterns of cortisol secretion, since gender and menopause in particular have an effect on HPA responsiveness to psychosocial stress (Kajantie and Phillips, 2006); and women tend to have a flatter cortisol slope in the evening than men (Sjögren et al., 2006), suggesting that women may have more difficulties in unwinding after a workday.

**Methods**

Study participants came from the Whitehall II study, which was established in 1985 and included 10,308 British civil servants from 20 London-based departments (Marmot and Brunner, 2005). Phase 9 (year 2007-2009) was chosen as the baseline for this analysis due to the availability of detailed data on caregiving and cortisol. A total of 6,761 people (response rate 84.5%) participated in this wave. From the 5,963 people, who agreed to participate in the cortisol collection, 4,128 participants had valid cortisol measures (Appendix A: Flowchart). Excluding those with missing on caregiving information (n=263) and participants with missing information on covariates (n=138), the study population encompassed 3,727 participants.

**Informal caregiving**

People were asked if they provided regular care for any of the following in a self-administered questionnaire: a) Children, b) Grandchildren, c) Disabled or ill partner/spouse, d) Disabled or ill parent, e) Other disabled or ill relative, f) Disabled or ill friend. Participants with affirmative response to question c, d, e or f constituted the group of informal caregivers, since caregiving for children and grandchildren is not included in the definition of informal caregiving, unless they are chronically sick or disabled (USLegal, 2017).
In addition, participants were asked how many hours per week they provided care for each of these persons. In line with previous research, we classified participants into three groups depending on the hours of weekly caregiving: 1-8 hours, 9-20 hours, 20-100 hours, and >100 hours weekly (Lee et al., 2003). Long-term caregivers were defined as those, who answered that they provided care for an aged or disabled relative in the phase preceding our baseline (2-3 years earlier) and with affirmative response to questions c, d or e, at baseline. Category f (care for a disabled or ill friend) was not included in this category, since the question in the previous phase concerns caregiving for relatives only. Short-term caregivers were categorized as those, who provided informal caregiving at baseline, but not in the preceding phase.

**Cortisol**

Participants were requested to provide six saliva samples in salivettes over the course of a normal weekday at waking, 30 minutes from awakening, 2.5 hours from awakening, 8 hours from awakening, 12 hours from awakening, and at bedtime. Participants were instructed not to brush teeth or eat or drink anything for 15 min before sample collection. An instruction booklet was used to record information on the day of sampling including date of collection, wake time, and time each sample was taken. Salivettes were centrifuged at 3,000 rounds per minute for 5 minutes, resulting in a clear supernatant of low viscosity. Salivary cortisol levels were measured using a commercial immunoassay with chemiluminescence detection (CLIA; IBLHamburg, Hamburg, Germany). The lower concentration limit of this assay is 0.44 nmol/L; intra- and inter assay coefficients of variance were below 8%. Any sample over 50 nmol/L was reanalyzed (Badrick et al., 2007).
**Covariates**

Confounders were selected based on current knowledge of factors which may influence caregiving and diurnal cortisol levels (Adam and Kumari, 2009), using Directed Acyclic Graphs (Appendix B) (Greenland et al., 1999). Analyses were adjusted for age, ethnicity, married/cohabiting, annual household income (<20,000£, 20,000-50,000£, >=50,000£) (Goren et al., 2014), employment status (in main effect analyses on caregiving), and wakeup time (Adam and Kumari, 2009). Based on results from a study by Burton et al. (Burton et al., 2004) and in line with our previous studies on informal caregiving (Mortensen et al., 2016a; Mortensen et al., 2016b), we argue that lifestyle factors such as current smoking and high alcohol consumption, leisure time physical inactivity are likely to be a consequence of caregiver stress. Therefore, we have not included these factors as confounders in our analyses, as this would attenuate the effect of caregiving stress on cortisol levels mediated through these pathways. This is also the case with psychological disease such as depression, which is a likely consequence of caregiver stress (Capistrant, 2014; Pinquart and Sörensen, 2003).

**Statistical analyses**

The CAR was calculated by subtracting the cortisol measure at awakening from the cortisol measure at approximately 30 minutes from awakening. Conventionally, analyses were restricted to wakeup samples that were collected within 10 minutes of waking because of a reduced CAR in those with longer delays (Kudielka et al., 2003). Furthermore, the second measure was restricted to samples collected no later than 45 min from awakening (Kudielka et al., 2003). The CAR was analyzed in a standard regression model and cortisol slopes were analyzed in a multilevel linear regression model with random slopes and intercept and hours as the time unit. In the multilevel model, measurement time was used as a level one identifier and person as a level two identifier. Interaction with time was included in the model for the caregiving exposure and included confounders. The five time points from the 30 min peak until nadir was used for calculating...
cortisol slopes (Adam and Kumari, 2009). Because of right-skewed distributions of diurnal cortisol levels, data on cortisol slopes were log transformed. For all analyses, participants with cortisol values outside ±3 SD of the mean were considered outliers and removed from analyses (Adam and Kumari, 2009; Stalder et al., 2015). Also, participants, who woke up before 4am or after 11am, were removed from analyses as diurnal cortisol patterns may not be accurately determined with such measurements (Karlamangla et al., 2013). Both CAR (nmol/L) and cortisol slope (log nmol/L/hour) were analyzed as the outcome in the following models, separately for men and women: We tested the difference in β-coefficients (95% CI) in the following analyses, with non-caregivers as the reference: informal caregiving, caregiving according to care recipients (either spouse or parent, relative, and friend), weekly caregiving hours categorized as 1-8 hours, 9-20 hours, 20-100 hours, and >100 hours, and finally short- and long-term caregiving. Test for trend on weekly hours of caregiving was analyzed using the categorical variable generated. We also created four mutual exclusive categories to investigate the double burden of caregiving and work: 1. Non-caregivers, non-workers, 2. Non-caregivers, workers, 3. Caregivers, non-workers, 4. Caregivers, workers. We assessed additive interaction by including a product term in the model (von Elm et al., 2007). For difference in the CAR, a negative β represents a blunted response, while for the difference in cortisol slope, a negative β represents a steeper slope.

Different approaches have been suggested in analyzing the CAR (Stalder et al., 2015). Based on this, we made sensitivity analyses for CAR adjusted for the cortisol level at wakeup, and secondly we analyzed the ratio between the CAR and time difference between the wake-up measure and peak response (Adam and Kumari, 2009; Stalder et al., 2015). These other approaches to analyze the association between informal caregiving and the CAR yielded similar results as the main analyses (Appendix C). According to recommendations by International Society of Psychoneuroendocrinology, we present cortisol means and standard deviations for the cortisol response at wakeup (Stalder et al., 2015), showing that there was no difference in wakeup response for caregivers and non-caregivers (Appendix C).
Results

In the study population, 286 (10%) men and 128 (13%) women provided informal caregiving. More men than women were married or cohabiting, and men had higher average annual household income. Among women, caregivers were more likely to be married than non-caregivers, whereas male caregivers were not more likely to be married than non-caregivers (Table 1).

We observed a gender difference in diurnal cortisol patterns, as male caregivers had a more blunted CAR than women ($P_{interaction}=0.03$). As seen in figure 1, we found that providing care was associated with a blunted CAR ($\beta$: -1.39 % CI: -2.74; -0.04 (nmol/L)) in men. For women, we found that caregiving was associated with a steeper CAR ($\beta$: 1.33 % CI: -0.86; 3.51 (nmol/L)), but the results were not statistically significantly different from zero. For cortisol slopes, we found no difference between caregivers and non-caregivers, neither for men ($\beta$: 0.001; 95% CI: -0.006; 0.008 (log nmol/L/hour)), nor women ($\beta$: 0.001; 95% CI: -0.011; 0.012 (log nmol/L/hour)).

As seen in table 2, women were more likely to provide many hours of weekly care and more often provided long-term care than men. For men, we found a dose-response relationship between weekly hours of caregiving and the CAR, showing that more hours of care was associated with a more blunted CAR ($P_{trend}=0.03$). Furthermore, among men, we found that short-term caregiving was associated with a markedly blunted CAR ($\beta$: -3.27; 95% CI: -5.35; -1.19 (nmol/L)) and a non-significant tendency for a flattened slope ($\beta$: 0.009; 95% CI: -0.002; 0.020 (log nmol/L/hour)) compared with non-caregiving. The same was not found for long-term caregiving. For women, providing care for a spouse was associated with a markedly elevated CAR compared with non-caregivers ($\beta$: 4.53; 95% CI: 0.54; 8.51 (nmol/L)).

As seen in table 3, providing care was only associated with a blunted response among men in paid work ($P_{interaction}=0.07$). Male caregivers in paid work had a blunted CAR compared with men, who did not work and did not provide care ($\beta$: -3.23; 95% CI: -5.73; -0.72 (nmol/L)); while caregiving was not associated with a blunted CAR among men outside paid work ($\beta$: -0.71; 95% CI: -2.33; 0.91 (nmol/L)). For women, there was an interaction between caregiving and paid work, with caregivers in paid work having a
steeper cortisol slope than would be expected from the effects of caregiving and work alone ($P_{interaction}=0.01$). Among non-caregiving women, we found that those in paid work had a flattened slope relative to those, who were not in paid work ($\beta=0.014; 95\% CI: 0.004;0.025$ (log nmol/L/hour)). Unadjusted and multiple adjusted analyses yielded similar results (Appendix C).

**Discussion**

The main finding of this study was that male caregivers had a blunted CAR compared to non-caregivers. This association was not found for women. In line with our hypotheses, being employed and having many hours of weekly caregiving was associated with a more blunted CAR, but only among male caregivers. For women, we found an interaction, suggesting that the double burden of caregiving and paid work was associated with a steeper cortisol slope than expected from the individual effects of caregiving and paid work. We also found that male short-term caregivers had a blunted CAR compared to non-caregivers, whereas the blunted CAR was attenuated for long-term caregivers.

A recent meta-analysis found that being caregiver for a family member with dementia was associated with higher cortisol levels throughout the day (Allen et al., 2017), and studies included in the meta-analysis, found a blunted CAR in caregivers compared with non-caregivers (de Vugt et al., 2006; Fonareva et al., 2011). This association was driven by higher cortisol levels at wakeup for caregivers compared with non-caregivers. In line with this, individuals with low wakeup levels of cortisol tend to have a steep CAR, whereas individuals with high wakeup levels have a blunted CAR (Stalder et al., 2015). We found in our study that male caregivers had a blunted CAR compared with non-caregivers in a dose-response relation, showing that more weekly hours of caregiving were associated with a more blunted CAR. In contrast to studies included in the meta-analysis (de Vugt et al., 2006; Fonareva et al., 2011), we found no difference in cortisol levels at wakeup between caregivers and non-caregivers. For women, we found that caregivers tended to have a steeper CAR compared with non-caregivers. Although this finding was not
statistically significant, it is consistent with the hypothesis that caregiving responsibilities may influence the physiological stress response differently in men and women (Stafford et al., 2013).

We stratified analyses by work status and found that men in paid work had a blunted, 3.23 nmol/L lower CAR compared to that in non-caregivers not in paid work. The size of this effect is meaningful as it has been shown that experiencing a major life event such as divorce (which is thought to be a chronic stressor) is associated with a comparable 2.79 nmol/L lower CAR compared with the CAR among currently married (Stafford et al., 2013). For women, we found an interaction showing that caregivers in paid work had a steeper cortisol slope than would be expected from the effects of caregiving and work alone. A higher peak did not explain this result, as we did not find a higher CAR for working women also providing care. Steeper slopes have previously been associated with better health status, as it may indicate that these individuals find it easier to unwind before bedtime (Adam and Kumari, 2009). Thus, our result may point to a ‘healthy caregiver effect’, where more privileged women, who provide care, stay in the labor market due to good working conditions in contrast to less privileged women, who quit the labor market because of caregiving responsibilities. This explanation is partly supported by previous findings, which shows that less privileged individuals have flatter cortisol slopes (Karlamangla et al., 2013).

In contrast to our hypothesis, we found that short-term caregiving - and not long-term caregiving - was associated with a blunted CAR in men. A possible explanation may be that long-term caregivers have learned to cope with the role as caregiver, whereas short-term caregivers may struggle with adapting to the new role and the associated life changes. In line with this, a study among caregivers in paid work have shown that in severe care situations, with high care demands and burden, caregivers adapt their work situation (Oldenkamp et al., 2017); suggesting that the double burden from caregiving and paid work may be diminished in long-term caregivers.

Women providing spousal caregiving had a markedly elevated CAR compared with non-caregivers, whereas care for parents, friends, or other relatives was associated with a very small non-
significant elevated CAR. We hypothesized a blunted CAR as a result of chronic stress or burnout, and we hypothesized that this would be more pronounced for spousal caregivers (Lee et al., 2003), because of high intensity caregiving from living in the same household (Hunt et al., 2015). However, an elevated CAR as found presently in caregiving for spouses may be a consequence of acute stress reactivity in the morning, which may not necessarily be unhealthy for these women, as results on cortisol slopes suggest that they do not have more difficulties unwinding in the evening.

Methodological considerations

Menopause has been suggested to alter diurnal cortisol levels (Kajantie and Phillips, 2006). Information on menopause was not available at the baseline of our study. However, the majority of women in the UK have completed menopause by the age of 55, and the mean age of participants in the present study was 66 years. The study population encompassed British adults with a working history in the civil service. Since three in four of the participants were retired, our result may not generalize to the working population. A limitation of this study is that cortisol was measured on a single weekday, and may therefore not necessarily be representative of their diurnal cortisol levels in general. Thus, having cortisol measures for several weekdays would have strengthened the validity of our results (Karlamangla et al., 2013). Another limitation is that we had no information on whether participants provided care for disabled or chronically ill children. Thus, there could potentially be informal caregivers in the non-caregiving group, which were not identified by the questionnaire. This misclassification could attenuate the true effect of informal caregiving on diurnal cortisol levels. Further, we do not know the level of illness or disability in the care recipient.

A high number of eligible participants did not return cortisol samples, probably due to the cumbersome task of collecting six saliva samples at particular time intervals. This non-compliance was associated with older age and higher household income, but not with gender. It could be suspected that non-compliance would be most common among those who are mostly stressed by the burden of informal
caregiving. If, this is the case, then results may have presented a more healthy stress response in informal caregivers, than would be seen in the total population of eligible participants. However, non-compliance was associated with higher household income, and thus spousal caregivers, which was hypothesized to be those mostly stressed by the burden of informal caregiving, are likely to be underrepresented among non-compliers.

Conclusion

This is apparently the first study on various aspects of informal caregiving such as the relation with the care recipient, weekly intensity of caregiving, and caregiving duration in relation to diurnal cortisol levels. For male caregivers we found a blunted CAR, which in other studies has been associated with chronic stress and burnout. This observed association was especially pronounced for those working, those providing many weekly hours of care, and short-term caregivers. For female caregivers we found the opposite tendency, showing an elevated CAR compared with non-caregiving women. We also found a potential healthy caregiver effect, showing that the steepest cortisol slope among women, was seen in those who provided care and where still active in the labor market. Although inconclusive, results from this study support a causal link between informal caregiving and cortisol levels in men, while findings in women provide a more inconsistent picture.
Acknowledgements

This work was supported by the Danish Work Environment Foundation (grant no. 12-2013-03). Mika Kivimäki is supported by the UK Medical Research Council (K013351), NordForsk, the Academy of Finland (311492), and a Helsinki Institute of Life Science Fellowship. JH is supported by the UK Economic and Social Research Council (ES/L002892/1). The Whitehall II Study is supported by grants from The UK Medical Research Council (MR/K013351/1; G0902037), British Heart Foundation (RG/13/2/30098, PG/11/63/29011), and the US National Institutes of Health (R01HL36310, R01AG013196) have supported collection of data in the Whitehall II Study. We thank all participants, researchers and support staff who has contributed to the cohort studies. The first author would further like to thank Associate Professor Theis Lange and Post doc Adam Hulman for valuable feedback on the analytical strategy.
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https://doi.org/10.1097/01.PSY.0000058374.50240.BF


Pinquart, M., Sörensen, S., 2003. Differences between caregivers and noncaregivers in psychological health and


Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Study population</th>
<th>Men (n=2,772)</th>
<th>Women (n=955)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Caregivers (n=286)</td>
<td>Non-caregivers (n=2,486)</td>
</tr>
<tr>
<td>Age, mean (±SD)</td>
<td>66 (±6)</td>
<td>66 (±6)</td>
</tr>
<tr>
<td>Married/cohabitating</td>
<td>84%</td>
<td>84%</td>
</tr>
<tr>
<td>In paid work</td>
<td>30%</td>
<td>32%</td>
</tr>
<tr>
<td>Non-Caucasian</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>Low annual household income (&lt;20,000£)</td>
<td>16%</td>
<td>13%</td>
</tr>
</tbody>
</table>
The CAR estimates is presented as difference in $\beta$ (95%CI) (nmol/L) and slope estimates is presented as difference in $\beta$ (95%CI) (log nmol/L/hour). Multiple adjusted for age, ethnicity, marital status, employment status, income category, wake-up time. Interaction between informal caregiving and gender for the CAR ($p=0.03$). For difference in the CAR, a negative $\beta$ represents a blunted response, and for the difference in cortisol slope, a negative $\beta$ represents a steeper slope.
Table 2. Various aspects of informal caregiving and the association with differences in cortisol awakening response (CAR) and cortisol slopes

<table>
<thead>
<tr>
<th></th>
<th>Men (n=2,772)</th>
<th>Women (n=955)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number (%)</td>
<td>Difference in CAR (nmol/L)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>β (95%CI)</td>
</tr>
<tr>
<td>Care recipient:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spouse</td>
<td>89 (3%)</td>
<td>-1.96 (-4.32;0.39)</td>
</tr>
<tr>
<td>Parent, relative or friend</td>
<td>197 (7%)</td>
<td>-1.32 (-2.94;0.30)</td>
</tr>
<tr>
<td>Non-caregivers</td>
<td>2,486 (90%)</td>
<td>0</td>
</tr>
<tr>
<td>Weekly caregiving hours:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;100 hours</td>
<td>33 (1%)</td>
<td>-2.38 (-6.15;1.40)</td>
</tr>
<tr>
<td>20-100 hours</td>
<td>40 (1%)</td>
<td>-3.17 (-6.60;0.25)</td>
</tr>
<tr>
<td>9-20 hours</td>
<td>60 (2%)</td>
<td>-1.46 (-4.27;1.35)</td>
</tr>
<tr>
<td>1-8 hours</td>
<td>128 (5%)</td>
<td>-0.37 (-2.36;1.63)</td>
</tr>
<tr>
<td>Non-caregivers</td>
<td>2,485 (91%)</td>
<td>0</td>
</tr>
<tr>
<td>Test for trend</td>
<td></td>
<td>p=0.03</td>
</tr>
<tr>
<td>Duration of caregiving:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-term caregiving</td>
<td>142 (5%)</td>
<td>-0.87 (-2.74;1.00)</td>
</tr>
<tr>
<td>Short-term caregiving</td>
<td>115 (4%)</td>
<td>-3.26 (-5.33;-1.18)</td>
</tr>
<tr>
<td>Non-caregivers</td>
<td>2,421 (90%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Multiple adjusted Age, ethnicity, married/cohabiting, gainful employment, income category, and wakeup time. For difference in the CAR, a negative β represents a blunted response, and for the difference in cortisol slope, a negative β represents a steeper slope.
Table 3. Joint effects of informal caregiving and paid work on differences in cortisol awakening response (CAR) and cortisol slopes

<table>
<thead>
<tr>
<th></th>
<th>Men (n=2,772)</th>
<th></th>
<th>Women (n=955)</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Number (%)</td>
<td>Difference in CAR (nmol/L) β (95%CI)</td>
<td>Number (%)</td>
<td>Difference in CAR (nmol/L) β (95%CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(log nmol/L/hour) β (95%CI)</td>
<td></td>
<td>(log nmol/L/hour) β (95%CI)</td>
</tr>
<tr>
<td>Caregiving, in paid work</td>
<td>86 (3%)</td>
<td>-3.23 (-5.73; -0.72)</td>
<td>30 (3%)</td>
<td>-0.27 (-4.79; 4.26)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.004 (-0.003; 0.009)</td>
<td></td>
<td>-0.014 (-0.036; 0.009)</td>
</tr>
<tr>
<td>Caregiving, not in paid work</td>
<td>200 (7%)</td>
<td>-0.71 (-2.33; 0.91)</td>
<td>98 (10%)</td>
<td>1.41 (-1.16; 3.98)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.000 (-0.008; 0.009)</td>
<td></td>
<td>0.009 (-0.003; 0.022)</td>
</tr>
<tr>
<td>Non-caregivers, in paid work</td>
<td>805 (29%)</td>
<td>0.23 (-0.86; 1.31)</td>
<td>206 (22%)</td>
<td>-1.79 (-3.97; 0.40)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.002 (-0.008; 0.018)</td>
<td></td>
<td>0.014 (0.004; 0.025)</td>
</tr>
<tr>
<td>Non-caregivers, not in paid work</td>
<td>1,681 (61%)</td>
<td>0</td>
<td>621 (65%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Multiple adjusted Age, ethnicity, married/cohabiting, gainful employment, income category, and wakeup time. CAR interaction: men p=0.07, women p=0.97. Slope interaction: men p=0.84, women p=0.01. For difference in the CAR, a negative β represents a blunted response. For the difference in cortisol slope, a negative β represents a steeper slope.
Appendix A. Flowchart, Whitehall II

Participants in phase 9 (n=6,761)

Agreed to participate in cortisol collection (n=5,963)

Valid cortisol data (n=4,128)

Included in analyses (n=3,727)

- No returned samples (n=857)
- Missing CAR samples (n=70)
- Wakeup <4am or >11am (n=76)
  - >3SD cortisol (n=179)
  - >10 min wakeup measure (n=612)
  - >45 min awakening response (n=40)
- Corticosteroids (n=1)

- Missing on caregiving (n=263)
- Missing on confounders (n=138)
Appendix B. Directed acyclic graph of the causal effect of informal caregiving on cortisol levels
### Appendix C. Sub- and sensitivity analyses

#### C1. Joint effects of informal caregiving and paid work on cortisol awakening response and diurnal cortisol slope

<table>
<thead>
<tr>
<th></th>
<th>Men (n=2,772)</th>
<th>Women (n=955)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Difference in CAR</td>
<td>Difference in CAR</td>
</tr>
<tr>
<td></td>
<td>Unadjusted, β (95%CI)</td>
<td>Multiple adjusted, β (95%CI)</td>
</tr>
<tr>
<td>Caregivers, workers</td>
<td>-3.227 (-5.657;-0.797)</td>
<td>-3.225 (-5.729;-0.720)</td>
</tr>
<tr>
<td>Caregivers, non-workers</td>
<td>-0.814 (-2.433;0.805)</td>
<td>-0.709 (-2.328;0.911)</td>
</tr>
<tr>
<td>Non-caregivers, workers</td>
<td>0.339 (-0.593;1.271)</td>
<td>0.226 (-0.858;1.309)</td>
</tr>
<tr>
<td>Non-caregivers, non-workers</td>
<td>0 (ref.)</td>
<td>0 (ref.)</td>
</tr>
</tbody>
</table>

|                  | Difference in cortisol slope | Difference in cortisol slope | Difference in cortisol slope | Difference in cortisol slope |
|                  | Unadjusted, β (95%CI) | Multiple adjusted, β (95%CI) | Unadjusted, β (95%CI) | Multiple adjusted, β (95%CI) |
| Caregivers, workers | -0.000 (-0.013;0.013) | 0.005 (-0.008;0.018) | -0.015 (-0.038;0.007) | -0.014 (-0.036;0.009) |
| Caregivers, non-workers | -0.000 (-0.009;0.009) | 0.000 (-0.008;0.009) | 0.005 (-0.008;0.017) | 0.009 (-0.003;0.022) |
| Non-caregivers, workers | -0.001 (-0.006;0.004) | 0.003 (-0.003;0.009) | 0.004 (-0.005;0.014) | 0.014 (0.004;0.025) |
| Non-caregivers, non-workers | 0 (ref.) | 0 (ref.) | 0 (ref.) | 0 (ref.) |

CAR: Cortisol Awakening Response. Slopes were analyzed using log(cortisol) with hours as the underlying time axis. Multiple adjusted: Age, ethnicity, married/cohabiting, gainful employment, income category, wakeup time. CAR: Interaction, men p=0.07, women p=0.97. Slope: Interaction, men p=0.84, women p=0.01. For difference in the CAR a negative β represents a blunted response, and for the difference in cortisol slope a negative β represents a steeper slope.
C2. Associations between various aspects of informal caregiving and cortisol awakening response

<table>
<thead>
<tr>
<th></th>
<th><strong>Men (n=2,772)</strong></th>
<th><strong>Women (n=955)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Difference in CAR</strong></td>
<td><strong>Difference in CAR</strong></td>
</tr>
<tr>
<td></td>
<td>Unadjusted, β (95%CI)</td>
<td>Multiple adjusted, β (95%CI)</td>
</tr>
<tr>
<td>Informal caregiving</td>
<td>-1.633 (-2.991;-0.275)</td>
<td>-1.392 (-2.740;-0.044)</td>
</tr>
<tr>
<td>Care recipient:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spouse</td>
<td>-2.208 (-4.539;0.123)</td>
<td>-1.965 (-4.316;0.386)</td>
</tr>
<tr>
<td>Parent, relative or friend</td>
<td>-1.368 (-2.982;0.246)</td>
<td>-1.320 (-2.938;0.298)</td>
</tr>
<tr>
<td>Weekly caregiving hours:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-8 hours</td>
<td>-0.416 (-2.411;1.579)</td>
<td>-0.367 (-2.361;1.628)</td>
</tr>
<tr>
<td>9-20 hours</td>
<td>-1.596 (-4.406;1.214)</td>
<td>-1.462 (-4.270;1.346)</td>
</tr>
<tr>
<td>20-100 hours</td>
<td>-3.184 (-6.611;0.244)</td>
<td>-3.173 (-6.601;0.254)</td>
</tr>
<tr>
<td>&gt;100 hours</td>
<td>-2.565 (-6.333;1.203)</td>
<td>-2.375 (-6.148;1.398)</td>
</tr>
<tr>
<td>Test for trend</td>
<td>p=0.026</td>
<td>p=0.023</td>
</tr>
<tr>
<td>Duration of caregiving:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-term caregiving</td>
<td>-1.015 (-2.880;0.850)</td>
<td>-0.921 (-2.786;0.944)</td>
</tr>
<tr>
<td>Short-term caregiving</td>
<td>-3.295 (-5.343;-1.247)</td>
<td>-3.090 (-5.142;-1.037)</td>
</tr>
</tbody>
</table>

CAR=Cortisol Awakening Response (nmol/L). Non-caregivers is the reference group in all analyses. Multiple adjusted: Age, ethnicity, married/cohabiting, gainful employment, income category, wakeup time. For difference in the CAR a negative β represents a blunted response.
### C3. Associations between various aspects of informal caregiving and diurnal cortisol slopes

<table>
<thead>
<tr>
<th></th>
<th>Men (n=2,772)</th>
<th>Women (n=955)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Difference in Slope</td>
<td>Difference in Slope</td>
</tr>
<tr>
<td></td>
<td>Unadjusted, β (95%CI)</td>
<td>Multiple adjusted, β (95%CI)</td>
</tr>
<tr>
<td>Informal caregiving</td>
<td>0.000 (-0.007;0.008)</td>
<td>0.001 (-0.006;0.008)</td>
</tr>
<tr>
<td>Care recipient:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spouse</td>
<td>0.008 (-0.005;0.020)</td>
<td>0.007 (-0.006;0.020)</td>
</tr>
<tr>
<td>Parent, relative or friend</td>
<td>-0.003 (-0.012;0.006)</td>
<td>-0.002 (-0.010;0.007)</td>
</tr>
<tr>
<td>Weekly caregiving hours:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-8 hours</td>
<td>-0.000 (-0.011 ;0.010)</td>
<td>0.002 (-0.009;0.012)</td>
</tr>
<tr>
<td>9-20 hours</td>
<td>0.010 (-0.005;0.025)</td>
<td>0.012 (-0.003;0.027)</td>
</tr>
<tr>
<td>20-100 hours</td>
<td>-0.012 (-0.031;0.006)</td>
<td>-0.015 (-0.033;0.003)</td>
</tr>
<tr>
<td>&gt;100 hours</td>
<td>-0.009 (-0.028;0.011)</td>
<td>-0.011 (-0.030;0.009)</td>
</tr>
<tr>
<td>Test for trend</td>
<td>p=0.476</td>
<td>p=0.443</td>
</tr>
<tr>
<td>Duration of caregiving:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-term caregiving</td>
<td>-0.009 (-0.019;0.002)</td>
<td>-0.008 (-0.018;0.003)</td>
</tr>
<tr>
<td>Short-term caregiving</td>
<td>0.008 (-0.003;0.020)</td>
<td>0.009 (-0.002;0.020)</td>
</tr>
</tbody>
</table>

Non-caregivers is the reference group in all analyses. The underlying time axis is hours. Slopes are analysed using log(cortisol). Multiple adjusted: Age, ethnicity, married/cohabiting, gainful employment, income category, wakeup time. For difference in cortisol slope a negative β represents a steeper slope.
C4. Sensitivity analyses for the association between informal caregiving and various analyses on cortisol awakening response

<table>
<thead>
<tr>
<th></th>
<th>Men (n=2,772)</th>
<th></th>
<th>Women (n=955)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Difference in CAR</td>
<td></td>
<td>Difference in CAR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Multiple adjusted, β (95%CI)</td>
<td>P-value</td>
<td>Multiple adjusted, β (95%CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>Informal caregiving, main analysis</td>
<td>-1.523 (-2.882;-0.163)</td>
<td>p=0.028</td>
<td>1.436 (-0.805;3.678)</td>
<td>p=0.209</td>
</tr>
<tr>
<td>Adjusted for morning cortisol</td>
<td>-1.480 (-2.784;-0.177)</td>
<td>p=0.026</td>
<td>1.363 (-0.781;3.506)</td>
<td>p=0.213</td>
</tr>
<tr>
<td>CAR/time difference</td>
<td>-0.049 (-0.092;-0.006)</td>
<td>p=0.026</td>
<td>0.044 (-0.027;0.114)</td>
<td>p=0.227</td>
</tr>
</tbody>
</table>

CAR: Cortisol Awakening Response. Multiple adjusted: Age, ethnicity, married/cohabiting, gainful employment, income category, wakeup time. For difference in the CAR a negative β represents a blunted response.
C5. Cortisol levels at wakeup, at 30 min, and cortisol awakening response (CAR) according to gender and caregiving status

<table>
<thead>
<tr>
<th></th>
<th>Men (n=2,772)</th>
<th>Women (n=955)</th>
<th>Total population (n=3,727)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Caregivers (n=286)</td>
<td>Non-caregivers (n=2,486)</td>
<td>Caregivers (n=128)</td>
</tr>
<tr>
<td>Cortisol at awakening, Mean (±SD)</td>
<td>14.95 (±7.39)</td>
<td>14.87 (±7.25)</td>
<td>13.63 (±6.68)</td>
</tr>
<tr>
<td>Cortisol at 30 min, Mean (±SD)</td>
<td>19.82 (±10.21)</td>
<td>21.37 (±11.40)</td>
<td>22.83 (±13.16)</td>
</tr>
<tr>
<td>CAR, Mean (±SD)</td>
<td>4.87 (±10.07)</td>
<td>6.50 (±11.05)</td>
<td>9.20 (±12.83)</td>
</tr>
</tbody>
</table>

CAR presented in nmol/L
Study 2

Informal caregiving as a risk factor for type 2 diabetes in individuals with favourable and unfavourable psychosocial work environments: a longitudinal multi-cohort study

Diabetes & Metabolism 2017. Early online: http://dx.doi.org/10.1016/j.diabet.2017.04.001

Informal caregiving as a risk factor for type 2 diabetes in individuals with favourable and unfavourable psychosocial work environments: A longitudinal multi-cohort study


Abstract

**Aim.** To examine whether informal caregiving is associated with increased risk of type 2 diabetes (T2D), and whether job strain and social support at work modify the association.

**Methods.** Individual participant’s data were pooled from three cohort studies—the French GAZEL study, the Swedish Longitudinal Occupational Survey of Health (SLOSH) and the British Whitehall II study—a total of 21,243 study subjects. Informal caregiving was defined as unpaid care for a closely related person. Job strain was assessed using the demand-control model, and questions on co-worker and supervisor support were combined in a measure of social support at work. Incident T2D was ascertained using registry-based, clinically assessed and self-reported data.

**Results.** A total of 1058 participants developed T2D during the up to 10 years of follow-up. Neither informal caregiving (OR: 1.09, 95% CI: 0.92–1.30) nor high job strain (OR: 1.04, 95% CI: 0.86–1.26) were associated with T2D risk, whereas low social support at work was a risk factor for T2D (OR: 1.18, 95% CI: 1.02–1.37). Also, informal caregivers who were also exposed to low social support at work were at higher risk of T2D (OR: 1.40, 95% CI: 1.08–1.82) compared with those who were not informal caregivers and had high social support at work (multiplicative test for interaction, P = 0.04; additive test for interaction, synergy index = 10).

**Conclusion.** Informal caregiving was not independently associated with T2D risk. However, low social support at work was a risk factor, and informal caregivers with low social support at work had even higher risks of T2D.

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allostasis load, which is a cumulative biological marker of ill health [6], and our team has recently shown that informal caregiving predisposes to long-term sickness absence among women [7].

Type 2 diabetes (T2D) is a major global health problem, leading to serious complications such as retinopathy, neuropathy, nephropathy and atherosclerosis [8]. Stress-induced secretion of cortisol stimulates glucose production in the liver and antagonizes insulin production [9], which means that stress is hypothesized to play a causal role in the aetiology of T2D. In support of this hypothesis, a meta-analysis found that depression and emotional stressors, such as anxiety, sleep problems, anger and hostility, were associated with greater risk of T2D [10]. Furthermore, an unhealthy lifestyle encompassing strong risk factors for T2D [11] may be a consequence of caregiving stress [12]. However, the relationship between informal caregiving stress and risk of T2D has never been investigated in population-based studies.

Among gainfully employed individuals, workplace characteristics may modify the association between informal caregiving and risk of T2D. A recent large-scale meta-analysis by the Individual Participant Data in Working Populations (IPD-Work) consortium found that job strain, defined as the combination of high psychological demands at work and low job control, is a risk factor for T2D [11]. In addition, a longitudinal study found that job strain was a risk factor for T2D in women, and the association was stronger for women who also had low perceived social support at work [13]. Thus, social support at work may mitigate the effect of psychosocial stressors on T2D risk.

The overall objective of the present study was to assess the association between informal caregiving and incident T2D in gainfully employed individuals. A further aim was to determine whether there is any interaction between informal caregiving and psychosocial work factors on T2D risk based on two alternative hypotheses (Fig. 1). First, based on the role-strain model [14], it was hypothesized that the accumulation of stress from caregiving and work may be particularly harmful. Therefore, the present study aimed to assess whether the combined effect of informal caregiving and job strain was greater than the sum of their individual effects on T2D risk. Second, according to the stress-buffer hypothesis [15], it is to be expected that a supportive work environment may function as a positive resource for informal caregivers. Thus, our study also aimed to determine whether social support at work can reduce the risk of T2D associated with informal caregiving.

Methods

Study population

The present study used longitudinal data from the GAZEL study in France [16], the Swedish Longitudinal Occupational Survey of Health (SLOSH) [17] and the Whitehall II study from the UK [18]. These cohort studies were chosen because they offer information on informal caregiving, psychosocial work factors and diabetes, and represent a wide range of employees from different social-care systems. The GAZEL study was established in 1989 and included 20,625 employees of the French national gas and electricity company. SLOSH is an open cohort established in 2006 and comprises 40,877 individuals representative of the Swedish workforce. Whitehall II was established in 1985 and included 10,308 British civil servants from 20 London-based departments. Data from the year 2000 were used as baseline in the GAZEL (response rate: 71%), while year 2008 data were used from SLOSH (response rate: 61%) and the years 1991–1994 from Whitehall II (response rate: 87%).

A total of 24,636 men and women ≥ 30 years were gainfully employed at baseline. We excluded 805 subjects with diabetes at baseline (self-reported or diagnosed), and 2588 subjects with missing information on diabetes, informal caregiving and/or ≥ 1 covariate(s), leaving a total study population of 21,243 subjects (Appendix A; see supplementary materials associated with this article online).

Participants gave their informed consent to participate in the cohort studies, and all three studies had been approved by their respective ethics committees.

Informal caregiving

To assess informal caregiving, individuals were asked whether they provided regular care for an aged person (> 65 years) in GAZEL, and for an aged or disabled relative in Whitehall II and SLOSH. Further information on the number of weekly hours of caregiving was available for Whitehall II and SLOSH.

Psychosocial work factors

Job demands were assessed by five items in GAZEL and SLOSH, and by four items in Whitehall II, and comprised statements such as: “My job requires working very fast”. High job demands were defined as a score above the median within the specific study population [19]. Job control (decision latitude) comprised two subscales: skill discretion and decision authority. Skill discretion was assessed by four items in all cohorts, and encompassed statements such as: “My job requires a high level of skill”. Decision authority was assessed by two items in all cohorts, and included statements such as “I have a lot of say about what happens on my job”. The two items of decision authority were assigned the same weight as the four items of skill discretion in calculating the job control scores. Low job control was defined as a score below the median within the specific cohort study [19]. In accordance with the job strain model [20] and using the harmonized version

<table>
<thead>
<tr>
<th>Hypothesis</th>
<th>Exposure</th>
<th>Modifiers</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Role strain</td>
<td>Informal caregiving</td>
<td>Social support</td>
<td>Type 2 diabetes</td>
</tr>
<tr>
<td>Stress-buffer</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fig. 1. Chart of the study aim to determine whether there is any interaction between informal caregiving and psychosocial work factors on type 2 diabetes risk, based on two alternative hypotheses, in gainfully employed workers.
proposed by the IPD-Work consortium [19], high job strain was defined as the combination of high job demands and low job control; all other combinations of job demand and job control were defined as no high job strain.

Social support at work was defined as the combined support from both superiors and co-workers as per the iso-strain model by Karasek and Theorell [20]. The two aspects of work support were based on one question each and scored on a 1–4 Likert scale (1 = never, 2 = seldom, 3 = sometimes, 4 = often). For social support from superiors, the question was: “My superior is concerned about the well-being of those under him/her” in GAZEL, “Does your manager show that he/she cares about you?” in SLOSH and “How often is your immediate superior willing to listen to your problems?” in Whitehall II. For co-worker support, the question was: “The colleagues with whom I work show an interest in me” in GAZEL, “My colleagues are there for me” in SLOSH and “How often do you get help and support from your colleagues?” in Whitehall II. A score of 3 or 4 for both the supervisor and co-worker support questions was considered high social support at work (the reference category), and all other combinations were considered low social support at work. In GAZEL, information on psychosocial work factors in 1999 was used as a proxy for data in 2000, as these factors were not measured in the 2000 part of the study.

Type 2 diabetes

Individuals aged < 30 years were excluded to minimize the risk of incident type 1 diabetes [21]. We used a combination of diagnosed, clinically determined and self-reported information on T2D presently. In GAZEL, self-reported T2D incidence was based on the question: “Here is a list of health problems. Enter here the ones you have or have had over 12 months”: in SLOSH, the question was: “Do you have or have had any of the following long-term or serious illnesses or complaints the past two years?”; and in Whitehall II, the question was: “Has a doctor ever told you that you have diabetes?”. In Whitehall II, objective measures of diabetes ascertained by oral glucose tolerance tests were also available [22], along with self-reported diabetes medications. In SLOSH, self-reported information was supplemented with information on diabetes from hospital admissions. Incident T2D was assessed with up to 10 years of follow-up (with only 6-year follow-up for SLOSH).

Covariates

Potential confounders were identified based on currently available knowledge using directed acyclic graphs (Appendices B–D; see supplementary materials associated with this article online) [23]. These included age, gender, married/cohabiting (yes/no) and occupational grade (low-wage and manual labourers, lower non-manual and midlevel managers, and upper non-manual workers and managerial staff). Follow-up time was also included to make the statistical model resemble a Cox model, with time from exposure as the underlying time variable. The included time points were at 2 years, 4 years, 6 years and 10 years. Additional analyses included smoking (yes/no) and body mass index (BMI: < 25 kg/m² = underweight/normal weight, 25–30 kg/m² = overweight and ≥ 30 kg/m² = obese), which may be strong risk factors for T2D, but are also likely to be consequences of caregiving and work stress [24] and, thus, intermediate variables.

Statistical analyses

Logistic regression was applied in random-effects multilevel analyses using the individual participants’ data [25]. Heterogeneity in cohort-specific estimates was assessed with I² statistics. We estimated odds ratio (OR) and 95% confidence interval (CI) for the associations between informal caregiving, job strain, social support at work and incidence of T2D over the 6-year or 10-year follow-ups. In addition, individuals who were informal caregivers and exposed to job strain/low social support at work were compared with those who were not caregivers and had either no high strain or high social support (the reference groups). Moreover, any potential interactions were determined by assessing deviations from multiplicativity (by including a product term in the logistic regression models) and from additivity (using the synergy index [SI]), as per recommendations in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [26]. The SI can be interpreted as the excess risk due to double exposures where there is interaction relative to risk from exposure without interaction [27]. However, CIs for the SI were not calculated because of highly imprecise intervals due to dividing by values close to zero.

Three analytical models were constructed: model 1 was unadjusted; model 2 was adjusted for potential baseline confounders (age, gender, married/cohabiting, occupational grade, follow-up duration); and model 3 was further adjusted for smoking and BMI. Model 2 was presented here as the main analysis, as smoking and BMI are likely to be intermediate variables on the causal pathway between informal caregiving and T2D [12]. As there were no interactions between gender and informal caregiving/psychosocial work factors, our present analyses are for men and women combined. Also, subanalyses using data from SLOSH and Whitehall II investigated the impact of h/week of caregiving (divided into no caregiving, 1–4 h/week and > 4 h/week, with the lattermost corresponding to caregiving for an average of at least 1 h/weekday) to determine any potential dose–effect relationships [7].

In addition, sensitivity analyses were done to assess the robustness of results (Appendix E; see supplementary materials associated with this article online). First, supervisor and co-worker support was looked at separately, then in terms of interaction with informal caregiving, to see if one type of support (or lack thereof) was more strongly associated with T2D risk than the other. Second, time-to-event data from the GAZEL and Whitehall II studies were used to estimate the hazard ratio (HR) and 95% CI to determine whether such more detailed information on timing would affect the results. Third, weekly working hours were included as a potential confounder in analyses of Whitehall II and SLOSH data. As a fourth sensitivity analysis, the first 4 years of follow-up were excluded to minimize reverse causation [11], where people with undiagnosed diabetes may have symptoms that affect their sensitivity to and perception of job strain and social support. Lastly, the impact of duration of caregiving was investigated, using Whitehall II data, by looking at the risk of T2D in subjects who were caregivers at baseline as well as after 3–4 years compared with non-caregivers.

All analyses were carried out using the statistical software package Stata version 14/IC (StataCorp LP, College Station, TX, USA).

Results

A total of 1058 (5%) incident cases of T2D were registered in the up to 10 years of follow-up, with 433 (7%) in GAZEL, 208 (3%) in SLOSH and 417 (6%) in Whitehall II. As seen in Table 1, 16% of participants were informal caregivers. Additional data also showed that 86% of the caregivers in GAZEL had provided caregiving for > 6 months. A total of 22% experienced high job strain and 36% had low social support at work at baseline. While the distribution of these characteristics was reasonably comparable in both SLOSH and Whitehall II, a much larger proportion in GAZEL were informal caregivers (9% and 11% vs. 30%, respectively), and a considerably greater proportion had low social support at work (37% and 19% vs. 10.1016/j.diabet.2017.04.001
Table 1
Baseline characteristics of participants from the French GAZEL, the Swedish Longitudinal Occupational Survey of Health (SLOSH) and the British Whitehall II cohort studies.

<table>
<thead>
<tr>
<th></th>
<th>GAZEL (n = 6572)</th>
<th>SLOSH (n = 7590)</th>
<th>Whitehall II (n = 7081)</th>
<th>Total (n = 21,243)</th>
<th>Informal caregiver</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>34</td>
<td>56</td>
<td>30</td>
<td>41</td>
<td>44</td>
</tr>
<tr>
<td>Median age (IQR), years</td>
<td>52 (51–54)</td>
<td>50 (42–58)</td>
<td>48 (44–54)</td>
<td>51 (46–55)</td>
<td>52 (50–55)</td>
</tr>
<tr>
<td>Married/cohabiting</td>
<td>84</td>
<td>80</td>
<td>77</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>Low occupational grade</td>
<td>17</td>
<td>43</td>
<td>15</td>
<td>26</td>
<td>23</td>
</tr>
<tr>
<td>Smoking</td>
<td>16</td>
<td>14</td>
<td>13</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
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<td>3</td>
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<td>7</td>
<td>9</td>
</tr>
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<td>11</td>
<td>16</td>
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<tr>
<td>High job strain</td>
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<td>20</td>
<td>28</td>
<td>22</td>
<td>22</td>
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<tr>
<td>Low social support</td>
<td>55</td>
<td>37</td>
<td>19</td>
<td>36</td>
<td>45</td>
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</table>

All data are percentages unless otherwise stated.

55%, respectively). Furthermore, among the total study population, the proportions with low social support at work among caregivers vs. non-caregivers was 45% vs. 34%, respectively.

Fig. 2A–C shows the associations found between informal caregiving, high job strain, low social support and 10-year occurrence of T2D, respectively. Informal caregiving was not associated with T2D risk (OR: 1.09, 95% CI: 0.92–1.30; Fig. 2A). Of the two potential effect modifiers, high job strain was not associated with risk of T2D (OR: 1.04, 95% CI: 0.86–1.26), whereas low social support at work was associated with higher T2D risk (OR: 1.18, 95% CI: 1.02–1.37; Fig. 2B and C).

There was no excess risk of T2D in subjects who were informal caregivers and also exposed to high job strain (multiplicative: $P = 0.775$, additive: SI = 1; Fig. 3). However, there was both a multiplicative and additive interaction between informal caregiving and social support at work (multiplicative: $P = 0.048$, additive: SI = 10).

Analyzing data from SLOSH and Whitehall II revealed no association between h/week of caregiving and T2D over a 10-year follow-up in the groups providing 1–4 h/week (OR: 0.96, 95% CI: 0.64–1.43) and > 4 h/week (OR: 1.14, 95% CI: 0.79–1.63) of caregiving compared with no caregiving. Investigating the impact of duration of caregiving using Whitehall II data, subjects who were caregivers at both baseline and 3–4 years later had no increased risk of T2D compared with those who were non-caregivers at baseline and 3–4 years later (OR: 1.22, 95% CI: 0.78–1.88). Also, including the

![Fig. 2](http://dx.doi.org/10.1016/j.diabet.2017.04.001)
potential mediators of smoking and BMI had little impact on results. The same applied for analyses including family history of diabetes, number of work hours, time-to-event data and exclusion of the first 4 years of follow-up (see Appendix E for more details).

Discussion

Our present study found no association between informal caregiving and risk of T2D. However, low social support at work was associated with increased risk of T2D, and caregivers with low social support were at increased T2D risk compared with what would be expected from exposure to each factor on its own.

The results indicating no association between informal caregiving and T2D are contrary to our hypothesis, which was based on a potential causal path, from stress associated with informal caregiving, towards the development of T2D. Assuming that long-term stress may lead to T2D [9], it is likely that having a family member with a severe illness or disability may be stressful regardless of whether or not you are the caregiver [28]. However, our null finding might also be due to self-selection out of caregiving roles by those lacking the personal resources or health to provide informal caregiving [29]. Thus, the individuals most affected by the potential emotional strain of informal caregiving and, therefore, the most likely to develop T2D may have decided to leave the labour market to deal with the added responsibility of informal caregiving [30]. Based on this premise, the association between informal caregiving and T2D may have been underestimated due to a healthy caregiver bias.

The higher risk of T2D among those with low social support at work observed in our study is a novel finding, supporting the direct-effect hypothesis. Thus, low social support may be a stressor in itself, with a direct influence on psychological symptomatology irrespective of the presence of other stressful circumstances [31] that may potentially increase T2D risk [9]. Nevertheless, a previous study using Whitehall II data found no association between social support at work and T2D [13]. However, that analysis used the isostrain model, which includes four items each for co-worker support and supervisor support, and defines low social support as the lowest tertile. In the present study we included only one question each for co-worker and supervisor support, choosing the most comparable questions from each of the three cohort studies. A similar approach was applied in a previous study, using data from the same cohort studies, to investigate the association between supervisor support and days absent from work due to diabetes-related illness in diabetes patients [32]. Presently, low social support at work was more common among caregivers than among non-caregivers, which is a noteworthy finding, given the mitigating effect of social support at work on health [33–35].

Our present results do not support the stress-buffer hypothesis [15], as no individual association was found between informal caregiving and T2D. However, both multiplicative and additive interactions were found between low social support at work and informal caregiving, showing that the association between low social support at work and risk of T2D was amplified by informal caregiving. Thus, the impact of having no social support at work from supervisors and co-workers on risk of T2D may be greater in informal caregivers compared with non-caregivers.

Our study also found no association between high job strain and T2D, which contrasts with the large meta-analysis carried out by the IPD-Work consortium [11]. However, our study included only three of the 13 IPD-Work cohorts, which involved a total population of 124,808 subjects. Their study showed a weak association between job strain and T2D, whereas our present study may not have had sufficient power to replicate their findings.

Methodological considerations

The strengths of the present study are its longitudinal design and large study population of European workers. Thus, these representative samples of the Swedish workforce, civil servants in London, and workers in urban and rural districts in France, representing both blue- and white-collar workers, strengthen the generalizability of our findings to the general working population in Western countries. There were no follow-up data for 1546 eligible subjects. However, this non-response was not associated with our covariates and are therefore unlikely to have biased our estimates [36].

Informal caregiving was more prevalent in the GAZEL than in the SLOSH and Whitehall II studies. A likely explanation is that informal caregiving is embedded more deeply in French culture and law than it is in the UK and Sweden [37], although the discrepancy could also be due to how the questions on informal caregiving were phrased. The question in SLOSH and Whitehall II covered caregiving for disabled relatives in addition to care for the elderly, which may have led participants to only tick the box for informal caregivers if their relatives were severely disabled. In GAZEL, participants may have ticked the box even though their relatives had no severe disabilities, but nevertheless required some assistance with activities of daily living. Furthermore, in GAZEL, informal caregiving did not cover caregiving for disabled children.
and spouses (aged < 65 years), which may be a more emotionally demanding caregiving task than caring for parents or parents-in-law and, therefore, perhaps more detrimental to health [38]. This potential misclassification could have led to a small underestimation of the association between informal caregiving and T2D [36].

Our present study was not able to thoroughly investigate the impact of duration of informal caregiving. However, our sensitivity analyses found a tendency for caregivers at baseline who were still providing caregiving 3–4 years later to have a greater risk of T2D compared with results from the main analyses, which used only baseline information on caregiving. Thus, for long-term caregivers, the association with T2D may be stronger than for informal caregivers in general.

A large study based on data from 48 low- and middle-income countries revealed a larger percentage of informal caregivers in urban compared with rural areas [39], and people in urban areas are perhaps more likely to be diagnosed with T2D due to more frequent visits to a general practitioner. Based on this factor, there may have been a bias away from null due to the lack of adjusting for area of residence [36]. Physical inactivity and alcohol consumption were also not included in the analytical model, as they may be mediators on the pathway from informal caregiving to T2D and, therefore, should not be adjusted for. Furthermore, these variables were difficult to harmonize and were missing in a large number of cases and, thus, were not included in the sensitivity analysis along with smoking and BMI. In any case, analyses that included smoking and BMI showed that these lifestyle factors had little impact on the results, and the same may be suspected for physical inactivity and alcohol consumption.

Different measures for incident T2D were applied in the respective cohorts [40]. The GAZEL cohort only had self-reported data, with 7% of participants having incident T2D during the 10-year follow-up compared with 6% in Whitehall II; the older study population in GAZEL most likely explains this finding. Also, the T2D incidence of 3% in SLOSH was not surprising as there was only a 6-year follow-up in this cohort. Given the less-detailed information in GAZEL and SLOSH, there may have been an underestimation of T2D compared with the true number of people who would have been diagnosed had they all undergone oral glucose tolerance tests. However, any misclassification is unlikely to have been related to the question of informal caregiving and psychosocial work factors, making our study results unlikely to have been biased by this issue [36].

In conclusion, no association was found between informal caregiving at baseline and incident T2D although, for long-term caregivers, such an association may be more likely. However, we found that low social support at work was a risk factor for T2D and informal caregivers with low social support were at higher risk of T2D compared with what would be expected from having each factor on its own. These findings emphasize the importance of having social support in the workplace, especially for informal caregivers.

Authors’ contributions

J.M. analyzed the data and wrote the manuscript. N.H.R. was the main supervisor and participated in creating the study protocol and reviewed/edited the manuscript. A.C. and R.L. participated in creating the study protocol and reviewed/edited the manuscript. T.L. was the statistical advisor and reviewed/edited the manuscript. G.S.A. was our diabetes specialist and reviewed/edited the manuscript. I.E.H.M., R.R. and C.H.R.H. reviewed/edited the manuscript. M.K. is the PI of Whitehall II and reviewed/edited the manuscript, and J.H. is a Whitehall II researcher who also reviewed/edited the manuscript. M.G. and M.Z. are PIs of GAZEL and reviewed/edited the manuscript. H.W. is PI of SLOSH and reviewed/edited the manuscript. C.L. is data manager of SLOSH and reviewed/edited the manuscript. All authors approved the final version of the manuscript.

Disclosure of interest

The authors declare that they have no competing interest.

Acknowledgements

J.M. was financed by the Danish Work Environment Foundation for creating this study (grant No. 12-2013-03). The GAZEL Cohort Study was funded by EDF-GDF and INSERM, and received grants from the Cohortes Santé TGiR Program, the French National Research Agency (ANR-08-BLAN-0028) and French Agency for Environmental and Occupational Health Safety (AFSSET; EST-2008/1/35). The Whitehall II Study was supported by grants from the UK Medical Research Council (MR/K013351/1; G0902037) and British Heart Foundation (RG/13/2/30098, PG/11/63/29011), while the US National Institutes of Health (ROIHL36310, R01AG013196) supported the collection of data in the study. The SLOSH was supported by the Swedish Council for Working Life and Social Research (FAS; grant No. 2005-0734) and Swedish Research Council (VR; grant No. 2009-6192 and 2013-1645). We thank all the participants, researchers and support staff who contributed to the cohort studies.

Appendix A. Supplementary data

Supplementary (Appendices A–E) data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.diabet.2017.04.001.

References

Study 3

Weekly hours of informal caregiving and paid work, and the risk of cardiovascular disease


Mortensen J, Dich N, Lange T, Ramlau-Hansen CH, Head J, Kivimäki M, Leineweber C, Rod NH.
Weekly hours of informal caregiving and paid work, and the risk of cardiovascular disease

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Background: Little is known on the association between weekly hours of informal caregiving and risk of cardiovascular disease (CVD). The objective was to investigate the individual and joint effects of weekly hours of informal caregiving and paid work on the risk of CVD. Methods: Pooled analysis with 1396 informal caregivers in gainful employment, from the Swedish Longitudinal Occupational Survey of Health and the Whitehall II study. Informal caregiving was defined as care for an aged or disabled relative. The outcome was CVD during 10 years follow-up. Analyses were adjusted for age, sex, children, marital status and occupational grade. Results: There were 59 cases of CVD. Providing care >20 h weekly were associated with a higher risk of CVD compared to those providing care 1–8 h weekly (hazard ratio = 2.63, 95%CI: 1.20; 5.76), irrespectively of weekly work hours. In sensitivity analyses, we found this risk to be markedly higher among long-term caregivers (6.17, 95%CI: 1.73; 22.1) compared to short-term caregivers (0.89, 95%CI: 0.10; 8.08). Caregivers working >55 h weekly were at higher risk of CVD (2.23, 95%CI: 1.14; 4.35) compared to those working 35–40 h weekly. Those providing care >8 h and working <40 h weekly had a higher risk of CVD compared to those providing care 1–8 h working <40 h (3.23, 95%CI: 1.25; 8.37). Conclusion: A high number of weekly hours of informal caregiving as opposed to few weekly hours is associated with a higher risk of CVD, irrespectively of weekly work hours. The excess risk seemed to be driven by those providing care over long periods of time.

Methods

This is a multi-cohort study pooling individual level data from the Swedish Longitudinal Occupational Survey of Health (SLOSH) and the Whitehall II study from the UK. SLOSH is an open cohort and comprises 40 877 individuals, representative of the Swedish workforce. Whitehall II includes 10 308 British civil servants from 20 London-based departments. Year 2008 was the
baseline in SLOSH (response rate 61%), and years 1991–93 were the baseline in Whitehall II (response rate 87%). The total study population encompassed 1396 informal caregivers in gainful employment (Supplementary Appendix A). The cohorts have been approved by the appropriate ethics committees and participants have given consent to be included.

**Weekly hours of informal caregiving and paid work**

Informal caregiving was in both cohorts assessed by asking whether participants provided care for an aged or disabled relative. We included only those who answered ‘yes.’ We categorized weekly hours of caregiving in three groups; 1–8 h (reference), 9–20 h and >20 h. In Whitehall II, we had additional information on long-term caregiving, distinguishing those who provided informal care 2–3 years following baseline (long-term caregivers) from those provided care at baseline only (short-term caregivers).

For weekly work hours, individuals in SLOSH were asked how many hours they worked each week, and in Whitehall II individuals were asked how many hours they worked on a normal workday. To harmonize this information, we multiplied daily work hours in Whitehall II by five, based on the assumption that individuals in the civil service work 5 days a week. Weekly work hours were categorized as <35 h, 35–40 h (reference), 41–54 h and ≥55 h per week.

We investigated the joint effect of weekly hours of informal caregiving and paid work more thoroughly by dividing participants into four mutually exclusive groups: (1) Those providing care 1–8 h and working ≤40 h weekly, (2) providing care 1–8 h and working >40 h weekly, (3) providing care >8 h and working ≤40 h weekly and (4) providing care >8 h and working >40 h weekly.

**Ascertainment of CVD**

We used register-based information on diagnosis of CVD defined according to the 10th edition of the International Classification of Disease (ICD). CVD encompassed diagnoses CHD (ICD-10 codes I20–I25) and stroke (ICD-10 codes I60–I68). Individuals with a CVD diagnosis at baseline were excluded from the study.

**Covariates**

Confounding and mediating variables related to CVD were identified based on prior knowledge and using the method of directed acyclic graphs (Supplementary Appendix B). Confounding variables included age, sex, children (yes, no), marital status (yes, no) and occupational grade (low wage and manual laborers, lower non-manual and midlevel managers, and upper non-manual workers and managing staff). Smoking and BMI measured at baseline, were most likely mediating factors on the causal pathway from workload of caregiving and work and risk of CVD, and were only adjusted for in a sensitivity analysis.

**Statistical analyzes**

We applied a Cox regression model with time from baseline as the underlying time axis. The outcome was time until CVD, death from other causes or the end of follow-up, whichever came first; with 6 years follow-up in SLOSH and 10 years follow-up in Whitehall II. The Cox model was implemented in a random-effect meta-analysis and cohort specific estimates were combined and weighted in a joint model. The degree of heterogeneity between cohorts was assessed using $I^2$, which describes the percentage of total variation across studies due to heterogeneity. We considered $I^2$ values of 25%, 50% and 75% to represent low, moderate and high heterogeneity, respectively.

We applied a random effects model, because there may be between-group variation in SLOSH and Whitehall II on the investigated associations, due to different follow-up time and welfare-state differences. Analyzes showed no effect modification by sex (Supplementary Appendix C4).

We applied two analytical models: model 1 was adjusted for age and sex, and model 2 was also adjusted for children, marital status and occupational grade; analyzes of caregiving hours were further adjusted for work hours and those of work hours were adjusted for caregiving hours. Interaction was assessed on a multiplicative and additive scale according to recommendations by the STROBE guidelines. We assessed multiplicative interaction by including a product term between caregiving and work hour variables in the Cox model. Additive interaction was assessed with the synergy index, which represents the additional risk from exposure to informal caregiving and work hours when interaction is present, relative to the risk from exposure when there is no interaction. In supplemental analyzes, we investigated risk of CVD for long-term caregivers compared to short-term caregivers. Here, we excluded the first 3 years of follow-up to minimize risk of reverse causation bias.

**Results**

Among the 1396 informal caregivers, 59 participants (4%) developed CVD within 10 410 person-years at risk; 50 cases of CHD and 9 cases of stroke. In SLOSH, there were 14 (2%) cases during 6 years follow-up and in Whitehall II, there were 45 (6%) cases during 10 years follow-up. Baseline characteristics of participants are shown in table 1.

As seen in figure 1, compared to those who provided caregiving 1–8 h weekly, those who provided 9–20 weekly hours of caregiving (HR = 3.31, 95%CI: 0.53; 20.5) or >20 h weekly (HR = 2.63; 95%CI: 1.20; 5.76) were at higher risk of CVD (Supplementary Appendix C1). There was high heterogeneity with an $I^2$ value of 85% for the estimate on 9–20 h. Cohort specific estimates suggest that the risk of CVD was higher in SLOSH (HR = 8.71, 95%CI: 2.85; 26.6) compared to Whitehall II (HR = 1.35, 95%CI: 0.59; 3.13) (Supplementary Appendix C2, C3). There was no noteworthy heterogeneity for >20 weekly hours of caregiving. As also seen in figure 1, those working ≥55 h weekly had a higher risk of CVD compared to those working 35–40 h weekly (HR = 2.52, 95%CI: 1.14; 4.35). For those working <35 h and those working 41–54 h weekly there were no association with CVD. Additional analyzes showed that estimates attenuated slightly when adjusting for smoking and BMI (Supplementary Appendix C5).

In figure 2, we present the joint model of weekly hours of caregiving and work. We did not find a higher risk of CVD in the group who provided few hours (1–8 h weekly) of caregiving and working >40 h (HR = 1.34; 95%CI: 0.67; 2.68). However, individuals who provided >8 h of caregiving and working ≤40 h per week had a higher risk of CVD compared with the reference group (HR = 3.23, 95%CI: 1.25; 8.37) (Supplementary Appendix C6). There was moderate heterogeneity in the latter analysis: Those exposed to many caregiving hours and long work hours in SLOSH had a markedly higher risk of CVD (HR = 8.71, 95%CI: 2.85; 26.6) compared to those with few caregiving hours and short work hours, while this was less supported in Whitehall II (HR = 1.22, 95%CI: 0.33; 4.51) (Supplementary Appendix C7, C8).

In further analyzes using Whitehall II data (figure 3), we found that long-term caregivers providing >8 h weekly (HR = 4.41, 95%CI: 0.88; 22.0) and >20 h of weekly caregiving (HR = 6.17, 95%CI: 1.73; 22.1) were at markedly higher risk of CVD compared to long-term caregivers providing caregiving for 1–8 h. For short-term caregivers, there was no association with CVD in either group (Supplementary Appendix C9). We found a multiplicative interaction between long-term caregiving and weekly hours of caregiving using a binary variable with >8 h and ≤8 h of caregiving (multiplicative interaction: $P = 0.04$, additive interaction: synergy index = −1.49). In general, there was no attenuation of hazard.
Discussion

In this longitudinal study of informal caregivers in gainful employment, we found that those who provided many weekly hours of informal caregiving were at markedly higher risk of CVD opposed to few weekly hours, irrespectively of weekly work hours. In addition, we found that many caregiving hours were associated with a six times higher risk of CVD among long-term caregivers, whereas many caregiving hours were not associated with CVD risk among short-term caregivers. We also found that long working hours was associated with a higher risk of CVD, but there was only weak evidence to support a more detrimental effect among those with double burden from long caregiving- and work hours.

Based on results from the 2001 UK Census, it is estimated that 10% of the UK population provide informal caregiving, with a peak at age 45–59, in which almost 20% provide informal caregiving. Furthermore, it is estimated that around 75% of caregivers in the UK are gainfully employed (Scotland excluded). In Sweden, it is estimated that 25% of the population provides help to a relative or other dependent. Given the growing population of elderly reported by the World Health Organization, these numbers are likely to be increasing. Thus, caregiving seems to be a public health concern as gainfully employed caregivers who provide >20 h of weekly caregiving may have a markedly higher risk of CVD compared to those providing care for 1–8 h weekly.

In the Nurses’ Health Study, it was previously shown that female nurses providing weekly care for a disabled or ill spouse had a 1.8 times higher risk of CHD compared to non-caregivers. Our data complement these findings by showing that subjects providing >20 h of caregiving may have a markedly higher risk of CVD compared to those providing care for 1–8 h weekly.

In another study, there was no increased risk of CHD in caregivers providing >5 weekly hours of caregiving. However, non-caregivers were used as the reference group, and there is potentially a large difference in providing >5 weekly hours and >20 weekly hours of caregiving.

Table 1 Baseline characteristics of informal caregivers in SLOSH and Whitehall II

<table>
<thead>
<tr>
<th></th>
<th>SLOSH</th>
<th>Whitehall II</th>
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<tbody>
<tr>
<td></td>
<td>N = 700</td>
<td>N = 696</td>
<td>N = 1396</td>
</tr>
<tr>
<td>Informal caregivers</td>
<td></td>
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<tr>
<td>Women</td>
<td>68%</td>
<td>39%</td>
<td>54%</td>
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<tr>
<td>Age (Mean ± SD)</td>
<td>52 ± 9</td>
<td>50 ± 5</td>
<td>51 ± 7</td>
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<tr>
<td>Children</td>
<td>48%</td>
<td>63%</td>
<td>56%</td>
</tr>
<tr>
<td>Low occupational grade</td>
<td>12%</td>
<td>35%</td>
<td>23%</td>
</tr>
<tr>
<td>Smoking</td>
<td>19%</td>
<td>15%</td>
<td>17%</td>
</tr>
<tr>
<td>Obese</td>
<td>21%</td>
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<td>16%</td>
</tr>
<tr>
<td>Weekly caregiving hours</td>
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<td></td>
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<tr>
<td>1–8 h</td>
<td>69%</td>
<td>74%</td>
<td>72%</td>
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<tr>
<td>9–20 h</td>
<td>17%</td>
<td>16%</td>
<td>16%</td>
</tr>
<tr>
<td>&gt;20 h</td>
<td>14%</td>
<td>10%</td>
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<td>Weekly work hours</td>
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<tr>
<td>&lt;35 h</td>
<td>21%</td>
<td>4%</td>
<td>13%</td>
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<tr>
<td>≥55 h</td>
<td>12%</td>
<td>9%</td>
<td>11%</td>
</tr>
</tbody>
</table>

Abbreviations: SD, Standard Deviation.

Figures 1 and 2 illustrate the associations between weekly caregiving, work hours, and CVD during 10 years follow-up in 1396 informal caregivers from SLOSH and the Whitehall II study. Adjusted for age, sex, children, marital status, occupational grade, along with caregiving hours adjusted for work hours and vice versa.
hours of care. A study on married couples also investigated the association between spousal caregiving and the risk of CVD,3 but based on reports from the care recipient instead of the caregiver. Here, high intensity caregiving was defined as ≥14 h of weekly caregiving, and they found a 35% higher risk of CVD compared to a joint reference group of those providing <14 h of weekly caregiving and non-caregivers. In line with our study, they found that long-term caregivers had a higher risk of CVD compared to short-term caregivers, also using two consecutive waves separated by 2 years as the definition of long-term caregiving.25 We had no information of how many years prior to baseline individuals provided caregiving, and results on long-term caregiving may, therefore, be underestimated.

Including only caregivers provides a direct test of the effect of the number of hours of caregiving among people all exposed to some degree of caregiving strain. Furthermore, by including weekly work hours, we were able to investigate the joint workload of weekly caregiving and work hours, which has not been investigated previously. Our results from the joint model showed that many weekly hours of caregiving was associated with higher risk of CVD irrespectively of work hours, unless the caregiver worked >55 h weekly. In a previous large-scale meta-analysis, working >55 h weekly was found to be associated with a modest increased CVD risk,[13] whereas we found a more than double risk of CVD. The association seemed to be driven by those had provided long-term care. We also found that informal caregiving was associated with a higher risk of CVD, irrespectively of weekly work hours. This, association seemed to be stronger.3 Most likely because you are more likely to live in the same household as your spouse, while this is not always the case with a disabled parent. However, by adjusting for age we may have partially adjusted for some of the effect from care recipients. Thus, caregiving for a parent would be more common in younger age whereas caregiving for a spouse would be more common in older age.3

Conclusions
Previous studies have shown associations between informal caregiving and risk of CVD. In our study population of informal caregivers, we found that many as opposed to few weekly hours of informal caregiving was associated with a higher risk of CVD, irrespectively of weekly work hours. This, association seemed to be driven by those had provided long-term care. We also found that very long working hours were associated with a higher risk of CVD in informal caregivers, indicating that these workers may be a particularly vulnerable group. Our results emphasize the importance of preventive strategies and support systems for those who provide intensive and long-term caregiving.

Supplementary data
Supplementary data are available at EURPUB online.

Acknowledgement
The authors thank all participants, researchers and support staffs who have contributed to the cohort studies.
Funding

This work was supported by the Danish Work Environment Foundation (grant no. 12-2013-03). MK was supported by NordForsk, the MRC (K013351), and the Academy of Finland (311492). The SLOSH study was supported by the Swedish Council for Working Life and Social Research (FAS, grants no. 2005-0734) and the Swedish Research Council (VR, grants no. 2009-6192 and 2013-1645). The Whitehall II Study is supported by grants from The UK Medical Research Council (MR/K013351/1; G0902037), British Heart Foundation (RG/13/2/30098, PG/11/63/29011) and the US National Institutes of Health (R01HL63610, R01AG013196) have supported collection of data in the Whitehall II Study.

Conflicts of interest: Dr. Kivimäki reports grants from NordForsk, the MRC (K013351), and the Academy of Finland (311492), during the conduct of the study. Dr. Lange reports personal fees from Novo Nordisk outside the submitted work.

Key points

- In a population of informal caregivers, we show that more than 20 weekly hours of informal caregiving is associated with markedly higher risk of CVD compared to providing few weekly hours of caregiving, irrespectively of number of weekly work hours.
- The higher risk of CVD among caregivers seemed to be driven by those who had provided long-term care.
- Informal caregivers working more than 55 h weekly had more than twice the risk of developing CVD compared with those working 35–40 h weekly.

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Study 4

Job strain and informal caregiving as predictors of long-term sickness absence: a longitudinal multi-cohort study


Original article

Scand J Work Environ Health 2017;43(1):5-14
doi:10.5271/sjweh.3587

Job strain and informal caregiving as predictors of long-term sickness absence: A longitudinal multi-cohort study

This study is the first to investigate the joint effects of job strain and informal caregiving on long-term sickness absence. The main finding was that informal caregiving responsibilities and/or high job strain predicted long-term sickness absence among women.

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Refers to the following text of the Journal: 2015;41(5):421-507

The following article refers to this text: 2017;43(1):1-96

Key terms: gender difference; informal caregiving; interaction; job strain; long-term sickness absence; multi-cohort; predictor; sick leave; sickness absence; unpaid care; women

This article in PubMed: www.ncbi.nlm.nih.gov/pubmed/27556905

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Job strain and informal caregiving as predictors of long-term sickness absence: A longitudinal multi-cohort study

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Objectives The aim of this study was to investigate the individual, joint and interactive effects of job strain and informal caregiving on long-term sickness absence with special attention to gender differences.

Methods The study comprised a prospective cohort study of 6798 working adults from France, 14,727 from Finland, and 5275 from the UK. A total of 26,800 participants, age 52 (interquartile range 47–56) years participated in the study. Job strain was assessed using the demand–control model. Informal caregiving was defined as care for a sick, disabled, or elderly person. Long-term sickness absence spells defined as absence >14 consecutive days were registered during two years follow-up. We used recurrent-events Cox regression in random-effects meta-analyses.

Results A total of 12% men and 21% women had ≥1 long-term sickness absence spell. Among women, both high job strain [hazard ratio (HR) 1.08, 95% confidence interval (95% CI) 1.00–1.17] and informal caregiving (HR 1.13, 95% CI 1.04–1.23) were associated with a modestly higher risk of sickness absence. Women doubly exposed to high job strain and informal caregiving also showed a moderately higher risk of sickness absence (HR 1.20, 95% CI 1.03–1.41), but the excess risk was not more than expected from joint exposure to caregiving and job strain. Neither job strain nor informal caregiving predicted sickness absence for men.

Conclusions High job strain and informal caregiving predicted long-term sickness absence among women. However there was no noticeable interaction in the presence of both exposures.

Key terms gender difference; interaction; sick leave; unpaid care; women.

Informal caregiving, defined as unpaid assistance with activities of daily living for sick, disabled, or elderly relatives, contributes invaluably to the well-being of populations in western countries and is becoming a key issue in many countries due to rapid population aging (1). Informal caregiving may entail benefits such as satisfaction and meaning for the caregiver (2). However, the combination of prolonged distress, physiological demands, financial strain and social isolation that sometimes accompanies informal caregiving may eventually compromise the caregivers’ own health (3–6).

According to the role accumulation theory, having multiple roles from paid work and informal caregiving may carry positive effects for the caregiver (7) as one role may buffer stressors related to other roles (8). In contrast, the role strain theory hypothesizes that individuals who provide informal caregiving may be particularly vulnerable to its potential health consequences if they are simultaneously exposed to other stressors such as a high-strain job (9). This double exposure may lead to work–family conflicts introduced by the experience of role conflict (ie, being subject to conflicting...
demands) or role overload (ie, having too much to do) (10) and eventually render the caregiver more vulnerable to negative health consequences.

Sickness absence has a large impact on employees, work sites, and society and provides a measure of work incapacity as a social consequence of morbidity (11). In two recent longitudinal studies from Australia and Belgium and a case–control study from Brazil, it has been shown that high job strain predicts long-term sickness absence (12–14). In contrast, one study only found an association for men in adjusted models (15), and another study found no association for either men or women in adjusted models (16). A few studies have also investigated the association between work–family conflicts and sickness absence (17–19). A large study including workers from 31 European countries found that work–life imbalance predict sickness absence (19), and a Finnish study showed that spillover from work into family life predicted a heightened rate of sickness absence spells (17). However, research on work–family conflicts has so far primarily focused on perceived imbalances between work and family life without distinguishing between different sources to this imbalance (20). Only few studies have investigated the combined effect of work and family factors on sickness absence (21–24). Two studies, based on the same occupational cohort, showed that the combination of high work and family demands predicted all-cause sickness absence and sickness absence due to mental health disorders (21, 22). In those studies, family demands were defined by the number of individuals the participant supported economically. Informal caregiving, however, involves both physically and mentally straining elements and is thus different from providing economic support. Looking specifically at informal caregiving, a study from Austria has shown that a time-based conflict between informal eldercare and paid work was related to the intended job change of female workers and that the intensity of caregiving provided was related to male workers’ anticipated labor market exit (25). However, to our knowledge no studies have investigated the association between informal caregiving and sickness absence due to paid work.

Quantifying the separate and joint effects of job strain and informal caregiving on sickness absence will help in the identification of high-risk workers. Such information is important for policy-makers and employers to develop special need support and efficient preventive strategies (26).

Women are traditionally more engaged in informal caregiving than men, and it has been suggested that women may be especially vulnerable to the joint health effects of demanding work and life circumstances (27, 28). Furthermore, women in general still carry the largest household workload, and it has been shown that women have higher evening cortisol levels than men (29), indicating that they may have difficulties relaxing and unwinding after work.

In this multi-cohort study, the objective was to investigate the joint effects of job strain and informal caregiving on long-term sickness absence with special attention to gender differences, using data from three large European occupational cohorts. Based on the role strain theory (9), we hypothesized that the joint effects of high job strain and informal caregiving on long-term sickness absence exceed the combination of their individual associations. We additionally hypothesized that women were at greater risk of sickness absence compared to men when exposed to both high job strain and informal caregiving.

**Methods**

**Study participants**

We used longitudinal data from the GAZEL cohort from France (30), the Finnish Public Sector Study (FPS) from Finland (31), and the Whitehall II study from the UK (32). These cohorts were chosen as they have detailed data on job strain, informal caregiving, and longitudinal register-based data on sickness absence.

The GAZEL cohort was established in 1989 and includes 20 625 employees of the French national gas and electricity company (response rate, approximately 75% annually).

FPS was established in 1997 and comprises all 151 901 public employees in ten towns and five hospital districts in Finland. A nested open cohort with 16 948 responders at baseline (baseline response rate, 70%), FPS includes data on psychosocial work and domestic factors, along with health outcomes.

Whitehall II was established in 1985 and includes 10 308 British civil servants from 20 London-based departments (baseline response rate, 73%).

Further information about each cohort can be found in the cohort profiles (30–32). We used data from year 2000 as baseline in GAZEL, year 2012 in FPS, and years 1991–1994 in Whitehall II, due to the availability of data on informal caregiving in the present years. We included individuals in paid work and excluded individuals on sick leave at the day of the baseline questionnaires. The present study comprised 6798 individuals from GAZEL, 14 727 individuals from FPS, and 5275 individuals from Whitehall II, a total of 26 800 individuals in paid work. Participants gave written consent to participate in the cohort studies, and all three cohorts have been approved by the respective human ethics committees. The data selection procedure is presented in a flow chart in the appendix (www.sjweh.fi/index.php?page=data-repository).
Measures

Informal caregiving. Informal caregiving was treated as a binary (yes/no) variable based on slightly different questions in each cohort. In GAZEL, individuals were asked if they provide regular care for an aged person (>65 years); in FPS individuals were asked if they provide care for a sick, disabled, or aged relative; and in Whitehall II individuals were asked if they provide care for an aged or disabled relative. To investigate the effect of weekly hours of informal caregiving, we applied a cut-off at ≥4 weekly hours, indicating caregiving of ≥1 hour (average) on each weekday. Information on weekly hours of caregiving was only available in FPS and Whitehall II.

Job strain. Job strain (33) was assessed using the Job Content Questionnaire in GAZEL and FPS and the Demand–Control Questionnaire in Whitehall II (34). High job strain was in accordance with the job strain model (33) defined as the combination of high job demands and low job control; all other combinations of job demands and job control were defined as no high strain (34). Job demands were assessed with five items in GAZEL and four items in Whitehall II and FPS, and encompass statements such as “My job requires working very fast”. High job demands were defined as a score above the median score of the specific study population. Job control (decision latitude) is comprised of two subscales: skill discretion and decision authority. Skill discretion was assessed with four items in all cohorts, and encompasses statements such as “My job requires a high level of skill”. Decision authority was assessed with two items in all cohorts, and encompasses statements such as “I have a lot of say about what happens on my job”. The two items in decision authority are weighted the same as the four items in skill discretion, in calculation of job control scores. Low job control was defined as a job control score below the median score of the specific study population (34). In GAZEL, job strain in 1999 was used as a proxy for information in 2000.

Long-term sickness absence. We used all-cause long-term sickness absence from paid work as the outcome, defined as spells of ≥14 consecutive days. Long-term sickness absence has shown to be a useful global measure of health differentials between employees (11, 35, 36), as opposed to shorter sickness absence spells, which may in some cases represent healthy coping behaviors to avoid serious morbidity (11, 35, 36). Furthermore, long-term spells were used as opposed to number of days absent, as spells ≤14 days are sometimes based on self-report in the three cohorts, and we wanted to prevent any reporting bias. Sickness absence information was from national registers in FPS and Whitehall II, and company register in GAZEL (17, 22, 37). Recorded sickness absence was due to own morbidity and not absence due to, eg, maternity leave or care for a sick child. We used a follow-up period of two years in registration of long-term sickness absence. This period was chosen as longer follow-up might entail a weaker causal path between baseline exposures and later sickness absence.

Confounders

We identified confounders for analyses using directed acyclic graphs (DAG) (38) (see appendix, www.sjweh.fi/index.php?page=data-repository). Included variables were: age of children (0, 1–3, >3 years), occupational grade in three groups (low included low wage and manual laborers, intermediate included lower non-manual and midlevel managers, and high included upper non-manual workers and administrative staff), married/cohabiting, death of a close relative and/or divorce within the past 12 months, ≥1 spell of long-term sickness absence in the two years preceding baseline, ≥1 longstanding illness at baseline (diabetes, cardiovascular disease, cancer or respiratory disease).

Statistical analysis

We used individual participant data in Cox proportional hazards random effects meta-analyses (39). This approach can be thought of as a type of multilevel model (with cohorts as cluster units) on the proportional hazard scale. Heterogeneity among cohort specific estimates were assessed with I² statistics (40). A random effects model was chosen to allow for the true effect to vary between the included cohorts; eg, the effect size of informal caregiving on sickness absence could be greater when questions on caregiving encompass sick, disabled, or aged relatives in FPS and Whitehall II compared to only aged relatives in GAZEL.

Person-years at risk encompassed time until the occurrence of a long-term sickness absence spell or until censoring due to retirement, disability pension/incapacity benefit, death, or leaving the workplace. Sickness absence for spells ≤14 days were included in time-at-risk of long-term sickness absence based on the argument that one would still be at risk of long-term sickness absence during shorter spells of sickness absence.

To account for recurrent events of long-term sickness absence we used the Prentice, Williams and Peterson Total Time (PWP-TT) model (41), which is appropriate if the occurrence of the first event increases the likelihood of a recurrence. In PWP-TT, multiple events are ordered by stratification based on the prior number of events, such that all participants are at risk of an event in the first stratum, but only those with a prior event are at risk for a successive event (41). We truncated analy-
ses at two spells of long-term sickness absence during follow-up, due to small number of individuals with a greater number of spells.

We estimated hazard ratios (HR) and 95% confidence intervals (CI) with long-term sickness absence as the event of interest, for the individual associations with job strain and informal caregiving and the joint associations compared to those with no high strain and no informal caregiving as reference group (42). We then carried out similar analyses adjusted for the mentioned confounders. Confounders are presented in table 1 along with possible mediating lifestyle factors including smoking, alcohol, and overweight. We assessed additive interaction with the synergy index (SI) (43), which can be interpreted as the excess risk from double exposures when there is interaction relative to the risk from exposure without interaction, and further tested for multiplicative interaction. Analyses were conducted separately for men and women to address gender differences. It was not feasible to test formally for 3-way interaction with job strain, caregiving and gender due to lack of statistical power.

We carried out several sensitivity analyses to test the robustness of our results. In the first sensitivity analysis we used multiple imputation on the 14% of individuals with missing data, assuming that data were missing at random (44). We imputed missing data with a chained equation model and applied Rubin’s rules at the study level prior to meta-analysis (45). Results from the imputed analyses were compared to results from the complete case analyses to investigate selection bias introduced by excluding participants with missing data. Secondly, retirement may be a competing risk to long-term sickness absence and therefore we carried out a sensitivity analysis in which we excluded individuals >58 years at baseline to account for retirement from the workforce due to the statutory pension age. Thirdly, by only looking at number of spells >14 days, individuals with very long spells may not have contributed with risk time following the first spell, as the first spell may have lasted the whole follow-up period. This may potentially underestimate the consequences of job strain and caregiving exposure on the risk of sickness absence. Therefore, we also made a sensitivity analysis where we only looked at time to the first event of long-term sickness absence. In a fourth analysis, we included weekly work hours as a confounding variable (<36 hours, 36-40 hours, >40 hours). This information was only available in Whitehall II. We also looked whether job strain and caregiving predicted the length of long-term sickness absence spells in the subpopulation of individuals with long-term spells. Lastly, we did a sensitivity analysis were we looked at job demands and job control separately to see if they were better predictors of sickness absence than the combined job strain measure. We used the ipdmetan statistical software package in STATA v13/IC for analyses. Ipdmepan performs two-stage individual participant-data meta-analysis using the inverse-variance method. The syntax used is “ipdmetan, study(studyID) : stcox…”, which fits the model command once within each level of study ID.

**Results**

In this population of 26 800 employees, there were 5946 spells of long-term sickness absence during 46 794 person-years. A total of 12% of male and 21% of female participants experienced ≥1 spell of long-term sickness absence within a 2-year period. When truncating at two

**Table 1. Baseline characteristics according to cohort and gender.** [FPS=Finnish Public Sector Study; M=median; IQR=interquartile range.]

<table>
<thead>
<tr>
<th></th>
<th>GAZEL: France (Baseline, year 2000)</th>
<th>FPS: Finland (Baseline, year 2012)</th>
<th>Whitehall II: UK (Baseline, year 1994)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>% M IQR</td>
<td>% M IQR</td>
<td>% M IQR</td>
</tr>
<tr>
<td>Children a</td>
<td>95 71 82</td>
<td>87 74 68</td>
<td>84 66 63</td>
</tr>
<tr>
<td>Death of relative/divorce b</td>
<td>17 9 11</td>
<td>18 6 11</td>
<td>19 6 11</td>
</tr>
<tr>
<td>Low occupational grade</td>
<td>12 10 11</td>
<td>25 17 12</td>
<td>27 21 12</td>
</tr>
<tr>
<td>High alcohol intake</td>
<td>23 9 11</td>
<td>16 11 9</td>
<td>17 11 9</td>
</tr>
<tr>
<td>Overweight</td>
<td>63 23 29</td>
<td>66 23 29</td>
<td>66 23 29</td>
</tr>
<tr>
<td>Previous long-term sickness absence</td>
<td>14 23 22</td>
<td>22 22 22</td>
<td>22 22 22</td>
</tr>
<tr>
<td>Longstanding illness (≥1)</td>
<td>11 9 25</td>
<td>26 9 25</td>
<td>26 9 25</td>
</tr>
<tr>
<td>Informal caregiving</td>
<td>27 30 10</td>
<td>10 15 10</td>
<td>10 15 10</td>
</tr>
</tbody>
</table>

a Children in household in Whitehall II.
b In FPS, death of relative or divorce for the preceding part 2012 only (not one year previous to baseline).
years, the median length of the first event of long-term sickness absence spells was 29 days (15–436), 28 days (15–370), and 28 days (15–724) in Whitehall II, FPS and GAZEL, respectively. Clear gender differences were evident for marital status, with more men being married/cohabiting than women (table 1). Longstanding illness was most prevalent in FPS compared to GAZEL and Whitehall II. Both high job strain and informal caregiving were more prevalent for women (table 1), and informal caregiving was more prevalent in GAZEL with 27% of men and 30% of women providing care, compared to 10% and 15% in FPS and 10% and 13% in Whitehall II.

For men, neither informal caregiving nor high job strain were associated with a higher risk of long-term sickness absence in the unadjusted analyses and the multiple adjusted analyses, as seen in table 2. Among women, high job strain and informal caregiving were associated with long-term sickness absence in the unadjusted model, which was slightly attenuated in the multiple adjusted model, as seen in table 2.

Stratifying by hours of caregiving in a sub-analysis, caregiving >4 weekly hours was a risk factor for sickness absence among women in the unadjusted and multiple adjusted analyses, as seen in table 2. No associations were found between weekly hours of caregiving and long-term sickness absence for men in neither the unadjusted nor the multiple adjusted models.

Looking at the joint exposure, high job strain and no informal caregiving predicted long-term sickness absence for men in the unadjusted model with (HR 1.30, 95% CI 1.01–1.67). However, this was considerably attenuated in the multiple adjusted model with (HR 1.14, 95% CI 0.97–1.35), as seen in figure 1. For women, no high job strain and informal caregiving (HR 1.15, 95% CI 1.01–1.29) was a predictor of long-term sickness absence in the multiple adjusted model, but the excess risk from exposure to both high job strain and informal caregiving was not more than expected (HR 1.20, 95% CI 1.03–1.41), (P=0.766, SI=0.95), as seen in figure 1. All estimates in the joint exposure analyses for both men and women were attenuated in the multiple adjusted models compared to the unadjusted models.

Sensitivity analyses using multiple imputations did not change results substantially (appendix), indicating that the partial missing data have not introduced any noteworthy selection bias. Furthermore, there was no noteworthy change in results from the sensitivity analysis using only first event of long-term sickness absence or the analysis with exclusion of individuals >58 years of age. Also, no noteworthy change in estimates was found in analyses on Whitehall II including weekly work hours. In the sensitivity analyses looking separately at job demands and job control, double exposure to both high demands or low control and informal caregiving were predictors of sickness absence, with fairly similar estimates as with the main analyses using the combined job strain model. Furthermore, for men, joint exposure from low control and informal caregiving was less than expected given the size of their individual effects (P=0.02, SI=0.05). Detailed results are not shown but can be obtained from the first author upon request.

**Discussion**

We investigated the joint exposure of job strain and informal caregiving as predictors of long-term sickness

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**Table 2.** Individuals associations between job strain, informal caregiving and long-term sickness absence (SA). [HR=hazard ratio; HRadj=adjusted for age, married/cohabiting, children, occupational grade, death of relative and/or divorce, previous long-term sickness absence (SA), and longstanding illness; 95% CI=95% confidence interval.]

<table>
<thead>
<tr>
<th></th>
<th>Individuals with ≥1 long-term SA spell</th>
<th>Men</th>
<th></th>
<th></th>
<th>Women</th>
<th></th>
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<tbody>
<tr>
<td><strong>High job strain</strong></td>
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<tr>
<td>No</td>
<td>1114</td>
<td>1.00</td>
<td>95% CI: 1.00</td>
<td>1.00</td>
<td>2350</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>211</td>
<td>1.24</td>
<td>95% CI: 0.99–1.54</td>
<td>0.99–1.28</td>
<td>734</td>
<td>1.19</td>
<td>0.94–1.36</td>
</tr>
<tr>
<td><strong>Informal caregiving</strong></td>
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</tr>
<tr>
<td>No</td>
<td>1101</td>
<td>1.00</td>
<td>95% CI: 0.92–1.20</td>
<td>0.88–1.16</td>
<td>2572</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>260</td>
<td>1.05</td>
<td>95% CI: 0.80–1.55</td>
<td>0.85–1.34</td>
<td>654</td>
<td>1.15</td>
<td>1.02–1.30</td>
</tr>
<tr>
<td><strong>Weekly hours caregiving</strong></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>0</td>
<td>768</td>
<td>1.00</td>
<td>95% CI: 0.92–1.20</td>
<td>0.88–1.16</td>
<td>2283</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>1–4</td>
<td>53</td>
<td>1.10</td>
<td>95% CI: 0.84–1.43</td>
<td>0.83–1.43</td>
<td>207</td>
<td>0.78</td>
<td>0.29–2.08</td>
</tr>
<tr>
<td>&gt;4</td>
<td>25</td>
<td>0.89</td>
<td>95% CI: 0.55–1.45</td>
<td>0.80–1.53</td>
<td>205</td>
<td>1.25</td>
<td>1.09–1.44</td>
</tr>
</tbody>
</table>

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absence. Informal caregiving responsibilities were common with prevalence’s ranging between 10–30% across cohorts. With regards to sickness absence, 12% of men and 21% of women experienced ≥1 spell of long-term sickness absence during a 2-year period. We found that high job strain and informal caregiving were predictors of long-term sickness absence among women, and women jointly exposed to high job strain and informal caregiving had a 34% increased risk of sickness absence compared to women with no high strain and no informal caregiving. However, contrary to our hypothesis, being doubly exposed to informal caregiving and job strain was not associated with an excess risk of sickness absence compared to the expected risk from their individual effects. We found no associations between informal caregiving and job strain on sickness absence among men.

Informal caregiving as a predictor of long-term sickness absence among women may be a consequence of role overload ascribed to additional responsibilities in daily living (10). Women have been increasingly engaged in full-time employment, but still carry the largest household workload (23, 46), and might therefore be more likely than men to experience any health consequences due to the joint effects of paid work, household chores, and informal caregiving (47, 48). In line with this, previous studies have shown that women are more likely to take the role as primary caregiver (49–51), and more often assist with basic and instrumental activities of daily living (49, 52). Thus, the additional role as informal caregiver may be more burdensome for women compared to men.

A previous study using the GAZEL cohort (22), found no gender difference for individuals exposed to high work-family demands in risk of sickness absence. However, in that study family demands were defined as number of economically dependent family members, and informal caregiving may encompass a much greater emotional burden than having economically dependents. In line with our findings, a previous study from the GAZEL cohort also found tendencies for gender differences, but here, sickness absence was restricted to psychiatric disorders and family demands were also defined as number of economically dependents (21).

Job strain as a predictor of sickness absence in women is in line with findings from longitudinal studies in nurses (13, 53); and another longitudinal study covering a broader range of workers found that the strongest mediator in the association between gender and sickness absence was job strain (54). Also, a recent longitudinal population-based study on both men and women found support for the association between job strain and long-term sickness absence (12). In the latter study, long-term sickness absence was defined as absence >16 days, which is somewhat similar to our study. However, job strain was categorized in a variable with three groups: high, active or passive, and low strain. Thus, the reference category is different from our study. Other studies
have found high job demands (19) and low control (55) as predictors of sickness absence. One of the reasons why we chose to look at the combined job strain measure instead of demands and control separately was that it has been shown that job strain (even without positive interaction between job demands and control) predicts outcomes such as coronary heart disease better than low job control, when analyses are adjusted for socioeconomic status (56). Furthermore, sensitivity analyses on job demands and control did not change conclusions.

Even though we found a moderately higher risk of sickness absence among women who were exposed to both informal caregiving and job strain, this excess risk was not more than expected from their individual effects. These results are in line with recent findings showing no interactive effect of job strain and informal caregiving in relation to allostatic load (57), which is a biological measure of stress associated with poor health (58, 59). According to the role enhancement theory (7), a possible explanation for no interaction between high job strain and informal caregiving is that work may have acted as a buffer against stress from caregiving and vice versa (8). However, another possibility is a healthy caregiver effect, i.e., those who undertake informal caregiving tasks may have more personal resources to begin with and are therefore also less likely to suffer any negative health consequences from informal caregiving. Based on this, we may have underestimated the effect of caregiving on sickness absence. It is also important to consider that individuals may have diverse experience with caregiving responsibilities. A Canadian study for example showed that >70% of caregivers were positive about the caregiving role (60); another study found that, despite difficulties, caregivers in general expressed great satisfaction with providing caregiving (61). However, other studies have shown that informal caregiving may compromise the caregivers’ own health and interfere with working life (3–6). Unfortunately, we had no information on whether caregiving was perceived as burdensome in the present study. Hours of caregiving may be used as a proxy measure of workload, but our data on this variable was limited to Whitehall II, and we only found tendencies indicating that more hours of caregiving is associated with higher risk of sickness absence among women. Differentiating between those who experienced high and low caregiver burden in future studies may broaden our understanding of the relationship.

Informal caregiving was more prevalent in GAZEL compared to Whitehall II and FPS. This may seem counterintuitive as the question on informal caregiving in GAZEL only encompasses care for elderly relatives, whereas caregiving in the other cohorts also include care for sick and disabled relatives. However, a possible explanation for this discrepancy in prevalences is that France has a welfare system in which both family and state have legal obligations regarding caregiving of disabled and elderly family members; whereas in Finland the state has clear obligations but families do not. In the UK, the rules of legal obligations for sick/disabled family members were somewhat unclear in the 1990s (ie, the baseline of this study) (62) compared to today. Still, the wording of the question in Whitehall and FPS might also have lead the participants to understand that only care of people with severe disabilities was included. Despite the differences in the prevalence of caregiving and the questions applied, we found low heterogeneity in the association between caregiving and sickness absence in the three cohorts. This association would most likely have been stronger if the question in the GAZEL study had also encompassed care for disabled/handicapped children and spouses. A limitation of this study is the different time periods used for baseline. Based on this, it cannot be ruled out that there have been changes/developments in work- and family-related policies or culture between the time periods that could have affected the outcome. We found some heterogeneity in the job strain and sickness absence association, showing a tendency for a time trend; with no association in Whitehall (1994–1996), a tendency for an increased risk in GAZEL (2000–2002), and a stronger tendency in FPS (2012–2014). This, it may be a time-trend where sickness absence has become easier and more socially acceptable. However, the discrepancy in cohort estimates may also be due to cultural differences.

Variables such as alcohol intake, smoking status, body mass index, and depression have been included as potential confounders in similar studies (21, 22, 63). We have chosen not to include these variables in our analysis as they may be mediators on the causal pathway between job strain and sickness absence rather than confounding factors. Thus, a meta-analysis has shown that work–family interference and family–work interference have been associated with depression and substance use/abuse as outcomes (64); and depression, which may be partly a consequence of exposure to work stressors, has been shown to be a highly contributory cause of sickness absence (65). A limitation in our analyses is that other potentially important covariates shown in the directed acyclic graph (DAG) (www.sjweh.fi/index.php?page=data-repository) were not available, such as personality, spouse work status, household income and organizational changes at the workplace, which may be associated with informal caregiving, job strain and sickness absence (66, 67). However, household income is highly associated with being married and occupational grade (for which we adjusted), and the association between spouse work status and long-term sickness absence is likely to go through household income.

Sensitivity analyses on Whitehall II, including weekly work hours as a potential confounder, did not
change estimates. In line with this, there are some inconsistencies in findings from previous studies on the association between long work hours and sickness absence. A systematic review found that long work hours predict sickness absence and ill health (68), while another study found no association (69). A meta-analysis actually found that long working hours was a protective factor against sickness absence (19). The authors suggested the healthy worker effect as a plausible explanation and that some individuals with long working hours have highly demanding jobs and may feel pressure to be working even though they are sick (19).

To our knowledge, this is the first study to prospectively investigate the joint effects of job strain and informal caregiving on long-term sickness absence. Based on this large population of European workers, we have shown that informal caregiving is common among European workers and women with high job strain and/or informal caregiving responsibilities are at higher risk of long-term sickness absence compared to women with no high strain and no informal caregiving responsibilities. Presently, there may be unmeasured confounding from factors such as personality traits and organizational changes at workplaces.

Acknowledgements

We gratefully acknowledge the work of the teams behind the GAZEL, FPS, and Whitehall II cohorts.

The Danish Work Environment Foundation financially supported the first author (grant no. 12-2013-03).

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Scand J Work Environ Health 2017, vol 43, no 1


Received for publication: 27 November 2015
Co-authorship declarations
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**Title of PhD thesis:**

Informal caregiving, psychosocial work factors, and risk of stress-related disease and sickness absence

**This declaration concerns the following article:**

Informal caregiving and diurnal patterns of salivary cortisol in economically gainful and non-gainful men and women: Result from the Whitehall II study

**The PhD student's contribution to the article:**

*Please use the scale A,B,C below as benchmark ( )*  

| 1. Formulation/identification of the scientific problem that from theoretical questions need to be clarified. This includes a condensation of the problem to specific scientific questions that is judged to be answerable by experiments | A/B |
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| 3. Involvement in the experimental work | A/C |
| 4. Presentation, interpretation and discussion in a journal article format of obtained data | A/C |

*Benchmark scale of the PhD student's contribution to the article*

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B. refers to:  
Has contributed considerably to the co-operation  
34-66 %

C. refers to:  
Has predominantly executed the work independently  
67-100 %

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Title of PhD thesis:
Informal caregiving and psychosocial work factors as risk factors for sickness absence and stress-related disease

This declaration concerns the following article:
Informal caregiving as a risk factor for type 2 diabetes in individuals with favourable and unfavourable psychosocial work environments: A longitudinal multi-cohort study

The PhD student’s contribution to the article:

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C. refers to: Has predominantly executed the work independently 67-100 %

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**Title of PhD thesis:** Informal caregiving, psychosocial work factors, and risk of stress-related disease and sickness absence

This declaration concerns the following article:

Weekly hours of informal caregiving and paid work and risk of cardiovascular disease

**The PhD student's contribution to the article:**

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- Involvement in the experimental work

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## Title of PhD thesis:

Informal caregiving and psychosocial work factors as risk factors for sickness absence and stress-related disease

## This declaration concerns the following article:

Job strain and informal caregiving as predictors of long-term sickness absence: A longitudinal multi-cohort study

## The PhD student’s contribution to the article:

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