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

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Abstract

Aim: To examine whether informal caregiving is associated with increased risk of type 2 diabetes and whether job strain and social support at work modify this association. Research Methods: We pooled individual-participant data from three cohort studies (the French GAZEL cohort, the Swedish Longitudinal Occupational Survey of Health, and the British Whitehall II study), 21,243 individuals. Informal caregiving was defined as unpaid care for a closely related person. Job strain was assessed with the demand/control model and questions on coworker and supervisor support were combined in a measure of social support at work. Incident type 2 diabetes was ascertained using register-based, clinically assessed, and self-reported data. Results: 1,058 participants got type 2 diabetes during 10 years follow-up. Neither informal caregiving (OR=1.10, 95%CI:0.92-1.30) nor high job strain (OR=1.04, 95%CI:0.86-1.26) were associated with type 2 diabetes risk. Low social support at work was a risk factor for type 2 diabetes (OR=1.18, 95%CI:1.02-1.37). Individuals jointly exposed to informal caregiving and low social support at work were at higher risk of type 2 diabetes (OR=1.40, 95%CI:1.08-1.82) compared to individuals with no informal caregiving and high social support at work; test for interaction (multiplicative: p=0.04, additive: synergy index=10). Conclusion: Informal caregiving was not independently associated with risk of type 2 diabetes. However, low social support at work was a risk factor for type 2 diabetes and caregivers with low social support at work had an even higher risk of type 2 diabetes.

Keywords: Type 2 diabetes, Informal caregiving, Meta-analysis, Social support, Job strain, Interaction

Introduction

Individuals who provide informal caregiving for disabled and elderly relatives make a large contribution to the lives of these people and save the health-care system considerable expenses [1]. Informal caregiving, which is defined as unpaid care for a sick, disabled or elderly family member or other closely related persons [2], may be associated with positive aspects such as companionship and a feeling of reward [3]. However, providing informal caregiving may also render individuals vulnerable to negative health consequences due to the potential emotional and physical strain, which may accompany informal caregiving responsibilities [4, 5]. It has previously been shown that informal caregiving is associated with high levels of allostatic load, which is a cumulative biological marker of ill health [6]; and we have recently shown that informal caregiving predicts long-term sickness absence in women [7].

Type 2 diabetes 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], and stress is therefore hypothesized to play a causal role in the etiology of type 2 diabetes. 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 higher risk of type 2 diabetes [10]. Furthermore, an unhealthy lifestyle, which encompass strong risk factors for type 2 diabetes [11] may be a consequence of caregiving stress [12]. However, the relationship between informal caregiving stress and risk of type 2 diabetes has not yet been investigated in population-based studies.

Among gainfully employed individuals, work characteristics may modify the association between informal caregiving and risk of type 2 diabetes. A recent large-scale meta-analysis by

the Individual-Participant Data in Working population (IPD-Work) consortium found that job strain, i.e. the combination of high psychological demands at work and low job control, is a risk factor for type 2 diabetes [11]. In addition, a longitudinal study found that job strain was a risk factor for type 2 diabetes for 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 risk of type 2 diabetes.

The overall objective of the present study was to assess the association between informal caregiving and incident type 2 diabetes in gainfully employed individuals. We further aimed to determine whether there was an interaction between informal caregiving and psychosocial work factors on risk of type 2 diabetes based on two alternative hypotheses (Figure 1). First, according to the role strain model [14] we hypothesized that accumulation of stress from caregiving and work may be particularly harmful and therefore we assessed whether the joint effect of informal caregiving and job strain exceed the combination of their individual effects in risk of type 2 diabetes. Second, according to the stress-buffer hypothesis [15] we expected that a supportive work environment may function as a resource for informal caregivers and we aimed to determine whether social support at work reduces the risk of type 2 diabetes associated with informal caregiving.

Methods

Study population

We used longitudinal data from the GAZEL cohort from 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 have information on informal caregiving, psychosocial work factors and diabetes, and they represent a wide range of

employees from different social care systems. The GAZEL cohort was established in 1989 and includes 20,625 employees of the French national gas and electricity company. SLOSH is an open cohort, which was established in 2006 and comprises 40,877 individuals representative of the Swedish workforce. Whitehall II was established in 1985 and includes 10,308 British civil servants from 20 London-based departments. We used data from year 2000 as baseline in GAZEL (response rate 71%), year 2008 in SLOSH (response rate 61%), and years 1991-1994 in Whitehall II (response rate 87%). A total of 24,636 men and women were gainfully employed at baseline. We excluded 805 individuals with diabetes at baseline (self-reported or diagnosed) and 2,588 due to non-response or missing information on diabetes, informal caregiving and/or ≥1 covariate(s). The total study population constituted 21,243 individuals (Appendix A). Participants gave consent to participate in the cohort studies and all three cohorts were approved by the respective ethics committees.

Informal caregiving

For assessment of informal caregiving, individuals were asked if they provide regular care for an aged person (>65 years) in GAZEL and if they provide care for an aged or disabled relative in Whitehall II and SLOSH. Further information on weekly hours of caregiving was available in Whitehall II and SLOSH.

Psychosocial work factors

Job demands were assessed with five items in GAZEL and SLOSH and four items in Whitehall II, and encompass statements such as: “My job requires working very fast”. High job demands were defined as a score above the median score within 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 were assigned the same weight as the four items in skill discretion, in calculation of the job control scores. Low job control was defined as a score below the median score within the specific cohort study [19]. In accordance with the job strain model [20] and using the harmonized version proposed by the IPD work consortium [19], we defined high job strain 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 job strain.

Social support at work was defined as a combination of support from superiors and co-workers, in line with the iso-strain model by Karasek [20]. Both aspects of work support were based on one question and were 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 coworker 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 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. In GAZEL, information on psychosocial work factors in 1999 was used as a proxy for information in 2000, as these factors were not measured in the 2000 wave of the study.

Type 2 diabetes

We excluded individuals <30 years to minimize the risk of incident type 1 diabetes in the study [21]. We used a combination of diagnosed, clinically determined and self-reported

information on type 2 diabetes. In GAZEL self-reported incidences 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 complains the past two years?", and in Whitehall II, the question was: "Has a doctor ever told you that you have diabetes?". In Whitehall II we also had objective measures of diabetes ascertained by Oral Glucose Tolerance Test [22] along with self-reported diabetes medication. In SLOSH, self-reported information was supplemented with information on diabetes from hospital admissions. Incident type 2 diabetes was assessed during 10 years follow-up (only six years follow-up in SLOSH).

Covariates

We identified potential confounders based on existing knowledge using directed acyclic graphs (Appendix B-D) [23]. These included: Age, sex, married/cohabiting (yes/no), occupational grade (low wage and manual laborers, lower non-manual and midlevel managers, and upper non-manual workers and managing staff), and follow-up time to make the statistical model resemble a cox model with time from exposure as the underlying time variable. Time points included were two years, four years, six years, and 10 years. Further, in sensitivity analyses we included smoking (yes/no) and BMI (<25: underweight/normal weight, 25-30: overweight, and ≥30: obese), which may be strong risk factors for type 2 diabetes, but are likely to be consequences of caregiving and work stress [24], and thereby intermediate variables.

Statistical analyses

We applied logistic regression in random effect multi-level analyses with individual participant data [25]. Heterogeneity among cohort specific estimates was assessed with I^2 statistics. We estimated odds ratios (OR) and 95% confidence intervals (CI) of the associations between informal caregiving, job strain, social support at work and incident type

2 diabetes in up to 10 years follow-up. We looked at individuals jointly exposed to informal caregiving and job strain/low social support at work, with individuals with no caregiving and no high strain/high social support as the reference groups. We determined the potential interaction by assessing both deviation from multiplicativity (by including a product term in the logistic regression models) and deviation from additivity using the synergy index, in accordance with the recommendations in the STROBE guidelines [26]. The synergy index can be interpreted as the excess risk from double exposures when there is interaction relative to the risk from exposure without interaction [27]. CI's for the synergy index were not calculated because of highly imprecise intervals, due to division with values close to zero. We made three analytic models; Model 1 was unadjusted, Model 2 was adjusted for potential baseline confounders: age, sex, married/cohabiting, occupational grade, and follow-up time, and Model 3 was further adjusted for smoking and BMI. Model 2 is presented as the main analysis since smoking and BMI are likely to be intermediate variables on the causal pathway between informal caregiving and type 2 diabetes. There were no interactions between sex and informal caregiving/psychosocial work factors and analyses are therefore presented combined for men and women. In sub analyses using data from SLOSH and Whitehall II we investigated the impact of weekly hours of caregiving (divided into no caregiving, 1-4 weekly hours of caregiving per week, and >4 hours of caregiving per week, the latter corresponding with caregiving at on average at least one hour each weekday) to determine potential dose-effects relations [7].

Sensitivity analyses were carried out to assess the robustness of results (Appendix E). First, we looked separately at supervisor and coworker support and the interaction with informal caregiving, on the risk of type 2 diabetes, to see if one type of support (or lack of) was stronger associated with type 2 diabetes than the other. Secondly, we utilized time-to-event data available in GAZEL and Whitehall II to estimate hazard ratios (HR) and 95% CI, in

order to assess whether this more detailed timing of information would affect the results. Thirdly, we included weekly work hours as a potential confounder in analyses of Whitehall II and SLOSH data. In a fourth sensitivity analysis, we excluded the first four years of follow-up to minimize reverse causation [11]; e.g. individuals with undiagnosed diabetes may have symptoms that may affect their sensibility and perception of job strain and social support. Lastly, we investigated the impact of duration of caregiving using Whitehall II data, by looking at the risk of type 2 diabetes in individuals who were caregivers at baseline and 3-4 years later compared to non-caregivers. We used the statistical software package STATA version 14/IC for all analyses.

Results

A total of 1,058 incident cases of type 2 diabetes were registered in up to 10 years 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 provided informal caregiving. Additional data showed that 86% of caregivers in GAZEL had provided caregiving for >6 months. A total of 22% experienced high job strain, and 36% low social support at work at baseline. While the distribution of these characteristics were reasonably comparable in SLOSH and Whitehall II, a much larger proportion provided informal caregiving in GAZEL (30% vs. 9% and 11%), and a considerable higher proportion experienced low social support at work (55% vs. 37% and 19% in SLOSH and Whitehall II, respectively). Furthermore, in the total study population low social support at work differed between caregivers and non-caregivers with 45% and 34% respectively.

Figures 2a-c show the results of the associations between informal caregiving, high job strain, low social support and 10-year occurrence of type 2 diabetes, respectively. Informal caregiving was not associated with risk of type 2 diabetes (OR=1.10, 95%CI: 0.92-1.30) as

seen in Figure 2a. Of the two potential effect modifiers high job strain was not associated with risk of type 2 diabetes, (OR=1.04, 95%CI: 0.86-1.26), whereas low social support at work was associated with higher risk type 2 diabetes (OR=1.18, 95%CI:1.02-1.37) (Figure 2b and Figure 2c).

We found no excess risk of type 2 diabetes for individuals jointly exposed to informal caregiving and high job strain (multiplicative: p=0.78, additive: synergy index=1) as seen in Figure 3. However, for informal caregiving and low social support there were both a multiplicative and additive interaction between informal caregiving and social support at work, showing that there was an excess risk of type 2 diabetes from double exposure, compared to what would be expected from their individual associations (multiplicative: p=0.04, additive: synergy index=10).

Using data from Whitehall II and SLOSH we found no association between weekly caregiving hours and type 2 diabetes during 10 years follow-up, in groups providing 1-4 (OR=0.96, 95%CI: 0.64-1.43) and >4 hours (OR=1.14, 95%CI: 0.79-1.63) of weekly caregiving compared with no caregiving. Investigating the impact of duration of caregiving using Whitehall II data, individuals who were caregivers at baseline and 3-4 years later, were not at increased risk of type 2 diabetes compared to individuals who were non-caregivers at baseline and 3-4 years later (OR=1.22, 95%CI: 0.78-1.88). Including potential mediators, smoking and BMI had very little impact on results. The same applies for analyses including family history of diabetes, number of work hours, time-to-event data and exclusion of the first four years of follow-up. See Appendix E for further details.

Discussion

We found no association between informal caregiving and risk of type 2 diabetes. However, we found that low social support at work was associated with increased risk of type 2 diabetes, and caregivers with low social support were at increased risk of type 2 diabetes compared to what would be expected from their individual associations with type 2 diabetes.

Results showing no association between informal caregiving and type 2 diabetes are in contrast to our hypothesis, which was based on the potential causal path from stress associated with informal caregiving to the development of type 2 diabetes. Assuming that long-term stress may lead to type 2 diabetes [9], it is likely that having a family member with severe illness or disability may be stressful regardless of whether or not you provide caregiving for this person [28]. However, our null finding may also be due to self-selection out of caregiving roles for individuals not having the personal resources or health to provide informal caregiving [29]. Thus, those individuals who are most affected by the potential emotional strain of informal caregiving and thus being more likely to develop type 2 diabetes may have left the labor market to cope with the responsibilities of informal caregiving [30]. Based on this premise, the association between informal caregiving and type 2 diabetes may be underestimated due to a healthy caregiver bias.

The higher risk of type 2 diabetes among those with low social support at work observed in this study is a novel finding, supporting the direct effect hypothesis. Thus, low social support may be a stressor in itself with direct influences upon psychological symptomatology, irrespective of the presence of other stressful circumstances [31], which may potentially increase risk of type 2 diabetes [9]. A previous study using Whitehall II data found no association between social support at work and type 2 diabetes [13]. However, they used the iso-strain model, which includes four items on coworker support and supervisor support respectively, and define low social support as the lowest tertile. Due to harmonization issues, we included only one question on coworker and supervisor support respectively, choosing the

most comparable questions across cohort studies. A similar approach has been applied in a previous study investigating the association between supervisor support and sickness absence in diabetic individuals, using the same cohort studies [32]. Low social support at work was more common among caregivers compared to non-caregivers, which is a noteworthy finding, given the mitigating effect of social support at work on health [33-35].

Results did not support the stress-buffer hypothesis [15] as we found no individual association between informal caregiving and type 2 diabetes. However, we found both a multiplicative and additive interaction between low social support at work and informal caregiving, showing that the association between low social support at work and risk of type 2 diabetes was amplified by informal caregiving. Thus, the impact of not having social support at work from supervisors and coworkers on risk of type 2 diabetes may be greater for individuals providing informal caregiving compared to non-caregivers.

We found no association between high job strain and type 2 diabetes, which is in contrast to the large meta-analysis by the IPD-Work consortium [11]. However, we only included three of the 13 IPD-Work consortium cohorts including a total population of 124,808 individuals. They showed a weak association between job strain and type 2 diabetes, but we may not have had sufficient power to replicate this finding.

Methodological considerations

Strengths of the study are the longitudinal design and the large study population of European workers. Thus, the representative sample of the Swedish workforce, a sample of civil servants from London, and a sample of workers from urban and rural districts in France representing both blue and white-collar workers, strengthen the generalizability to the general working population in western countries. There was no follow-up data on 1,546 eligible individuals.

However, this non-response was not associated with our exposures and therefore it is unlikely that non-response have biased our estimates [36].

Informal caregiving was more prevalent in GAZEL compared to SLOSH and Whitehall II. A likely explanation is that informal caregiving is embedded in the French culture and law, to a higher degree than the UK and Sweden [37], but the discrepancy could also be due to the different phrasing of the question on informal caregiving. The question in Whitehall II and SLOSH covers caregiving for disabled relatives in addition to care for the elderly, which may lead participants to only tick the box as informal caregivers if their relatives have severe disabilities. In GAZEL, participants may have ticked the box even though their relatives have no severe disabilities, but still require some assistance with activities of daily living. Further, in GAZEL informal caregiving does not cover caregiving for disabled children and spouses (≤65 years), which may be a more emotional demanding caregiving task than care for parents or parents in-law, and may therefore be more detrimental for your health [38]. This potential misclassification could lead to a small underestimation of the association between informal caregiving and type 2 diabetes [36].

We were not able to thoroughly investigate the impact of duration of informal caregiving. However, in a sensitivity analysis we found a tendency that caregivers at baseline who were still providing caregiving 3-4 years later, had a greater risk of type 2 diabetes compared to results from the main analyses, with only baseline information on caregiving. Thus, for long-term caregivers the association with type 2 diabetes may be underestimated.

A large study based on data from 48 low- and middle-income countries have shown that there is a higher percentage of informal caregivers in urban areas compared with rural areas [39], and individuals in urban areas are probably more likely to be diagnosed with type 2 diabetes, due to more frequent visits with general practitioners. Based on this, there may be bias away

from the null due to lack of adjustment of area of residence [36]. Physical inactivity and alcohol consumption was not included in the analytical model as they may be mediators on the pathway from informal caregiving to type 2 diabetes, and therefore should not be adjusted for. Furthermore, these variables were difficult to harmonize and had a great number of missing values, and thus, was not included in the sensitivity analysis along with smoking and BMI. In addition, the analyses including smoking and BMI also showed that these lifestyle factors had little impact on results, and the same would be suspected from physical inactivity and alcohol consumption.

Different measures for incident type 2 diabetes were applied in the respective cohorts [40]; However, in GAZEL were we only had self-reported data, 7% of participants had incident type 2 diabetes during 10 years follow-up, with only 6% in Whitehall II. The older study population in GAZEL most likely explains this finding. An incidence of 3% in SLOSH is also not surprising as we had only six years follow-up in this cohort. Based on the less detailed information in GAZEL and SLOSH, there may be an under-ascertainment of type 2 diabetes compared to the true number of individuals who would have been diagnosed, had all individuals undergone an oral glucose tolerance test. However, this misclassification is unlikely to be related to the questions on informal caregiving and psychosocial work factors, and results are not likely biased by this issue [36].

In conclusion, we found no association between informal caregiving at baseline and incident type 2 diabetes, but for long-term caregivers the association may be stronger. We found that perceived low social support at work may be a risk factor for type 2 diabetes and caregivers with low social support were at higher risk of type 2 diabetes compared to what would be expected from their individual associations with type 2 diabetes. These findings emphasize the importance of social support at work, especially for individuals providing informal caregiving.

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References

1. Gibson MJ, Houser A. Valuing the Invaluable: A New Look at the Economic Value of Family Caregiving. AARP Public Policy Institute. 2007.

2. Informal caregiving definition [Internet]. [cited 20th October 2016]. Available from: http://definitions.uslegal.com/i/informal-caregiver/

3. Cohen CA, Colantonio A, Vernich L. Positive aspects of caregiving: rounding out the caregiver experience. Int J Geriatr Psychiatry 2002:184-8.

4. Nielsen M, Hansen J, Ritz B, Nordahl H, Schernhammer E, Wermuth L, Rod N. Cause-Specific Mortality Among Spouses of Parkinson Disease Patients. Epidemiology 2014;25:225-32.

5. Roepke S, Mausbach B, Patterson T, Von Känel R, Ancoli-Israel S et al. Effects of Alzheimer Caregiving on Allostatic Load. Journal of Health Psychology 2011;16:58-69.

6. Dich N, Lange T, Head J, Rod NH. Work stress, caregiving, and allostatic load: prospective results from the Whitehall II cohort study. Psychosomatic medicine 2015;77:539.

7. Mortensen J, Dich N, Lange T. Job strain and informal caregiving as predictors of long-term sickness absence: A longitudinal multi-cohort study. Scand J Work Environ Health. 2017;43:5-14.

8. Weng W, Liang Y, Kimball ES, Hobbs T, Kong SX, Sakurada B, Bouchard J. Decreasing incidence of type 2 diabetes mellitus in the United States, 2007-2012: Epidemiologic findings from a large US claims database. Diabetes research and clinical practice 2016;117:111-8.

9. Tabák AG, Jokela M, Akbaraly TN, Brunner EJ, Kivimäki M, Witte DR. Trajectories of glycemia, insulin sensitivity and insulin secretion preceding the diagnosis of type 2 diabetes: the Whitehall II study. Lancet. 2009;373:2215-2221.

10. Kupper N, Aiaanse MC, Pouwer F. Does emotional stress cause Type 2 Diabetes Mellitus? A review from the European Depression in Diabetes (EDID) Research Consortium. Discovery Medicine 2010;9:112-8.

11. Nyberg ST, Fransson EI, Heikkilä K, Ahola K, Alfredsson L, Bjorner JB, et al. Job strain as a risk factor for type 2 diabetes. Diabetes Care. 2014;37:2268-2275.

12. Burton W, Chen C, Conti D, Pransky G, Edington D. Caregiving for Ill Dependents and Its Association with Employee Health Risks and Productivity. Journal of Occupational and Environmental Medicine 2004;46:1048-56.

13. Heraclides A. Psychosocial Stress at Work Doubles the Risk of Type 2 Diabetes in Middle-Aged Women. Diabetes Care. 2009;32:2230-5.

14. Goode WJ. A theory of role strain. New York, NY: American sociological review; 1960. 483-496.

15. Cohen S, Wills TA. Stress, Social Support, and the Buffering Hypothesis. Psychological Bulletin 1985;98:310-57.

16. Goldberg M, Leclerc A, Bonenfant S, Chastang JF, Schmaus A, Kaniewski N, Zins M. Cohort profile: the GAZEL Cohort Study. International journal of epidemiology 2007;36:32-9.

17. Leineweber C, Baltzer M, Magnusson Hanson LL, Westerlund H. Work-family conflict and health in Swedish working women and men: a 2-year prospective analysis (the SLOSH study). European journal of public health 2013;23:710-6.

18. Marmot M, Brunner E. Cohort Profile: the Whitehall II study. International journal of epidemiology 2005;34:251-6.

19. Fransson EI, Nyberg ST, Heikkilä K, Alfredsson L, Bacquer DD, Batty DG, et al. Comparison of alternative versions of the job demand-control scales in 17 European cohort studies: the IPD-Work consortium. BMC Public Health. 2012;12:62.

20. Karasek R, Theorell T. Healthy work. New York: Basic Books Inc.; 1990.

21. Lau CJ, Pisinger C, Husemoen LLN. Effect og general health screening and lifestyle counseling on incidence of diabetes in general population: Inter99 randomized trial. Preventive Medicine 2016;91:172-9.

22. Virtanen M, Ferrie JE, Tabak AG et al. Psychological Distress and Incidence of Type 2 Diabetes in high risk and low risk populations: The Whitehall II Cohort Study. Diabetes Care. 2014;3:2091-2097.

23. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. Epidemiology. 1999:10:37-48.

24. Schulz R, Sherwood PR. Physical And Mental Health Effects Of Family Caregiving. Journal of Social Work Education 2008;44:105-13.

25. DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. Contemporary clinical trials 2015;45:139-45.

26. Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, Poole C, Schlesselman JJ, Egger M. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. PLoS medicine 2007;4:1628-54.

27. de Mutsert R, Jager KJ, Zoccali C, Dekker FW. The effect of joint exposures: examining the presence of interaction. Kidney international 2009;75:677-81.

28. Amirkhanyan AA, Wolf DA. Caregiver Stress and Noncaregiver Stress: Exploring the Pathways of Psychiatric Morbidity. The Gerontologist 2003;43:817-27.

29. O'Reilly D, Connolly S, Rosato M, Patterson C. Is caring associated with an increased risk of mortality? A longitudinal study. Social science & medicine. 2008;67:1282-90.

30. Lee Y, Tang F. More caregiving, less working: caregiving roles and gender difference. Journal of applied gerontology. 2015;34:465.

31. Thoits PA. Social Support: Theory, Research and Applications. Kluwer; 1985:52-72.

32. Ervasti J, Kivimäki M, Dray-Spira R, Head J, Goldberg M, Pentti J, Jokela M, Vahtera J, Zins M, Virtanen M. Psychosocial factors associated with work disability in men and women with diabetes: a pooled analysis of three occupational cohort studies. Diabetic Medicine 2015:1-10.

33. Michie S, Williams S. Reducing Work Related Psychological Ill Health and Sickness Absence: A Systematic Literature Review. Occupational and Environmental Medicine 2003;60:3-9.

34. Netterstrøm B, Conrad N, Bech P, Fink P, Olsen O, Rugulies R, Stansfeld S. The Relation between Work-related Psychosocial Factors and the Development of Depression. Epidemiologic Reviews 2008;30:118-32.

35. Theorell T, Jood K, Jarvholm LS, Vingard E, Perk J, Ostergren PO, Hall C. A systematic review of studies in the contributions of the work environment to ischaemic heart disease development. 2016;26:70-77.

36. Savitz DA. Interpreting epidemiologic evidence. Oxford: Oxford University Press; 2003.

37. Sundstrom G, Malmberg B, Castiello MS, del Barrio E, Castejon P, Tortosa Ma, Johansson L. Family Care for Elders in Europe: Policies and Practices1. Caregiving contexts: cultural, familial, and societal implications 2007:235.

38. Lee S, Colditz GA, Berkman LF, Kawachi I. Caregiving and risk of coronary heart disease in U.S. women. American Journal of Preventive Medicine 2003;24:113-9.

39. Hosseinpoor AR, Bergen N, Chatterji S. Socio-demographic determinants of caregiving in older adults of low- and middle-income countries. Age and ageing 2013;42:330-8.

40. Oksanen T, Kivimäki M, Pentti J, Virtanen M, Klaukka T, Vahtera J. Self-Report as an Indicator of Incident Disease. Annals of Epidemiology 2010;20:547-54.

Table 1. Baseline characteristics of participants from GAZEL, Whitehall II and SLOSH

	GAZEL	**SLOSH**	**Whitehall II**	**Total**	**Informal caregiving**	
	n=6,572	n=7,590	n=7,081	n=21,243	Yes, n=3,411	No, n=17,832
Women	34%	56%	30%	41%	44%	40%
Age	52 (51-54)	50 (42-58)	48 (44-54)	51 (46-55)	52 (50-55)	51 (45-55)
Married/cohabiting	84%	80%	77%	80%	80%	80%
Low occupational grade	17%	43%	15%	26%	23%	25%
Smoking	16%	14%	13%	14%	15%	14%
Obese	9%	3%	9%	7%	9%	6%
Informal caregiving	30%	9%	11%	16%	-	-
High job strain	20%	20%	28%	22%	22%	23%
Low social support	55%	37%	19%	36%	45%	34%

Age is median (IQR).

Figure 2a. Informal caregiving and the association with incident type 2 diabetes during 10 years follow-up

Adjusted for age, sex, married/cohabiting, occupational grade, and follow-up time

Figure 2b. High job strain and the association with incident type 2 diabetes during 10 years follow-up

Adjusted for age, sex, married/cohabiting, occupational grade, and follow-up time

Figure 2c. Social support at work and the association with incident type 2 diabetes during 10 years follow-up

Adjusted for age, sex, married/cohabiting, occupational grade, and follow-up time

Figure 3a-b. The joint association between informal caregiving, psychosocial work factors and incident type 2 diabetes during 10 years follow-up

Adjusted for age, sex, married/cohabiting, occupational grade, and follow-up time