

Mentally tiring work and type 2 diabetes in women: a 22-year follow-up study

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Abstract

Hypothesis: Previous work suggested no or inconsistent associations between components of work-related stress and type 2 diabetes risk, but suggested sex-specific differences should be further investigated, as women potentially had higher risks.

Methods: We analyzed data from 73 517 women, mostly teachers, from the E3N cohort study followed for 22 years (1992–2014), to study the association between mentally tiring work, used as a proxy of job demands, and type 2 diabetes risk. Univariate and multivariable Cox regression models were used to estimate hazard ratios and 95% confidence intervals.

Results: A total of 4187 incident cases of type 2 diabetes cases were observed. There was a higher type 2 diabetes risk for women with a 'Very mentally tiring work' when compared to women with 'Little or not mentally tiring work' (HR = 1.21 (1.09–1.35)). This association was independent of unhealthy lifestyle and traditional metabolic factors. An interaction between mentally tiring work and BMI was detected ($P < 0.0001$), with a stronger association being observed in non-overweight women, HR = 1.26 (1.08–1.47) vs HR = 1.14 (0.98, 1.32), in overweight women.

Conclusions: We observed an increased risk of type 2 diabetes associated with mentally tiring work, used as a proxy of job demands. These observational results suggest the importance of taking into consideration the potential long-term metabolic impact of work-related stress for women working in a demanding environment. Increased support for such women should be investigated in intervention studies.

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Introduction

The influence of work environment and work-related stress on metabolic disorders such as type 2 diabetes is complex and multifactorial, as several traits must be jointly dealt with when addressing the question. Besides, even if positive associations between work-related stress and heart disease (1, 2, 3, 4) or the metabolic syndrome (5) have been highlighted, previous work have provided mixed results for the risk of type 2 diabetes (6). Several theoretical models have been developed to characterize work-related stress (6), the most famous being the 'job

strain model', by Karasek and Theorell (7), which includes the following components: job demands, job control and job strain.

A recent meta-analysis based on a very limited number of studies has concluded in favor of a lack of association between work-related stress components and risk for type 2 diabetes, with inconsistent results for job demands and job control but with an association between job strain and type 2 diabetes risk in women only (6). These results suggest sex-specific differences for the influence of a

mental environment on metabolic outcomes, with women being potentially more vulnerable. The authors of that meta-analysis concluded that other sex-specific studies were needed in order to disentangle the association between work-related stress components and type 2 diabetes risk from other factors to limit the risk of publication bias. As work-related stress is associated with behaviors such as smoking (8), unhealthy dietary patterns (9) and poor sleep (9, 10), that are all type 2 diabetes risk factors, it is of major importance to evaluate this association in large, population-based studies with a large set of covariates available to control for.

Our aim was to study the association between mentally tiring work, as a proxy of job demands (11), and the long-term risk of type 2 diabetes in 73 517 women from the E3N cohort study who were followed for 22 years, between 1992 and 2014. A majority of these women were teachers, which allowed us to minimize the impact of the type of occupation on the association between job demands and the risk of diabetes. In addition, we tested for potential interactions between unhealthy factors and perceived mental burden of the work on the risk of type 2 diabetes.

Subjects and methods

The study population

The E3N (*Etude Epidémiologique auprès des femmes de la Mutuelle Générale de l'Education Nationale*) is a French prospective cohort study of 98 995 women born between 1925 and 1950, initiated in 1990 (12). E3N study participants are insured by a health insurance plan that mostly covers employees of the French National Education system (MGEN, *Mutuelle Génération de l'Education Nationale*). E3N is the French component of the European Prospective Investigation into Cancer and Nutrition (EPIC) and is part of EPIC-InterAct, a case-cohort study on type 2 diabetes nested within EPIC (13). Participants gave their written informed consent and completed self-administered questionnaires that have been sent biennially since 1990. The average response rate to a follow-up questionnaire is 83%, with a total loss to follow-up since 1990 below 3%. Furthermore, for each cohort member, the health insurance plan provided data that included all outpatient reimbursements for health expenditure since January 1, 2004; these data included brand names, doses and dates of drug reimbursements. The study was approved by the French National Commission for Data Protection and Privacy (ClinicalTrials.gov Identifier: NCT03285230).

Population for analysis and follow-up

Follow-up started in 1992. Participants contributed person-years of follow-up until the date of diagnosis of type 2 diabetes, the date of the last completed questionnaire, or November 17, 2014 (the date at which the last E3N questionnaire we used was sent to participants), whichever occurred first. We included 75 546 women who completed the 1992 follow-up questionnaire, who had already worked and who had responded to the question on mentally tiring work. We then excluded prevalent cases of type 2 diabetes ($n=638$) and participants with no follow-up after 1992 ($n=1391$), leaving a final sample of 73 517 women for this study.

Assessment of mentally tiring work

Information on mentally tiring work was collected in the questionnaire sent in 1992 and is used here as a validated proxy for work-related psychological demands (11). Participants were asked: 'Do you (or did you) find your work mentally tiring?'. Answers were categorized as 'Little or not mentally tiring', 'Mentally tiring' and 'Very mentally tiring'.

Assessment of type 2 diabetes cases

Before 2004, all potential cases were identified through follow-up questionnaires with self-reporting of diabetes, diabetes-specific diet, diabetes drugs and hospitalization for diabetes. All potential cases were then contacted and asked to answer a diabetes-specific questionnaire that included questions on the circumstances of diagnosis (year of diagnosis, symptoms, biological exams and fasting or random glucose concentration at diagnosis), diabetes therapy (prescription of diet or physical activity, list of glucose-lowering drugs taken) and last concentrations of fasting glucose and Hb1Ac. In order to be validated, a potential case had self-reported in the diabetes-specific questionnaire for at least one of the following three criteria (1) fasting plasma glucose ≥ 7.0 mmol/L or random glucose ≥ 11.1 mmol/L at diagnosis and/or (2) use of glucose-lowering medication and/or (3) last values of fasting glucose ≥ 7.0 mmol/L or HbA1c concentrations $\geq 7\%$. After 2004, we identified cases through the drug reimbursement insurance database: all women who were reimbursed at least twice for any glucose-lowering medications during 1 year were considered to be validated cases of diabetes (14). In the final study population, there was a total of 4187 validated incident cases of type 2 diabetes between 1992 and 2014.

Participant involvement

Participants were not involved in setting the research question or the outcome measures, nor were they involved in developing plans for recruitment, design or implementation of the study. Results of the study will be disseminated to patient organizations and via the study web page (www.e3n.fr).

Statistical analysis

Baseline characteristics of the study population were described in the overall population and according to exposure to mentally tiring work, using the mean (standard deviation) or *n* (%); comparisons across the three groups were performed with multinomial regressions for continuous variables, and by chi-square tests for categorical data. We used Cox proportional hazards regression models, with age as the time scale, to estimate hazard ratios and 95% confidence intervals to evaluate the association between mentally tiring work and the risk of type 2 diabetes, using the category 'Little or not mentally tiring' as the reference category. Models were univariate and then further adjusted for the following list of established type 2 diabetes risk factors or variables leading to potential confounding: level of education (undergraduate or less/graduate/postgraduate or more), current activity status (in activity/retired), most recent profession (teacher affiliated to the French Ministry of Education/other than teacher affiliated to the French Ministry of Education/not affiliated to the French Ministry of Education), level of recreational physical activity (MET-h/week, continuous), BMI (<20 kg/m²/(20–25) kg/m²/(25–30) kg/m²/≥30 kg/m²), smoking status (non-smoker/former smoker/current smoker), hypertension (no/yes), cholesterol-lowering drugs use (no/yes), family history of diabetes (no/yes/unknown).

Interaction between mentally tiring work and age (<50/≥50 years), BMI (<25/≥25 kg/m²), smoking (current/former or non-smoker), level of recreational physical activity (<24/≥24 Met-h/week), family history of diabetes (no/yes/unknown) and profession (teacher affiliated to the French Ministry of Education/other than teacher affiliated to the French Ministry of Education/not affiliated to the French Ministry of Education) have been tested.

A sensitivity analysis was performed by further adjusting for dietary patterns (15) in Cox regression models starting in 1993, when diet was first assessed in the E3N study, instead of 1992, on 61 086 participants

including 3135 incident type 2 diabetes cases. A second sensitivity analysis was performed excluding participants who no longer worked at baseline in 1992, on 58 263 women.

All statistical analyses were performed using SAS 9.4 (SAS Institute Inc., PHREG procedure for Cox models). Missing values were <5% for all variables and were imputed with the median (quantitative variables) or the mode (qualitative variables) of the study population. All statistical tests were two-sided and we considered a *P* value <0.05 as statistically significant.

Results

Baseline participant characteristics

Baseline characteristics of the study participants are listed in [Table 1](#). Women who reported to have a very mentally tiring work (24% of the total study population) more frequently had a family history of diabetes than those with a little or not mentally tiring work (11.4 vs 9.9%). They also were more frequently overweight (20.7 vs 18.0%), less frequently smokers (13.7 vs 15.1%), used cholesterol-lowering drugs more frequently (7.0 vs 5.6%), had slightly more years of education (14.16 vs 13.52), were more frequently in activity at baseline (80.2% vs 74.7%) and were more frequently teachers affiliated with the French Ministry of Education (90.9 vs 43.0%).

Mentally tiring work and risk of incident type 2 diabetes

Hazard ratios for type 2 diabetes and 95% confidence intervals associated with mentally tiring work are listed in [Table 2](#). There was little difference between estimates from univariate and multivariable models. In the overall population, we observed that women with a 'Very mentally tiring work' were at increased risk of type 2 diabetes when compared to women with 'Little or not mentally tiring work' (HR=1.21 (1.09–1.35)). In the first sensitivity analysis, the adjustment for dietary patterns yielded similar results, with an increased risk of 23% (HR=1.23 (1.10; 1.38)). Moreover, repeating the analysis when excluding women who no longer worked at baseline did not materially change the association we observed for women with a 'Very mentally tiring work' when compared to women with 'Little or not mentally tiring work' (HR=1.22 (1.08–1.37)).

Table 1 Baseline characteristics of the study population (E3N Cohort, $n = 73\,517$ women).

Variables*	Overall ($n = 73\,517$)	Do you find your work mentally tiring?			P*
		Little or not mentally tiring ($n = 13\,622$)	Mentally tiring ($n = 42\,198$)	Very mentally tiring ($n = 17\,697$)	
Age (years)	50.98 (6.60)	50.91 (6.66)	50.95 (6.64)	51.12 (6.45)	<0.0001
Type 2 diabetes cases at the end of follow-up	4187 (5.7)	720 (5.3)	2302 (5.5)	1165 (6.6)	<0.0001
Family history of diabetes (yes)	7879 (10.7)	1345 (9.9)	4520 (10.7)	2014 (11.4)	<0.0001
Body mass index categories (kg/m ²)					<0.0001
<20	11 913 (16.2)	2201 (16.2)	6784 (16.1)	2928 (16.5)	
20–24.9	47 592 (64.7)	8961 (65.8)	27 524 (65.2)	11 107 (62.8)	
25–29.9	11 592 (15.8)	2033 (14.9)	6601 (15.6)	2958 (16.7)	
≥30	2420 (3.3)	427 (3.1)	1289 (3.1)	704 (4.0)	
Smoking status					<0.0001
Smokers	10 304 (14.0)	2058 (15.1)	5829 (13.8)	2417 (13.7)	
Former smokers	24 206 (32.9)	4230 (31.1)	14 257 (33.8)	5719 (32.3)	
Non smokers	39 007 (53.1)	7334 (53.8)	22 112 (52.4)	9561 (54.0)	
Recreational physical activity level (MET-h/week)	24.74 (21.24)	24.64 (21.80)	24.95 (21.06)	24.31 (21.21)	0.0072
Hypertension (yes)	7475 (10.2)	1348 (9.9)	4278 (10.1)	1849 (10.4)	0.2635
Cholesterol-lowering drugs use (yes)	4604 (6.3)	763 (5.6)	2611 (6.2)	1230 (7.0)	<0.0001
Years of education	14.17 (3.06)	13.52 (3.80)	14.38 (2.95)	14.16 (2.56)	<0.0001
Currently working (yes)	58 263 (79.3)	10 178 (74.7)	33 878 (80.2)	14 207 (80.2)	<0.0001
Last profession					<0.0001
Teacher affiliated to the French Ministry of Education (FME)	56 281 (76.6)	5853 (43.0)	34 346 (81.4)	16 082 (90.9)	
Other than teacher affiliated to the FME	13 518 (18.4)	5735 (42.1)	6456 (15.3)	1327 (7.5)	
Not affiliated to the FME	3718 (5.0)	2034 (14.9)	1396 (3.3)	288 (1.6)	

* n (%) and Chi² test derived P -values for categorical variables. Mean (s.d.) and multinomial regression derived P -values for continuous variables.

Interaction with BMI

There was no rank correlation between mentally tiring work and BMI at baseline ($\text{corr} = -0.01$). However, a statistical interaction between mentally tiring work and BMI was observed ($P < 0.0001$). There was no indication of statistical interactions between mentally tiring work and age ($P = 0.17$), smoking ($P = 0.94$), level of recreational

physical activity ($P = 0.57$), family history of diabetes (0.77) and profession (0.27). When stratifying by BMI, we observed that the increased risk associated with the category 'Very mentally tiring' was only statistically significant for women with a BMI <25 kg/m² (HR=1.26 (1.08–1.47)). Indeed, for women with a BMI over 25 kg/m², we observed a modest increased risk which did not reach the $P = 0.05$ threshold (HR=1.14 (0.98–1.32)).

Table 2 Hazard ratios and 95% confidence intervals associated with mentally tiring work in the overall population and stratified by body mass index categories (E3N Cohort, $n = 73\,517$ women).

	Mentally tiring work			$P_{\text{int}}^{\ddagger}$
	Little or not mentally tiring	Mentally tiring	Very mentally tiring	
Overall population ($n = 73\,517$)				
n cases (%)	720 (17)	2302 (55)	1165 (28)	
HR (95% CI)*	Reference	1.01 (0.93; 1.10)	1.19 (1.08; 1.31)	
HR (95% CI) [†]	Reference	1.06 (0.96; 1.16)	1.21 (1.09; 1.35)	
Body mass index				<0.0001
<25 kg/m ² ($n = 59\,505$)				
n cases (%)	356 (18)	1098 (55)	526 (27)	
HR (95% CI) [†]	Reference	1.08 (0.95; 1.23)	1.26 (1.08; 1.47)	
≥25 kg/m ² ($n = 14\,012$)				
n cases (%)	364 (16)	1204 (55)	639 (29)	
HR (95% CI) [†]	Reference	1.04 (0.92; 1.18)	1.14 (0.98; 1.32)	

*Age-adjusted model. [†]Further adjusted for level of education, current activity status, most recent profession, recreational physical activity level, body mass index, smoking status, hypertension, cholesterol-lowering drugs use, family history of diabetes. [‡] P_{int} for interaction between body mass index (<25/≥25 kg/m²) and mentally tiring work. Bold values indicate $P < 0.05$

There was no interaction between mentally tiring work and family history of diabetes nor profession.

Discussion

In this cohort of 73 517 women followed for 22 years, we observed for the 24% of women who declared having a 'very mentally tiring' work, a 21% higher risk of type 2 diabetes than women with 'little or not mentally tiring' work. This association remained stable even after adjusting for most known or potential risk factors or confounders. This increased risk seen in the overall population was actually found to be restricted to non-overweight women. We also illustrated that the use of a single item on the perception of the degree of mental tiredness at work can be used by default when detailed information on work-related stress is not available.

Comparison with previous studies

The most notable work with which we can compare our results is a recent meta-analysis between work-related stress factors and type 2 diabetes risk, based on seven prospective studies (6). The authors did not show any association between work-related stress components and type 2 diabetes risk overall, but they highlighted an association in women with an increased risk associated with job strain (HR=1.22 (1.01–1.46)). Regarding job demands, they showed an increased but not significant risk of 12% (HR=1.12 (0.83–1.51)) in women. We did not have the opportunity to analyze job strain in our study; however, we have found a similar direction in the association, with a greater magnitude and strength in the association between mentally tiring work, used as a proxy of job demands, and type 2 diabetes risk (HR=1.21 (1.09–1.35)). This gap could be explained by differences in the populations under study or for some, their limited size, which may lead to less variability in the participants' profiles. Our work is based on a larger population-based cohort, a longer follow-up and a greater statistical power than all the studies included in the meta-analysis. This could explain the differences with the results of the studies included in the meta-analysis and may suggest a potential long-term effect of job demands on type 2 diabetes risk that the other studies were not able to highlight. Besides, we did not find any results in the literature with which to compare our results on a potential interaction between job demands and BMI. Furthermore, the fact that the majority of the women studied were teachers limits some bias related to the heterogeneity in

the type of occupation and change overtime. Our study assessed the relationship between the perception of the degree of job demands and the risk of diabetes in women and not the degree of job constraints defined by the type of occupation (16). Our findings underscore the importance of perceived mental tiredness on metabolic outcomes among women, which has been very little investigated previously. To our knowledge, the increased risk of type 2 diabetes associated with mentally tiring work that was restricted to non-overweight women in our analysis, has not been previously reported, but could be explained by the fact that in overweight/obese individuals, the relative importance of adiposity on the risk of type 2 diabetes is so strong that it could mask the potential association between mentally tiring work and type 2 diabetes.

Potential mechanisms

Several mechanisms have been suggested to explain the elevated type 2 diabetes risk associated with components of work-related stress. The first one involves the activation of the hypothalamus–pituitary–adrenal axis and the sympathetic nervous system. This has been shown to be associated with elevated cortisol levels (17), which leads to an increased hepatic glucose output, decreased insulin secretion, insulin resistance and visceral obesity. The second potential mechanism is that people who work with high job strain or job demands tend to more frequently exhibit unhealthy lifestyle factors (18, 19, 20) – such as poor sleep, smoking, unhealthy dietary patterns – that are frequently related to a higher risk of type 2 diabetes. However, previous work in the Whitehall II study (21) and our own results are not in favor of this hypothesis.

Regarding the specific association observed in women, it has been hypothesized that the differences in the observed associations between men and women could be due to indirect effects related to differences in gender roles outside work (22). As women still spend more time than men on household tasks and childcare, this could result in less time to relax and therefore enhance the detrimental effect of a demanding job (23, 24, 25). A more direct biological effect can be hypothesized as well, as women could respond more intensely to work-related stress than men (26) by having higher cortisol levels during working days (27, 28, 29).

Strengths and limitations

This study has numerous strengths. We evaluated the associations between mentally tiring work and type

2 diabetes risk in a large population during 22 years of follow-up; the prevalence of exposure was high including 24% of the women; further, details on various type 2 diabetes risk factors and potential confounders were available. The prospective design reduces a differential bias in the reporting of mentally tiring work in relation to the outcome occurrence. The E3N study can be considered as a rather stable population in terms of job change compared to the general population, which reduces the risk of misclassification during the follow-up. The large number of participants and type 2 diabetes cases ensure a high statistical power. Incident cases were identified from an algorithm based on an extensive medico-administrative database, which reduced the risk of missing or false-positive cases.

This study has also some limitations. No information on the use of prescribed or self-medication related to the management of work-related stress was available for the study period. The E3N cohort is not representative of the general French population as it includes rather homogeneous health-conscious women. Although this might reduce the variability of certain characteristics and the possibility to extrapolate to the general population, it should not bias the estimates. Even though we controlled for most established type 2 diabetes risk factors, potential residual and unmeasurable confounding (sleep for instance) cannot be ruled out completely as our study is observational. Unfortunately, no information on biomarkers of interest was available and prevented us from investigating in more detail the potential mechanisms underlying the observed associations. In particular, future studies should include metabolomics studies to better understand the influence of work-related stress on health.

Implications of our findings

Both mentally tiring work and type 2 diabetes are increasingly prevalent phenomena. Therefore, our results can have substantial implications regarding both the understanding of the underlying mechanisms and the prevention of adverse effects of work-related stress. It is known that, in contrast to men, both intellectual and emotional demands determine occupational stress in women and that support in the workplace has a stronger impact on work-related stress in women than men (30). Consequently, an increase in the support of women in demanding work environments could be a tool for type 2 diabetes prevention.

Conclusions

We have been able to highlight an increased risk of type 2 diabetes associated with mentally tiring work, used as a proxy of job demands; the risk was preferentially observed in non-overweight women. We have also illustrated that using a single item on mentally tiring work can discriminate the risk of health events such as type 2 diabetes in large cohort studies where detailed information on work is not available. Based on our observational results, we recommend that intervention studies should investigate the potential beneficial effect on cardiometabolic health, of an increased support to women working in high stress environment.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

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Author contribution statement

G F conceived the study. G F wrote the first and successive drafts of the manuscript. G G modeled and analyzed the data. G F, D E F, G G, B B and F B contributed to study conception and design. G F and M-C B R collected the data. All authors revised the manuscript for important intellectual content. G F had full access to the data and takes full responsibility for the integrity of the data and the accuracy of the data analysis. G F is the study guarantor.

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