Original Article
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Obesity

Onset of Workplace Bullying and Risk of Weight Gain: A Multicohort Longitudinal Study

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Objective: This study aimed to examine the onset of workplace bullying as a risk factor for BMI increase.

Methods: Repeated biennial survey data from three Nordic cohort studies were used, totaling 46,148 participants (67,337 participant observations) aged between 18 and 65 who did not have obesity and who were not bullied at the baseline. Multinomial logistic regression was applied for the analysis under the framework of generalized estimating equations.

Results: Five percent reported onset of workplace bullying within 2 years from the baseline. In confounder-adjusted models, onset of workplace bullying was associated with a higher risk of weight gain of ≥1 BMI unit (odds ratio = 1.09; 95% CI: 1.01-1.19) and of ≥2.5 BMI units (odds ratio = 1.24; 95% CI: 1.06-1.45). A dose-response pattern was observed, and those exposed to workplace bullying more frequently showed a higher risk (P_{trend} = 0.04). The association was robust to adjustments, restrictions, stratifications, and use of relative/absolute scales for BMI change.

Conclusions: Participants with exposure to the onset of workplace bullying were more likely to gain weight, a possible pathway linking workplace bullying to increased long-term risk of type 2 diabetes.

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Study Importance

What is already known?

- Workplace bullying has been found to be associated with a 46% increased risk of developing type 2 diabetes.
- Evidence on the pathways linking workplace bullying to the development of type 2 diabetes remains equivocal, and weight gain might be one of these pathways.
- The few existing studies connecting workplace bullying to BMI were severely limited by the unclear timing of the exposure and the unknown sequence between onset of bullying and change in BMI.

What does this study add?

- Onset of workplace bullying is associated with a higher risk of BMI increase in a dose-response manner.

How might these results change the direction of research?

- Future studies should elucidate the effectiveness of comprehensive workplace bullying-prevention strategies on reducing diabetes risk.

Introduction

The burden of diabetes mellitus is increasing worldwide (1). Weight gain is a major risk factor for type 2 diabetes and it is often observed as an early sign of diabetes development even when the increase in weight is small (2). In working-age populations, every 1-unit increase in BMI was found to be associated with an approximately 10% to 25% higher risk of type 2 diabetes (3). In agreement with this, increase in BMI has been examined as a mediator between distal risk factors and type 2 diabetes in observational studies and used as a surrogate or intermediary outcome in diabetes trials (4-6). In recent research aimed at identifying novel risk factors for diabetes, workplace bullying was found to be associated with an increased risk of type 2

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diabetes, independent of other risk factors (7). The pathways underlying this association remain unclear, but BMI increase is hypothesized to be one of them.

Workplace bullying, defined as "harassing, offending, socially excluding someone, or negatively affecting someone's work," is relatively prevalent in working populations, with a prevalence of 9% in a multicohort study of employees from Sweden, Denmark, and Finland (7,8). Adverse health effects of workplace bullying are assumed to involve activation of the stress response system (9,10), which can affect endocrine regulation of appetite, potentially leading to an increase in consumption of energy-dense foods and compulsive overeating (11). Other plausible mechanisms may include the increased risk of negative emotions and sleep problems, contributing to neuroendocrine disturbances and psychotropic medication intake, which may subsequently cause weight gain (12-15). The changes in appetite, eating behaviors, and metabolism can all increase body weight.

To date, few studies have examined the relationship between workplace bullying and BMI. A cross-sectional study of 17,524 employees from the United States found that workplace bullying was associated with a higher prevalence of both overweight and obesity (16). A smaller longitudinal study of 601 male and 4,831 female Finnish hospital employees found that baseline BMI was not associated with the onset of workplace bullying 2 years later, but those who had obesity at the baseline were more likely to be bullied both at the baseline and at the follow-up (17). Without knowing the timing and sequence of the onset of workplace bullying and the occurrence of BMI increase, temporality between bullying and BMI remains unclear, and reverse causation cannot be ruled out as an explanation. In a recent study of workplace bullying and risk of type 2 diabetes, we found that the additional adjustment for BMI attenuated the estimated effect of bullying on type 2 diabetes by 33% (7). As workplace bullying and BMI were both measured at baseline, the timing and sequence between the two were still unknown, raising the question of whether BMI was a confounder or a mediator for the association between workplace bullying and type 2 diabetes (7).

To address these limitations, we used clearly defined inclusion and exclusion criteria and multicohort longitudinal data to assess whether onset of workplace bullying, among those who were not targets of bullying and did not have obesity at baseline, is a risk factor for the increase in BMI over time.

Methods

Study population

The study population was derived from three prospective cohort studies: the Swedish Longitudinal Occupational Survey of Health (SLOSH) (18), the Work Environment and Health in Denmark (WEHD) Study (19), and the Finnish Public Sector (FPS) Study (20) (Figure 1). SLOSH is a dynamic, population-based survey with follow-up at every second year from 2006 to 2018 (baseline years: 2006-2016) (18). In this study, we included all SLOSH participants who were gainfully employed at the time of participation. WEHD is a biennial cohort initiated in 2012; we included respondents of the 2012 survey who were followed by resurveys in 2014 and 2016 (baseline years: 2012 and 2014) (19). FPS is a dynamic survey established in 1997-1998 consisting of public sector employees from Finland; data on workplace bullying and BMI were available from a subcohort from surveys in 1998, 2000, and 2004 and from the total cohort from surveys conducted in 2014 and 2016 (baseline years: 1998 and 2014) (20). To be included in the present analysis, participants were restricted to those who responded to at least two consecutive survey waves (i.e., at the baseline and at the first follow-up in 2 years), were aged 18 to 65, and had nonmissing data on key variables (Figure 1). A detailed description of the cohorts included is provided in online Supporting Information. From all cohort studies, we excluded a total of 14% of participants who had obesity, 1% of participants who were underweight, and 11% who were bullied at the baseline or within 12 months before the baseline (Figure 1). After exclusion, a total of 46,178 participants corresponding to 67,337 participant observations met the inclusion and exclusion criteria for at least one 2-year baseline–follow-up cycle.

Assessment of workplace bullying

In all cohort studies, workplace bullying was measured using questionnaires asking whether participants were bullied within a certain time frame (Supporting Information Table S1). The time frames for the measurement of exposure to workplace bullying varied slightly across baseline waves. In SLOSH waves 2006/2008/2010, WEHD waves 2012/2014/2016, and FPS wave 2014/2016, exposure to bullying within the past 12 months was requested, whereas the rest of the SLOSH waves used a time frame of the past 6 months. In FPS 1998/2000, participants were asked whether they were currently being bullied at work. In all cases, we defined exposure to workplace bullying as giving an affirmative response to the question. With the information on frequency of exposure in SLOSH and WEHD, we further categorized the participants into frequently bullied (on a weekly or daily basis), occasionally bullied (less frequently than weekly), and not bullied.

Assessment of change in BMI

We calculated BMI using self-reported weight and height (weight in kilograms divided by height in meters squared). Median height was calculated based on all available waves to reduce the risk of report bias. Following categorizations suggested by the World Health Organization, BMI was categorized into underweight (<18.5 kg/m^2), normal (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2), and obesity (≥ 30 kg/m^2).

Absolute BMI change was calculated as the absolute difference between two consecutive waves (e.g., BMI at the first follow-up minus BMI at the baseline; Figure 2A) and was categorized into "increase" or "decrease" if there was a 1-unit or greater BMI increase or decrease, respectively, or "stable" if the BMI change was less than 1 BMI unit. A 1-unit increase, corresponding to a 2.9-kg increase for a person who is 170 cm tall, has been suggested because of its relevance to type 2 diabetes development (3).

We used relative BMI change as an alternative outcome. This was calculated as the percent change between waves: (BMI at the first follow-up minus BMI at the baseline) divided by BMI at the baseline; relative BMI change was classified into "increase," "stable," and "decrease" using 5% as the threshold.

Assessment of covariates

We selected potential confounders based on prior knowledge using the Directed Acyclic Graphs method (21). In addition to age and sex, we included country of birth, marital status, occupational grade, and poor mental health at the baseline. Information on country of birth was classified as "Nordic countries," "other European countries," and

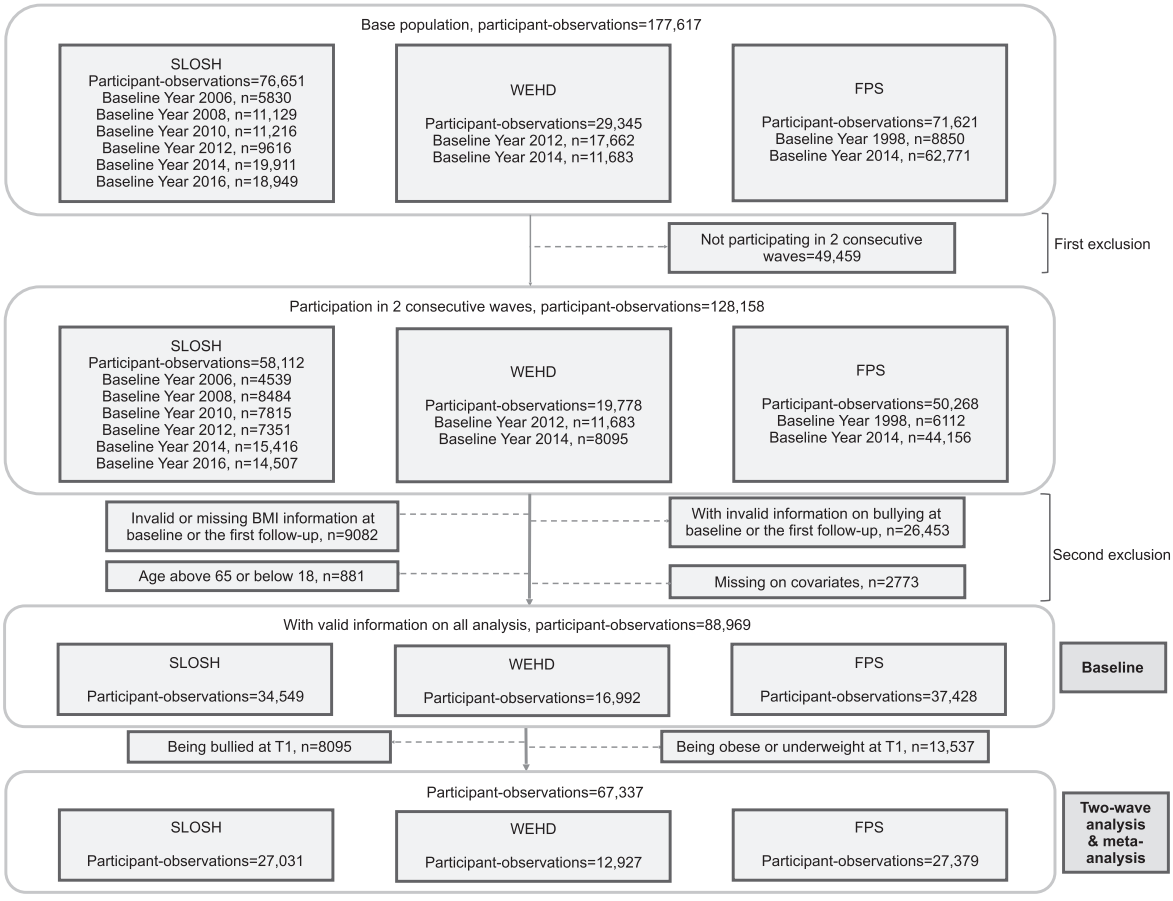

Figure 1 Flowchart of study population.

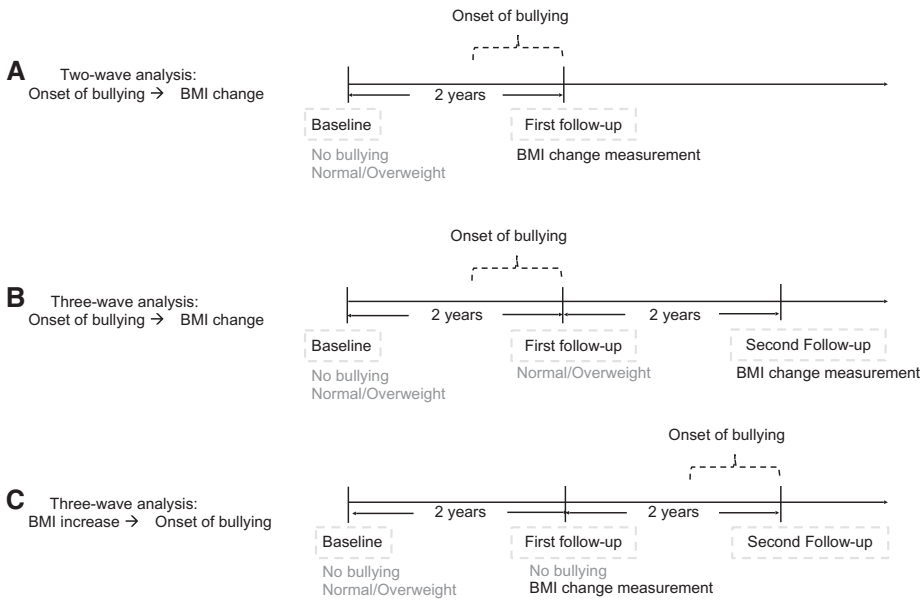

Figure 2 Statistical analysis procedure with inclusion and exclusion criteria.

"other continents" (in SLOSH and WEHD). In FPS, no information on country of birth was collected; the vast majority of the hospital employees in the cohort are from Nordic countries. Marital status was grouped into "married/cohabiting," "unmarried," "divorced/separated," and "widowed" using register-based (in SLOSH and WEHD) and self-reported (in FPS) information. Occupational grade (in SLOSH, WEHD, and FPS) was coded according to national adapted versions of the International Standard Classification of Occupation. It was classified into "high" (e.g., managers, professionals), "intermediate" (e.g., technicians, associate professionals), and "low" (e.g., service and shop sales workers, machine operators) (22).

Symptoms of major depression or poor mental health were identified using self-reported questionnaires, including a six-item version of the symptom checklist in SLOSH (23) and the Major Depression Inventory in WEHD (24). In FPS, these symptoms were measured using the 12-item version of the General Health Questionnaire in 1998, 2000, and 2004, whereas in 2014 and 2016, two screening questions were used (those who answered "yes" for both questions defined as cases) (25,26).

Although pregnancy is not recognized as a cause of workplace bullying, it is an important contributor to weight change and it was therefore considered as an important factor in this study. Detailed descriptions for pregnancy in each cohort can be found in online Supporting Information.

Type 2 diabetes was measured for an explorative reason in SLOSH, using national patient and cause of death registries (online Supporting Information) (27). For other cohorts, the number of diabetes cases was not sufficient for current analyses.

Statistical analysis

A brief overview of the analytical procedure can be found in Figure 2. For the main analyses, we used a two-wave design, including participants who were not bullied and did not have obesity ($18.5 < \text{BMI} < 30$) at the baseline (Figure 2A). Having obesity at the baseline was suggested to be associated with both the baseline and the subsequent exposure to workplace bullying (16,17) and therefore was removed from the main analysis. According to the specific time frame in each cohort, onset of bullying reflected bullying cases occurring in a period before the first follow-up, and BMI change was measured at the first follow-up, that is, comparing BMI between the first follow-up and the baseline (Figure 2A). In the main analysis, sex, country of birth, baseline year, and baseline information on age, occupational grade, marital status, and mental health were adjusted for. Sensitivity analyses included (i) sex stratification, (ii) stratifying by baseline BMI categories, and (iii) restricting the sample by excluding pregnant women. To ensure that the variations in the time frame were not a cause of heterogeneity, we also restricted our analysis to those waves in which workplace bullying was measured using the 12-month time frame. These analyses mentioned earlier were repeated using the alternative outcome of a relative BMI change.

With the well-established associations between workplace bullying and incident type 2 diabetes (7) and between BMI change and incident type 2 diabetes (3), we tested the effect of onset of bullying on type 2 diabetes development, stratified by BMI increase and not increase, in order to explore the role of BMI increase as a pathway linking workplace bullying to type 2 diabetes development. This explorative analysis was performed only in SLOSH. A Cox proportional hazards model was used (no violation of the proportional hazards assumption), with age as the underlying time scale, adjusted for sex, country of birth, and baseline information on age, occupational grade, marital status, mental health, and BMI.

As a complementary analysis, we applied a three-wave design to investigate the effect of the onset of workplace bullying on BMI increase, in which we included participants who were not bullied at the baseline and who had a normal weight or overweight ($18.5 < \text{BMI} < 30$) at both the baseline and the first follow-up (Figure 2B). Similar to the two-wave design, onset of bullying was measured with a time frame indicating bullying cases in a period before the first follow-up. However, change of BMI was measured at the second follow-up (i.e., absolute BMI difference between the first and second follow-up). To address reverse causality and examine the possibility of bidirectional associations (i.e., BMI increase predicting onset of bullying), we analyzed the association of BMI increase (measured at the first follow-up to make a contrast with the baseline BMI) to the onset of workplace bullying (reported between the first and the second follow-up) (Figure 2C).

We compared the respondents' characteristics between different waves to investigate the potential attrition bias.

To address the correlation structure of the data, analyses were performed under the framework of generalized estimating equations. Depending on whether BMI change or onset of bullying was treated as the outcome variable, multinomial or binomial logistic regressions were used, respectively. When BMI change was the outcome, the stable BMI group was used as the reference group. All analyses were conducted separately for each cohort using SAS version 9.4 (PROC LOGISTIC, PROC GENMOD, and PROC GEE) (SAS Institute Inc., Cary, North Carolina). The cohort-specific estimates were combined using fixed-effect meta-analyses (28), performed in the R package "meta" version 4.8-4. The I^2 statistic was used to test heterogeneity between the study-specific estimates (28).

BMI increase was the main focus of the paper. Results on BMI decrease as the side findings are presented in Supporting Information Figures S1-S2.

Results

Baseline characteristics: two-wave analysis

Study-specific baseline characteristics are shown in Table 1. Among 67,337 participant observations (46,148 participants), the prevalence of onset of bullying was higher among women, those with a lower occupational grade, or those with poor baseline mental health but was lower among those who were married or cohabiting or those born from Nordic countries.

Association between onset of bullying and BMI increase: two-wave analysis

In the two-wave design, 5% had onset of workplace bullying, and 21% had at least a 1-unit BMI increase. Those with onset of bullying had a slightly larger variation in BMI change than those who remained nonbullied in both waves (Supporting Information Figure S3). For example, among those who had a BMI increase at the first follow-up, 16% of bullied participants had a BMI increase of 2.5 units or more, while the corresponding proportion was 12% for those unexposed to bullying.

TABLE 1 Baseline characteristics of 67,337 participant observations in three Nordic cohort studies (46,148 participants)

				Total		
	SLOSH, *n* = 27,031	WEHD, *n* = 12,927	FPS, *n* = 27,379	Total, *N* = 67,337	Onset of bullying, *n* = 3,645	Not bullied, *n* = 37,587
Mean age (SD)	49 (9.4)	48 (10.0)	46 (9.7)	48	48	47
Women, %	58	53	80	66	69	66
Marital status, %						
Married or cohabiting	62	68	74	68	61	69
Unmarried	27	22	14	21	24	21
Divorced or separated	10	9	11	10	15	9
Widowed	1	1	1	1	1	1
Country of birth, % *						
Nordic countries	97	96	-	97	95	97
Other European countries	2	2	-	2	2	2
Other continents	1	2	-	1	3	1
Occupational grade, %						
Low	31	35	27	30	34	30
Intermediate	30	22	28	28	28	28
High	39	42	45	42	38	42
Having mental disorders, %	6	14	14	11	18	10
Onset of bullying, %	5	7	5	5	-	-

*Information available only in SLOSH and WEHD.
FPS, Finnish Public Sector (study); SLOSH, Swedish Longitudinal Occupational Survey of Health; WEHD, Work Environment and Health in Denmark.

Figure 3 presents the relationship between onset of workplace bullying and BMI increase. In the fully adjusted analysis, onset of workplace bullying was associated with a higher risk of BMI increase (odds ratio [OR] = 1.09; 95% CI: 1.01-1.19) with negligible heterogeneity across cohort-specific estimates ($I^2 < 0.01\%$, $P = 0.77$). Onset of bullying was more strongly associated with a weight gain of 2.5 BMI units or more (OR = 1.24; 95% CI: 1.06-1.45). We also observed a dose-response relationship ($P_{trend} = 0.04$) in which those being exposed to bullying on a weekly or daily basis (i.e., frequently) showed the highest risk of a BMI increase of at least 1 unit over 2 years (OR = 1.37; 95% CI: 0.96-1.94).

In sensitivity analyses (Supporting Information Figure S4), a stronger effect in women than in men was suggested, but the confidence intervals in these subgroups were highly overlapping. Our results were not affected by different adjustments and exclusions based on baseline BMI categories. Furthermore, excluding women who had been pregnant between the baseline and the first follow-up did not change the estimates. We observed no difference when pooling the data that used a 12-month time frame for workplace bullying measurement. Using relative BMI change as the outcome, we found a similar association between onset of bullying and BMI increase (OR = 1.13; 95% CI: 1.04-1.24).

In an explorative analysis using only SLOSH data (mean follow-up: 4.2 years), we observed 78 incident type 2 diabetes cases among 5,650 participants. Among those with BMI increase, onset of workplace bullying was associated with an almost five-times-higher (hazard ratio = 4.82; 95% CI: 1.67-13.90) risk for incident type 2 diabetes. The same tendency was not found among the group without BMI increase (hazard ratio = 0.80; 95% CI: 0.25-2.55).

Bidirectional association between onset of workplace bullying and BMI increase: three-wave analysis

When applying the three-wave design among 24,623 participant observations (16,481 participants), 5% had onset of workplace bullying, and 19% had a BMI increase between the first and second follow-up. In this stricter restriction on temporality, the association between the onset of bullying by the first follow-up and a BMI increase by the second follow-up (OR = 1.16; 95% CI: 1.02-1.33) was similar to the two-wave analysis. Analyses testing reverse causality were conducted only in SLOSH and WEHD with a total of 19,454 participant observations (11,517 participants), as sufficient data were not available from FPS. At the first follow-up, 19% had BMI increase, and 4% of participants reported new workplace bullying cases between the first follow-up and the second follow-up. The association between a 1-unit or higher BMI increase and the subsequent onset of bullying was not statistically significant (OR = 1.15; 95% CI: 0.98-1.36).

Attrition bias

The design we applied included two major exclusion steps (Figure 1), a step excluding people who did not participate in two consecutive waves (excluded 49,459 participant observations) and a step excluding people who did not have information on BMI, bullying, and other covariates (excluded 39,189 participant observations), generating an overall response proportion of 50%. However, after comparing characteristics of participant observations between the baseline population and population after the two exclusion steps, there were no obvious differences in mean age, proportion of women, being born in Nordic countries, being married or cohabiting, and having a low occupational grade (Supporting Information Table S2).

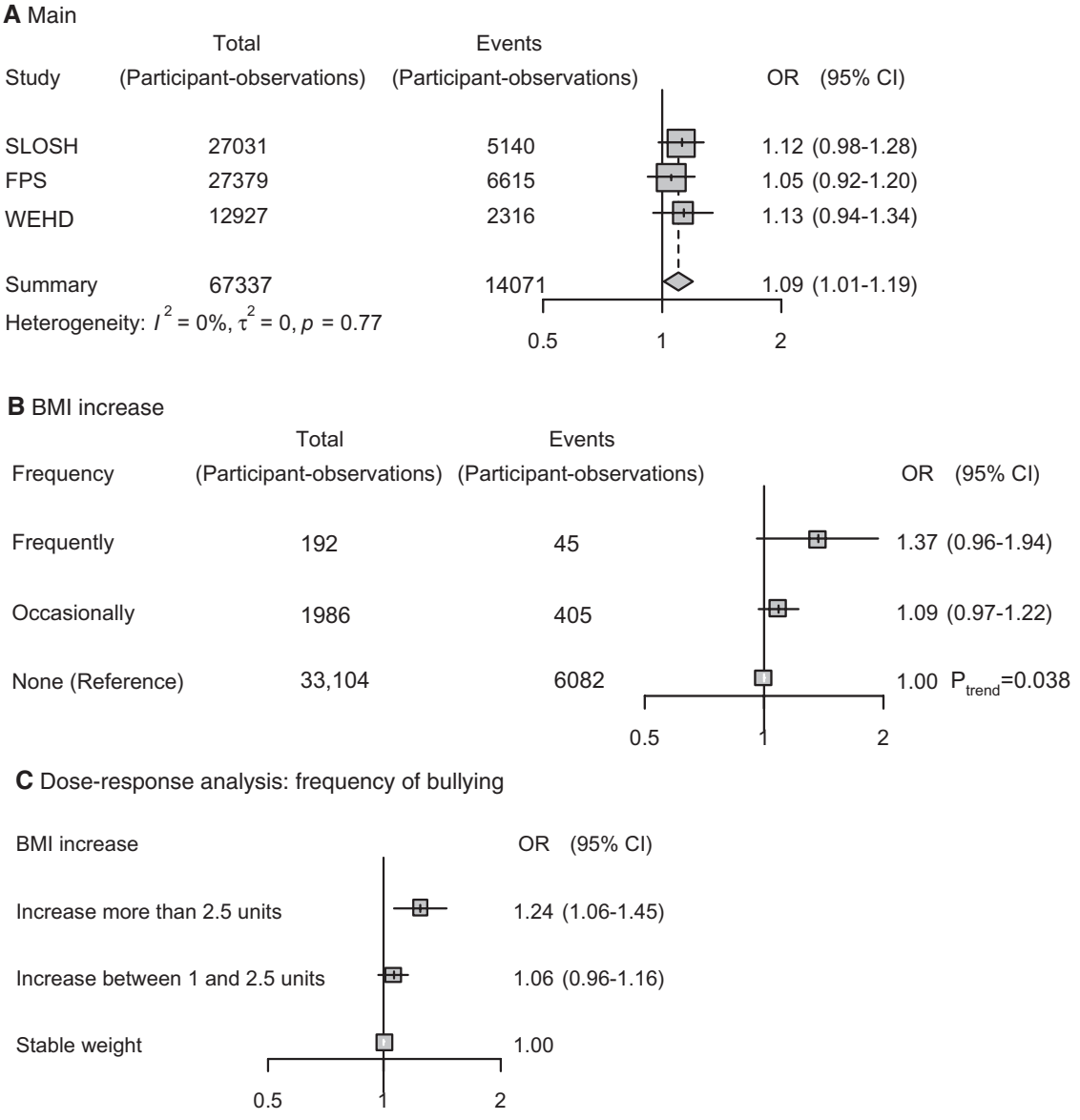

Figure 3 Association between onset of workplace bullying and BMI increase using fixed-effects meta-analysis, adjusting for baseline age, sex, baseline year, country of birth, marital status, baseline occupational grade, and baseline mental health for (**A**) main analysis, (**B**) BMI increase tendency, and (**C**) dose-response analysis on frequency of bullying.

Discussion

In this multicohort longitudinal study, onset of workplace bullying was associated with a modestly higher risk of BMI increase, with a moderate and stronger association observed for large weight gain (i.e., 2.5 BMI units corresponding to a 7.3-kg weight gain for a 170-cm-tall person). According to the US National Institute of Diabetes and Digestive and Kidney Diseases, a woman who is 40 years of age, 170 cm tall, 60 kg, with light workplace physical activity, and with moderate leisure time physical activity can increase 7.3 kg in her weight in 90 days, given a constant level of physical activity and an extra consumption of 746 kcal per day (e.g., an extra meal or three-fourths of a tube of potato chips) during the period (29). We also found that the association between workplace bullying and BMI increase followed a dose-response pattern, with more frequent bullying associated with the highest risk of weight gain. These associations were robust to adjustments, restrictions, stratifications, and use of relative/absolute scales for BMI change. We also found a markedly higher risk of developing type 2 diabetes among those who became bullied and gained weight, although this association could be explored in only one cohort. These findings are consistent with the hypothesis that an increase in BMI is a potential pathway linking workplace bullying to increased risk of type 2 diabetes.

To the best of our knowledge, no previous studies have used longitudinal data to examine the relationship between onset of workplace bullying and BMI change in adults. Nevertheless, our results are in

line with findings from prospective studies on negative social relations and change in BMI. In a Danish study of 236 twins, those who were bullied at school had a 1.4-unit-higher BMI after 4 years of follow-up (30). In a larger study of 2,232 participants from the United Kingdom, the strongest association was observed for chronically bullied children (OR = 1.95) (31). Among adults, our results also corroborate findings on perceived lifetime racism, with 0.48-kg-higher weight increase when comparing the highest level of racism with the lowest (32). In another study, perceived weight-based discrimination among adults older than 50 years was associated with a 1.66-kg-higher weight gain (33).

Mechanisms

Our results are biologically plausible. Onset of bullying as a severe chronic stressor can directly lead to changes in eating behaviors and energy balance via, for example, comfort eating behavior induced by activation of the hypothalamic-pituitary-adrenal axis and changes in intestinal microbiota, which is sensitive to stress, hormonal changes, and type of food ingested (9-11,34,35). Indirectly, stress-induced impaired sleep may decrease leptin and increase ghrelin at the circulating level, in turn contributing to adverse changes in diurnal eating patterns (15,36). Likewise, evidence has shown that bullying induces unfavorable mental states, such as prolonged depressive mood (13,34), possibly resulting in an alteration of fat dynamics in the adipose tissue through pathways from a cerebral neural or hormonal connection. On the contrary, it is also the case that prolonged mental distress can reversely act on workplace victimization, as such states may affect the victims' work performance as well as communication style and make it easier to interpret behaviors in a negative light (37). This may generate a vicious circle including feedback from a BMI increase to later perceptions of workplace bullying, as suggested by the conceivable bidirectional association in our study.

Even a relatively small weight gain can contribute to the development of diabetes (2,3). This increase in body weight may lead to metabolic abnormalities such as ectopic fat deposition, insulin resistance, and impaired glucose tolerance (34). In an explorative analysis, we found that the effect between onset of bullying and type 2 diabetes was more pronounced among those who experienced BMI increase. Nonetheless, increased BMI may not fully explain the mechanisms of type 2 diabetes development for those being bullied, and it is crucial to consider mechanisms other than BMI increase, such as visceral fat accumulation manifesting in intra-abdominal adipose, as a consequence of stress-induced cortisol response (11). Adipose tissue changes may reflect the magnitude of overflow of fatty acids from subcutaneous depots (38). Abdominal obesity may further influence weight changes and has been suggested to be of great relevance to diabetes development among people with normal weight but with impaired fasting glucose (38,39).

Methodological considerations

Workplace bullying was measured using slightly different time frames in different baseline years, which might result in some degree of exposure misclassification. However, we obtained a similar result after restricting the analyses to data waves with a 12-month time frame. BMI was calculated using self-reported weight and height, with a common tendency of underreporting among people who have a normal weight or overweight (40). Nevertheless, underreporting is considered to be stable across survey waves, and absolute change of BMI is less likely to be affected (40). Furthermore, we had no information on genetic factors, personality, and childhood adversities (7,37), and although we adjusted for mental health at the baseline, there may be residual confounding. Thus, we cannot fully exclude further potential confounding effects from, for example, preexisting exhaustion and hostile or obsessive-compulsive traits (7,37). Additionally, the explorative stratified analysis of type 2 diabetes was underpowered, and these results need to be interpreted with caution.

Our sensitivity analysis showed that, although we used the two-wave analysis design, attrition bias may not be of significant concern. This is in line with previous analyses using SLOSH data for non-responders, regarding their exposure to bullying and the mean BMI (18).

We used repeated measures, which may be affected by "regression to the mean," making it difficult to judge whether the effect on BMI change arose from a real change or was due to natural variation (40). To rule out this possibility, we selected participants based on the measurement of BMI both at the baseline and the first follow-up in the three-wave design. The three-wave design showed similar results as the two-wave design; however, the selection criteria of this design may be too strict, reducing the possibility of capturing immediate or short-term effects (40).

The strengths of the study include individual-level participant data with repeated information on workplace bullying and BMI from three large, well-established cohort studies. Unlike previous studies (7,16,17), the present study applied both two-wave and three-wave analyses, which complemented each other and supported the robustness of our results in disentangling the temporality between the occurrence of bullying and BMI change. The large sample size allowed application of careful selection criteria of study participants and enabled a range of sensitivity analyses.

Public health implications

Weight gain may be a crucial factor linking workplace bullying to an increased risk of type 2 diabetes. Even a small increase in weight because of workplace bullying may affect the risk of developing type 2 diabetes. Therefore, elimination of workplace bullying could add to the prevention of type 2 diabetes. Bullied employees may also seek help from psychotherapy, which often aims at understanding and dealing with the problem, including establishing a new life perspective for those bullied (8). The importance of combining workplace stress prevention/management and wellness programs has been highlighted in the past few years (41). In the future, psychotherapy can be integrated with weight-control programs to prevent obesity and type 2 diabetes at an early stage. Future studies should elucidate the effectiveness of comprehensive workplace bullying-prevention strategies on reducing diabetes risk.

Conclusion

We find evidence of a moderate but consistent relationship between workplace bullying and weight gain, which indicates that weight gain may be an important factor linking workplace bullying to an increased long-term risk of type 2 diabetes and other weight-related health problems.

Acknowledgments

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Author contributions: TX and NHR contributed to the conception and design of the study, the analysis and interpretation of the data, and the drafting of the article. JP contributed to the analysis of the Finnish data. JKS and MN contributed to the preparation of the Danish data for analysis. AKE contributed to the proofreading of the statistical codes. LLMH, AJC, HW, AKE, JP, RR, SS, JV, MV, IEHM, ÅMH, JKS, MN, RGJW, TO, MK, and NHR contributed to the conception and design of the study and the critical revision of the article. All authors have read and approved submission of the manuscript. NHR is guarantor of the study.

Supporting information: Additional Supporting Information may be found in the online version of this article.

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