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Interplay between chronic widespread pain and lifestyle factors on the risk of type 2 diabetes: longitudinal data from the Norwegian HUNT Study

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ABSTRACT

Introduction Chronic widespread pain (CWP) and diabetes commonly co-occur; however, it is unclear whether CWP infers an additional risk for diabetes among those with known risk factors for type 2 diabetes. We aimed to examine if CWP magnifies the effect of adverse lifestyle factors on the risk of diabetes.

Research design and methods The study comprised data on 25 528 adults in the Norwegian HUNT Study without diabetes at baseline (2006–2008). We calculated adjusted risk ratios (RRs) with 95% CIs for diabetes at follow-up (2017–2019), associated with CWP and body mass index (BMI), physical activity, and insomnia symptoms. The relative excess risk due to interaction (RERI) was calculated to investigate the synergistic effect between CWP and adverse lifestyle factors.

Results Compared with the reference group without chronic pain and no adverse lifestyle factors, those with BMI ≥30 kg/m^2 with and without CWP had RRs for diabetes of 10.85 (95% CI 7.83 to 15.05) and 8.87 (95% CI 6.49 to 12.12), respectively; those with physical activity <2 hours/week with and without CWP had RRs for diabetes of 2.26 (95% CI 1.78 to 2.88) and 1.54 (95% CI 1.24 to 1.93), respectively; and those with insomnia symptoms with and without CWP had RRs for diabetes of 1.31 (95% CI 1.07 to 1.60) and 1.27 (95% CI 1.04 to 1.56), respectively. There was little evidence of synergistic effect between CWP and BMI ≥30 kg/m^2 (RERI=1.66, 95% CI −0.44 to 3.76), low physical activity (RERI=0.37, 95% CI −0.29 to 1.03) or insomnia symptoms (RERI=−0.09, 95% CI −0.51 to 0.34) on the risk of diabetes.

Conclusions These findings show no clear interaction between CWP and adverse lifestyle factors on the risk of diabetes.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Diabetes and chronic pain are common conditions which frequently co-occur. Adverse lifestyle factors such as excessive body weight, physical inactivity, and poor sleep are known risk factors for diabetes and are commonly associated with chronic widespread pain. However, it is not known whether chronic widespread pain magnifies the risk of diabetes among people with adverse lifestyle factors.

WHAT THIS STUDY ADDS

⇒ The current study adds to the current literature on the association between chronic pain and diabetes, showing no clear synergistic effects between chronic widespread pain and adverse lifestyle factors on the risk of diabetes.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study indicates that chronic widespread pain marginally adds to the risk of diabetes among people with high body mass index, who are physically inactive or with insomnia symptoms. Therefore, preventive strategies for diabetes should target known lifestyle factors irrespective of chronic pain.

INTRODUCTION

Type 2 diabetes is the most common metabolic disorder and represents a significant global disease burden.[1] Type 2 diabetes is characterized by insulin resistance and pancreatic β-cell dysfunction.[2] Excessive weight, physical inactivity, poor sleep, and energy-dense diet represent strong risk factors for type 2 diabetes; thus, preventive interventions commonly rely on intensive lifestyle modification.[3 4]

Chronic widespread pain affects around 10% of the general adult population globally[5] and is the most common cause of long-term disability. Chronic widespread pain has been suggested to signal increased risk of type 2 diabetes,[6] although longitudinal evidence about this association is limited and conflicting.[7 8] Adverse lifestyle factors associated with increased risk of type 2 diabetes (eg, obesity, poor sleep, physical inactivity) often cluster in people with chronic widespread pain.[9–13] It has been shown that chronic pain combined with obesity may lead to worse functional status and quality of life and increased pain sensitivity compared with when these conditions occur in isolation.[14] The relation between chronic pain and obesity is thought

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to involve a complex interplay of systemic inflammation, biomechanical load, and autonomic dysregulation.[15] Obesity and chronic pain may also interact through psychological disturbances such as decrease in self-esteem and increase in depressive symptoms, which in turn impact on physical activity levels and sleep quality.[16]

Although chronic pain and diabetes commonly co-occur,[8 17] it is not clear whether chronic widespread pain infers an additional risk for type 2 diabetes among those with known risk factors for type 2 diabetes. Therefore, the aim of the current study was to examine the potential synergistic effect between chronic widespread pain and adiposity, leisure time physical activity, and insomnia symptoms on the risk of diabetes.

METHODS

Study population

The Norwegian HUNT Study is a longitudinal population-based study carried out in the geographical region of Nord-Trøndelag in Norway. The current study is based on data from the third (HUNT3, 2006–2008) and fourth (HUNT4, 2017–2019) surveys of the HUNT Study. All inhabitants aged 20 years or more residing in Nord-Trøndelag were invited to participate; 50 800 (54%) participated in HUNT3 and 56 042 (54%) in HUNT4.[18] All participants filled in extensive questionnaires on lifestyle and health and met for a clinical examination and blood sampling. A detailed description of participation rates, questionnaires, and clinical examinations can be found at https://www.ntnu.edu/hunt.

For this prospective study, we selected 33 819 people who participated in HUNT3 (ie, baseline) and who could be followed up in HUNT4 approximately 11 years later. Of these, we excluded 6087 people with incomplete information about musculoskeletal pain and diabetes at baseline and 999 people who reported prevalent diabetes at baseline. Additionally, 780 people with incomplete information about body weight and/or body height, physical activity and/or insomnia symptoms at baseline were excluded. Of the remaining 25 953 participants, 25 528 had complete information about diabetes status at follow-up in 2017–2019 and were included in the analysis.

Chronic widespread pain

The Standardised Nordic Questionnaire[19] was used to retrieve information about chronic musculoskeletal pain. Participants who reported having chronic musculoskeletal pain ticking 'yes' on the following question 'During the last year, have you had pain and/or stiffness in muscles or joints that lasted for at least 3 consecutive months?' were asked to indicate the affected body area(s), that is, neck, shoulders, upper back, elbows, low back, hips, wrists/hands, knees, and ankles/feet. Participants were also asked the following question: 'Have you been suffering from pain in both left and right sides of the body?'. Participants were defined to have chronic widespread pain if they reported chronic pain in the axial skeleton, above and below the waist, and in both left and right sides of the body. Participants were categorized into three groups: 'no chronic pain', 'any chronic pain' and 'chronic widespread pain'.

Diabetes

At baseline, information on diabetes was based on the following question: 'Have you had, or do you have diabetes?'. Participants who answered 'yes' were classified as having diabetes. A previous study from the HUNT population demonstrated that the single-item self-report is a highly valid measure of clinically diagnosed diabetes with high positive (96.4%) and negative (99.7%) predictive values.[20] At follow-up, incident cases of diabetes were classified based on answering 'yes' on the above self-reported question and/or a value of hemoglobin A1c (HbA1c) ≥48 mmol/mol, which is the recommended cut-off for diagnosing diabetes.[21] HbA1c was not available in HUNT3 and was therefore not used.

Body mass index

Body mass index (BMI) was calculated as weight divided by the square of height (kg/m^2) using standardized measurements of height (to the nearest centimeter) and weight (to the nearest half kilogram) from the clinical examination. We categorized participants as having BMI <25 kg/m^2, between 25 kg/m^2 and <30 kg/m^2, and ≥30 kg/m^2.[22] In a sensitivity analysis, we used waist circumference (in centimeters) as an additional measure of abdominal adiposity. We categorized participants as having waist circumference ≥94 cm and <94 cm (if males) and having waist circumference ≥80 cm and <80 cm (if females), that is, being above these cut-offs indicate overweight or obesity.[23]

Leisure time physical activity

Leisure time physical activity was assessed by the following two questions: (1) 'How often do you exercise (on average)', with response options 'never', 'less than once a week', 'once a week', 'two to three times a week' and 'nearly every day'; and (2) 'For how long do you exercise each time? (average)' with response options 'less than 15 min', '15–29 min', '30 min–1 hour', 'more than 1 hour'. Frequency was then recoded as '0' if participants reported to exercise less than once a week or never, '1' if they reported to exercise once a week, '2.5' if they reported to exercise two to three times a week and '5' if they reported exercising nearly every day. The exercise duration in each category was averaged to approximate the exercise duration in minutes, for example, if participants reported exercising for 15–29 min, this was coded as '22.5 (min)'; if they reported exercising for 30 min–1 hour, this was coded as '45 min'. The exercise frequency was then multiplied by the duration to derive the number of hours of exercise per week. Participants were then categorized as those exercising less than 2 hours/week and those exercising 2 hours/week or more. Two hours/week was chosen as cut-off since it approximates the recommendation for

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Table 1 Baseline characteristics of study population stratified by chronic pain status

	No chronic pain	Any chronic pain	Chronic widespread pain
Participants, n	12 433	9 258	3 837
Females, n (%)	6 570 (52.8)	5 381 (58.1)	2 748 (71.6)
Age, mean (SD), years	49.7 (13.8)	52.8 (13.0)	55.8 (11.1)
Higher education*, n (%)	2 844 (22.9)	1 818 (19.6)	572 (14.9)
Current smoker, n (%)	1 454 (11.7)	1 435 (15.5)	753 (19.6)
Body mass index, mean (SD), kg/m^2	26.6 (4.0)	27.2 (4.2)	28.1 (4.5)
Low leisure time physical activity†, n (%)	9 303 (74.8)	7 064 (76.3)	2 951 (76.9)
Insomnia symptoms‡, n (%)	2 084 (16.8)	2 579 (27.9)	1 788 (46.6)

*Based on HUNT2 data.
†Less than 2 hours/week.
‡At least one insomnia symptom ('difficulty falling asleep', 'difficulty maintaining sleep', or 'waking up too early').

moderate-to-vigorous physical activity per week according to current guidelines.[24]

Insomnia symptoms

Insomnia symptoms were assessed by three questions: (1) 'How often during the last 3 months have you had difficulty falling asleep at night?', (2) 'How often during the last 3 months have you woken up repeatedly during the night?', (3) 'How often during the last 3 months have you woken up too early and could not get back to sleep?' with three response options 'never/seldom', 'sometimes' and 'several times a week'. Participants were classified with having insomnia symptoms if they answered 'several times a week' to at least one of the three questions, while they were categorized as not having insomnia symptoms if they answered either 'never/seldom' or 'sometimes' to any of the three questions. These self-reported questions have demonstrated acceptable reliability.[25]

Possible confounders

All possible confounders were assessed at baseline (HUNT3, 2006–2008) except for education that was available at HUNT2, 1995–1997. Education was categorized into three groups: primary '7–10 years', intermediate '11–13 years', and higher education '>13 years'. Smoking status was assessed by questions related to current and past cigarette smoking and categorized as: 'never smoked', 'former or occasional smoker' and 'current smoker'. Confounder variables in multiadjusted model were selected depending on the association under study to avoid adjusting for mediators: for the joint effect of pain and BMI, age (continuous), sex (categorical), education (primary, intermediate, higher education), smoking status (never, former or occasional, current) and leisure time physical activity (<2 hours/week and ≥2 hours/week) were entered as covariates; for the joint effect of pain and physical activity, age, sex, education and smoking status were entered as covariates; for the joint effect of pain and insomnia, age, sex, education, smoking status, BMI (<18.5, 18.5–24.9, 25.0–29.0, ≥30.0 kg/m^2), and physical activity were entered as covariates. In supplementary analyses, comorbid conditions including mental health and other musculoskeletal conditions were added as potential confounding variables as these might be linked to both chronic pain and diabetes. Mental health conditions were assessed using the Hospital Anxiety and Depression Scale (HADS),[26] which includes 14 items scored on a 4-point Likert scale, of which 7 items assess depression (HADS-D) and 7 items assess anxiety (HADS-A). Both subscales range from 0 to 21 (higher scores indicating higher depression and anxiety levels). A cut-off score of ≥8 for each subscale was chosen to indicate the presence of depression and anxiety symptoms. Comorbid musculoskeletal conditions were assessed by asking participants about current and previous disease (rheumatic disease or degenerative joint disease).

Statistical analysis

We used a modified Poisson regression model to estimate the relative risk (RR) of diabetes within categories of a joint variable combining chronic pain status (no chronic pain, any chronic pain, chronic widespread pain) and either BMI (<25 kg/m^2 vs ≥25 kg/m^2 to <30 kg/m^2 vs ≥30 kg/m^2), physical activity (<2 hours/week vs ≥2 hours/week) and insomnia symptoms (no, yes). The precision of all estimated associations was assessed by a 95% CI using a robust variance estimator to account for the dichotomous nature of the outcome. The reference group for the three joint effect analyses were people without chronic pain and BMI <25 kg/m^2; people without chronic pain and who reported exercising ≥2 hours/week; and finally, people without chronic pain who reported no insomnia symptoms. Potential effect modification between the variables was estimated as the relative excess risk due to interaction (RERI).[27 28] A RERI >0 indicates a synergistic effect beyond additivity. Education, smoking and mental health conditions had 22.6%, 1.4% and 0.6% missing data, respectively, which were imputed (20 imputations) using all variables in the main analysis as predictors in the imputation model.

In a supplementary analysis, we used waist circumference and estimated the RR of diabetes within categories of the joint variable combining chronic pain status and waist

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Table 2 Joint effect of chronic pain and body mass index (BMI) on the risk of diabetes

Chronic pain variables	BMI <25				BMI ≥25 & <30				BMI ≥30			
	No of persons	No of cases	Age/sex-adjusted RR	Multiadjusted, RR* (95% CI)	No of persons	No of cases	Age/sex-adjusted RR	Multiadjusted, RR* (95% CI)	No of persons	No of cases	Age/sex-adjusted RR	Multiadjusted, RR* (95% CI)
No chronic pain	4 505	46	1.00	1.00 (reference)	5 482	228	3.17	3.15 (2.30 to 4.32)	1 936	236	9.09	8.87 (6.49 to 12.12)
Any chronic pain	2 905	34	1.10	1.07 (0.69 to 1.66)	4 124	182	3.29	3.17 (2.30 to 4.37)	1 760	253	10.28	9.72 (7.12 to 13.27)
Chronic widespread pain	954	12	1.15	1.06 (0.56 to 1.99)	1 689	92	4.23	3.95 (2.78 to 5.61)	941	149	11.67	10.85 (7.83 to 15.05)

*Multiadjusted for age (continuous), sex (male, female), education (primary, intermediate, higher education), leisure time physical activity (<2 hours/week, ≥2 hours/week), smoking (never, former or occasional, current).
RR, risk ratio.

circumference (<80 cm in females or <94 cm in males vs ≥80 cm in females or ≥94 cm in males). This analysis was performed to provide an alternative measure of abdominal adiposity. Further, to account for potentially differential variation in BMI across chronic pain status categories (eg, those with widespread pain and BMI ≥30 kg/m^2 having higher average BMI than those in the same BMI category but without chronic pain), we performed an analysis where we adjusted for continuously measured BMI within each BMI category (<25, 25–29, ≥30 kg/m^2). Similarly, we adjusted for continuously measured physical activity (hours/week) within each physical activity category (±2 hours/week) when examining the association between chronic pain and diabetes risk. This analysis was, however, not applicable to the sleep variable due to its dichotomous nature. Finally, within each pain category, we estimated the risk of diabetes associated with continuously measured BMI and assessed possible statistical interaction between the chronic pain categories and the continuous BMI variable. Interaction was evaluated by a likelihood ratio test of a product term of these two factors without the robust variance estimator since it is not supported by the likelihood ratio test.

All statistical analyses were performed using Stata for Windows, V.16.0 (StataCorp, College Station, Texas, USA).

RESULTS

Table 1 presents baseline characteristics of the study population stratified according to chronic pain status. The proportion of participants reporting any chronic pain and chronic widespread pain at baseline was 36.3% and 15.0%, respectively. After ~11 years of follow-up, a total of 1232 (4.8%) new cases of diabetes were reported.

Table 2 shows the joint effect between chronic pain and BMI on the risk of diabetes. Compared with the reference group of people without chronic pain and BMI <25 kg/m^2, those without chronic pain and BMI ≥30 kg/m^2 had an RR for diabetes of 8.87 (95% CI 6.49 to 12.12), while those with chronic widespread pain had RR of 1.06 (95% CI 0.56 to 1.99) if they had BMI <25 kg/m^2. The RR for those with chronic widespread pain and BMI ≥30 kg/m^2 was 10.85 (95% CI 7.83 to 15.05). There was little evidence of synergistic effect above additivity for the combination of chronic widespread pain and BMI ≥30 kg/m^2 on the risk of diabetes (RERI=1.66, 95% CI −0.44 to 3.76).

Table 3 shows the joint effect of chronic pain and leisure time physical activity on the risk of diabetes. Compared with the reference group of people without chronic pain and who were physically active 2 hours/week or more, people without chronic pain had an RR for diabetes of 1.54 (95% CI 1.24 to 1.93) if they were physically active less than 2 hours/week, while those with chronic widespread pain who were physically active 2 hours/week or more had RR of 1.55 (95% CI 1.09 to 2.22). Those with chronic widespread pain who were physically active less than 2 hours/week had an RR for diabetes of 2.26 (95%

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Table 3 Joint effect of chronic pain and leisure time physical activity on the risk of diabetes

	Physical activity ≥2 hours/week				Physical activity <2 hours/week			
	No of persons	No of cases	Age/sex-adjusted RR	Multiadjusted, RR* (95% CI)	No of persons	No of cases	Age/sex-adjusted RR	Multiadjusted, RR* (95% CI)
No chronic pain	3 037	93	1.00	1.00 (reference)	8 886	417	1.59	1.54 (1.24 to 1.93)
Any chronic pain	2 117	77	1.16	1.13 (0.84 to 1.53)	6 672	392	1.87	1.78 (1.42 to 2.22)
Chronic widespread pain	843	43	1.64	1.55 (1.09 to 2.22)	2 741	210	2.47	2.26 (1.78 to 2.88)

*Multiadjusted for age (continuous), sex (male, female), education (primary, intermediate, higher education), smoking status (never, former or occasional, current).
RR, risk ratio.

CI 1.78 to 2.88). We observed no clear synergistic effect above additivity for the combination of widespread pain and being physically active less than 2 hours/week on the risk of diabetes (RERI=0.37, 95% CI −0.29 to 1.03).

Table 4 shows the joint effect of chronic pain and insomnia symptoms on the risk of diabetes. Compared with the reference group of people without chronic pain and no insomnia symptoms, people without chronic pain had an RR for diabetes of 1.27 (95% CI 1.04 to 1.56) if they had insomnia symptoms, while those with chronic widespread pain who had no insomnia symptoms had an RR of 1.28 (95% CI 1.06 to 1.54). Those with chronic widespread pain who had insomnia symptoms had an RR for diabetes of 1.31 (95% CI 1.07 to 1.60). There was no evidence of a synergistic effect above additivity for the combination of widespread pain and insomnia symptoms on the risk of diabetes (RERI=−0.09, 95% CI −0.51 to 0.34).

Supplementary analysis

There was no clear evidence of a synergistic effect between chronic widespread pain and waist circumference on the risk of diabetes (RERI=0.07, 95% CI −1.08 to 1.22) (online supplemental table 1). The analysis adjusting for variation in BMI (continuous) within each BMI category showed that the small independent effect of widespread pain on diabetes within higher BMI categories was somewhat attenuated when controlling for the within-category variation in BMI (online supplemental table 2). Adjusting for variation in physical activity (continuous) within each physical activity category did not change the estimated association between widespread pain and diabetes risk (online supplemental table 3). The RRs of diabetes associated with the continuous BMI variable (kg/m^2) were 1.18 (95% CI 1.16 to 1.19), 1.18 (95% CI 1.16 to 1.20), and 1.14 (95% CI 1.12 to 1.17) among people with no chronic pain, any chronic pain and widespread pain, respectively (data not shown). Although there was some evidence of a slightly weaker association between BMI and diabetes risk in people with widespread pain, there was no indication of statistical interaction (p=0.10). Adjusting for comorbid conditions, that is, mental health and other musculoskeletal conditions, had a negligible effect on the RRs of diabetes for the joint effect of chronic pain and BMI, physical activity, and insomnia symptoms (online supplemental tables 4–6).

DISCUSSION

The current study adds to the current literature on the association between chronic pain and diabetes. People with chronic widespread pain and high BMI or who are physically inactive had a 20–60% higher risk of diabetes compared with those with the same adverse factors but without chronic pain. The risk of diabetes was similar among people with insomnia symptoms with and without chronic widespread pain. However, there was no evidence of a synergistic effect between chronic widespread pain and adverse lifestyle factors on the risk of diabetes.

Although chronic pain is common among people with diabetes,[8 17] few studies have attempted to disentangle the temporal association between these two conditions. A recent longitudinal study using data from the HUNT Study indicated that chronic low back pain is associated with an increased risk of diabetes among women at 10–11 years of follow-up[7]; however, this association was not observed among men. In contrast, a longitudinal study of Spanish

Table 4 Joint effect of chronic pain and insomnia symptoms on the risk of diabetes

	No insomnia symptoms				Insomnia symptoms			
	No of persons	No of cases	Age/sex-adjusted RR	Multiadjusted, RR* (95% CI)	No of persons	No of cases	Age/sex-adjusted RR	Multiadjusted, RR* (95% CI)
No chronic pain	9 949	400	1.00	1.00 (reference)	1 974	110	1.30	1.27 (1.04 to 1.56)
Any chronic pain	6 346	333	1.23	1.10 (0.96 to 1.27)	2 443	136	1.30	1.13 (0.94 to 1.36)
Chronic widespread pain	1 913	136	1.65	1.28 (1.06 to 1.54)	1 671	117	1.71	1.31 (1.07 to 1.60)

*Multiadjusted for age (continuous), sex (male, female), education (primary, intermediate, higher education), body mass index (<18.5, 18.5–24.9, 25–29.5, ≥30 kg/m^2), leisure time physical activity (<2 hours/week, ≥2 hours/week), smoking status (never, former or occasional, current).
RR, risk ratio.

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twins found no association between chronic low back pain and risk of diabetes at 2–4 years of follow-up.[8] The current study extends on these findings by investigating the possible synergistic effect of chronic widespread pain and adverse lifestyle factors on risk of diabetes. Notably, the two studies described above focused on low back pain and did not investigate the association between chronic widespread pain and risk of diabetes.

It is well established that adverse lifestyle factors, such as obesity, physical inactivity, and poor sleep, are associated with increased risk of diabetes.[4 29] The current study indicates that chronic widespread pain somewhat increases the risk of diabetes among people who are obese or physically inactive, although no statistically significant synergistic effect was observed. Shared biological mechanisms might partly explain a link between chronic pain and adverse lifestyle factors. For example, musculoskeletal conditions characterized by chronic widespread pain (eg, fibromyalgia) have been associated with elevated blood pressure,[30] as well as chronic systemic inflammation.[31] Both high blood pressure and chronic systemic inflammation have been suggested to be independent risk factors for type 2 diabetes.[32–34] Furthermore, adiposity is positively and dose dependently associated with increase in blood pressure[35] as well as an elevated level of systemic inflammation.[36] Similarly, elevated systemic inflammation and high blood pressure are more common among people who are physically inactive.[37 38] Thus, it is possible that the somewhat increased risk of diabetes among those with chronic widespread pain and obesity or physically inactive is mediated by high blood pressure and/or chronic systemic inflammation, that is, these conditions are likely to be more common among people who suffer from chronic widespread pain and who also are obese or physically inactive.

Our findings are based on a large and well-characterized population-based study.[39] The strengths of this study include the prospective design and adjustment for several potential confounders. Moreover, the large sample size provides sufficient statistical power for the estimation of the synergistic effect of chronic widespread pain and several adverse lifestyle factors associated with an increased risk of diabetes. However, some limitations should be considered in the interpretation of the results. First, incident cases of diabetes were assessed at the follow-up survey (ie, HUNT4) among those who were able and chose to participate in both HUNT3 and HUNT4. Thus, if participants who were overweight or obese, physically inactive, poor sleepers, or suffered from chronic widespread pain at baseline were less likely to participate at the follow-up survey, the estimated associations are likely to be underestimated. Second, the presence of diabetes at both baseline and follow-up was assessed by a self-report and it was not possible to distinguish between type 1 and type 2 diabetes; however, it is likely that most incident diabetes cases among adults will be type 2 diabetes. We additionally used measurements of HbA1c to further identify potential undiagnosed diabetes cases at follow-up. Third, both leisure time physical activity and insomnia symptoms were assessed by self-report and misclassification cannot be ruled out. The questionnaire-based nature of the data allows for subjective interpretation of the questions and individual perception of physical activity level[18 40] and insomnia symptoms.[25] The HUNT questionnaire on physical activity does not allow assessment of the relative importance of different exercise types (eg, endurance, strength, flexibility). However, a validation study in men showed that the HUNT questionnaire may be useful in classifying people into broad categories of physical fitness.[41] To facilitate the interpretation and applicability of our findings, we used a cut-off of 2 hours/week to classify participants into those meeting versus not meeting the recommendations for moderate-to-vigorous physical activity per week.[24] Finally, residual confounding due to unknown or unmeasured factors influencing the associations under study cannot be ruled out. For example, we cannot exclude the possibility that undetected diseases influenced our findings. Moreover, adjustments for variables commonly associated with diabetes, such as family factors, genetic predisposition[42] and stressful life events,[43] could be of importance.

In conclusion, the current study indicates no clear evidence of synergistic effects between chronic widespread pain and adverse lifestyle factors on the risk of diabetes. The development and implementation of preventive strategies for diabetes should target established risk factors irrespective of chronic pain.

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Contributors All authors contributed to the design of the study. AM, PJM, and TILN planned the analyses and AM carried out the analyses. AM and PJM drafted the main manuscript text with inputs from RC-M, BOÅ and TILN. All authors reviewed and approved the final version of the manuscript. PJM is the guarantor for the study, had access to the data and accepts full responsibility for integrity of the data and the accuracy of the data analyses, and controlled the decision to publish.

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in Central Norway (ref. 2020/104328). Participants gave informed consent to participate in the study before taking part.

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Data availability statement Data are available upon reasonable request. The data that support the findings of this study are available from HUNT Research Centre (https://www.ntnu.edu/hunt), but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the coauthor PJM (email ID: paul.mork@ntnu.no) upon reasonable request and with permission of HUNT Research Centre (https://www.ntnu.edu/hunt).

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REFERENCES

1 Khan MAB, Hashim MJ, King JK, *et al*. Epidemiology of type 2 diabetes–global burden of disease and forecasted trends. *J Epidemiol Glob Health* 2020;10:107–11.
2 Chatterjee S, Khunti K, Davies MJ. Type 2 diabetes. *Lancet* 2017;389:2239–51.
3 Ley SH, Schulze MB, Hivert MF, *et al*. Risk factors for type 2 diabetes. In: Cowie CC, CasagrandeSS, Menke A, eds. *Diabetes in America. 3rd ed*. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases (US), 2018.
4 Gao X, Sun H, Zhang Y, *et al*. Investigating causal relations between sleep-related traits and risk of type 2 diabetes mellitus: a mendelian randomization study. *Front Genet* 2020;11:607865.
5 Andrews P, Steultjens M, Riskowski J. Chronic widespread pain prevalence in the general population: a systematic review. *Eur J Pain* 2018;22:5–18.
6 Mäntyselkä P, Miettola J, Niskanen L, *et al*. Persistent pain at multiple sites—connection to glucose derangement. *Diabetes Res Clin Pract* 2009;84:e30–2.
7 Heuch I, Heuch I, Hagen K, *et al*. Is chronic low back pain a risk factor for diabetes? The Nord-Trøndelag health study. *BMJ Open Diabetes Res Care* 2018;6:e000569.
8 Dario A, Ferreira M, Refshauge K, *et al*. Mapping the association between back pain and type 2 diabetes: a cross-sectional and longitudinal study of adult Spanish twins. *PLoS One* 2017;12:e0174757.
9 Heuch I, Heuch I, Hagen K, *et al*. Body mass index as a risk factor for developing chronic low back pain: a follow-up in the Nord-Trøndelag health study. *Spine (Phila Pa 1976)* 2013;38:133–9.
10 Smith AD, Crippa A, Woodcock J, *et al*. Physical activity and incident type 2 diabetes mellitus: a systematic review and dose–response meta-analysis of prospective cohort studies. *Diabetologia* 2016;59:2527–45.
11 Heuch I, Heuch I, Hagen K, *et al*. Is there a U-shaped relationship between physical activity in leisure time and risk of chronic low back pain? A follow-up in the HUNT study. *BMC Public Health* 2016;16:306.
12 Mork PJ, Nilsen TIL. Sleep problems and risk of Fibromyalgia: longitudinal data on an adult female population in Norway. *Arthritis Rheum* 2012;64:281–4.
13 Skarpsno ES, Nilsen TIL, Hagen K, *et al*. Long-term changes in self-reported sleep quality and risk of chronic musculoskeletal pain: the HUNT study. *J Sleep Res* 2021;30:e13354.
14 Narouze S, Souzdalnitski D. Obesity and chronic pain: systematic review of prevalence and implications for pain practice. *Reg Anesth Pain Med* 2015;40:91–111.
15 Malfliet A, Quiroz Marnef A, Nijs J, *et al*. Obesity hurts: the why and how of integrating weight reduction with chronic pain management. *Phys Ther* 2021;101:pzab198.
16 Okifuji A, Hare BD. The association between chronic pain and obesity. *J Pain Res* 2015;8:399–408.
17 Hassoon A, Bydon M, Kerezoudis P, *et al*. Chronic low-back pain in adult with diabetes: NHANES 2009–2010. *J Diabetes Complications* 2017;31:38–42.
18 Åsvold BO, Langhammer A, Rehn TA, *et al*. Cohort profile update: the HUNT study, Norway. *Int J Epidemiol* 2023;52:e80–91.
19 Kuorinka I, Jonsson B, Kilbom A, *et al*. Standardised Nordic questionnaires for the analysis of musculoskeletal symptoms. *Appl Ergon* 1987;18:233–7.
20 Midthjell K, Holmen J, Bjørndal A, *et al*. Is questionnaire information valid in the study of a chronic disease such as diabetes? The Nord-Trøndelag diabetes study. *J Epidemiol Community Health* 1992;46:537–42.
21 American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes—2018. *Diabetes Care* 2018;41:S13–27.
22 World Health Organization. Available: https://www.who.int/europe/news-room/fact-sheets/item/a-healthy-lifestyle---who-recommendations [Accessed 21 Nov 2022].
23 Rao G, Powell-Wiley TM, Ancheta I, *et al*. Identification of obesity and cardiovascular risk in ethnically and racially diverse populations: a scientific statement from the American heart association. *Circulation* 2015;132:457–72.
24 World Health Organization. Available: https://www.who.int/news-room/fact-sheets/detail/physical-activity [Accessed 21 Nov 2022].
25 Engstrøm M, Ødegård SS, Sand T. The reliability of a new sleep screening questionnaire for large population-based studies: the third Nord-Trøndelag health study. *The Open Sleep Journal* 2011;4:14–9.
26 Bjelland I, Dahl AA, Haug TT, *et al*. The validity of the hospital anxiety and depression scale: an updated literature review. *J Psychosom Res* 2002;52:69–77.
27 Andersson T, Alfredsson L, Källberg H, *et al*. Calculating measures of biological interaction. *Eur J Epidemiol* 2005;20:575–9.
28 Richardson DB, Kaufman JS. Estimation of the relative excess risk due to interaction and associated confidence bounds. *Am J Epidemiol* 2009;169:756–60.
29 Carlsson S, Midthjell K, Tesfamarian MY, *et al*. Age, overweight and physical inactivity increase the risk of latent autoimmune diabetes in adults: results from the Nord-Trøndelag health study. *Diabetologia* 2007;50:55–8.
30 Gerdle B, Dahlqvist Leinhard O, Lund E, *et al*. Fibromyalgia: associations between fat infiltration, physical capacity, and clinical variables. *J Pain Res* 2022;15:2517–35.
31 Bäckryd E, Tanum L, Lind A-L, *et al*. Evidence of both systemic inflammation and Neuroinflammation in Fibromyalgia patients, as assessed by a multiplex protein panel applied to the cerebrospinal fluid and to plasma. *J Pain Res* 2017;10:515–25.
32 Kim M-J, Lim N-K, Choi S-J, *et al*. Hypertension is an independent risk factor for type 2 diabetes: the Korean genome and epidemiology study. *Hypertens Res* 2015;38:783–9.
33 Li S, Shin HJ, Ding EL, *et al*. Adiponectin levels and risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA* 2009;302:179–88.
34 Wang X, Bao W, Liu J, *et al*. Inflammatory markers and risk of type 2 diabetes: a systematic review and meta-analysis. *Diabetes Care* 2013;36:166–75.
35 Chang C-Y, Kuo C-C, Lin M-H, *et al*. Obesity, waist circumference, and appendicular muscle mass ratio in relation to blood pressure among the community-dwelling elderly population in Taiwan. *J Clin Hypertens (Greenwich)* 2022;24:184–90.
36 Ellulu MS, Patimah I, Khaza'ai H, *et al*. Obesity and inflammation: the linking mechanism and the complications. *Arch Med Sci* 2017;13:851–63.
37 Gleeson M, Bishop NC, Stensel DJ, *et al*. The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. *Nat Rev Immunol* 2011;11:607–15.
38 Hegde SM, Solomon SD. Influence of physical activity on hypertension and cardiac structure and function. *Curr Hypertens Rep* 2015;17:77.
39 Krokstad S, Langhammer A, Hveem K, *et al*. Cohort profile: the HUNT study, Norway. *Int J Epidemiol* 2013;42:968–77.
40 Vanhees L, Lefevre J, Philippaerts R, *et al*. How to assess physical activity? How to assess physical fitness. *Eur J Cardiovasc Prev Rehabil* 2005;12:102–14.

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41 Kurtze N, Rangul V, Hustvedt B-E, *et al*. Reliability and validity of self-reported physical activity in the Nord-Trøndelag health study—HUNT 1. *Scand J Public Health* 2008;36:52–61.
42 Cauchi S, Meyre D, Durand E, *et al*. Post genome-wide association studies of novel genes associated with type 2 diabetes show gene-gene interaction and high predictive value. *PLoS One* 2008;3:e2031.
43 Wang M, Gong W-W, Hu R-Y, *et al*. Associations between stressful life events and diabetes: findings from the China Kadoorie Biobank study of 500,000 adults. *J Diabetes Investig* 2019;10:1215–22.

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