BMJ Open

Hours lying down per day and risk of diabetes in young and middle-aged adults in Norway: a prospective cohort of the HUNT Study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-035010
Article Type:	Original research
Date Submitted by the Author:	15-Oct-2019
Complete List of Authors:	Asante, Ernest; Norwegian University of Science and Technology, Dept. of Public Health and Nursing Sun, Yi-Qian; Norwegian University of Science and Technology, Dept. of Clinical and Molecular Medicine; TkMidt-Center for Oral Health Services and Research Nilsen, Tom; Norwegian University of Science and Technology, Department of Public Health and Nursing; St. Olavs Hospital, Trondheim University Hospital, Clinic of Anesthesia and Intensive Care Åsvold, Bjørn; Norwegian University of Science and Technology, K.G. Jebsen Center for Genetic Epidemiology, Dept. of Public Health and Nursing; St. Olavs Hospital, Trondheim University Hospital, Department of Endocrinology Sørgjerd, Elin; The Norwegian University of Science and Technology, HUNT Research Centre, Department of public health and Nursing Mai, Xiao-Mei; Norwegian University of Science and Technology, Dept. of Public Health and Nursing
Keywords:	General diabetes < DIABETES & ENDOCRINOLOGY, EPIDEMIOLOGY, PUBLIC HEALTH

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Hours lying down per day and risk of diabetes in young and middle-aged adults in Norway: a prospective cohort of the HUNT Study

Ernest O. Asante (Asante_Ernest@outlook.com)[1], Yi-Qian Sun (yi-qian.sun@ntnu.no)[2,3], Tom IL Nilsen (tom.nilsen@ntnu.no)[1,4], Bjørn O. Åsvold (bjorn.o.asvold@ntnu.no)[5,6], Elin P. Sørgjerd (elin.p.sorgjerd@ntnu.no)[7], Xiao-Mei Mai (xiao-mei.mai@ntnu.no)[1*]

[1] Department of Public Health and Nursing, Faculty of Medicine and Health Sciences, NTNU, Norwegian University of Science and Technology, Trondheim, Norway.

[2] Department of Clinical and Molecular Medicine, Faculty of Medicine and Health Sciences, NTNU, Norwegian University of Science and Technology, Trondheim, Norway.

[3] Center for Oral Health Services and Research, Mid-Norway (TkMidt), Trondheim, Norway

[4] Clinic of Anesthesia and Intensive Care, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway

[5] K.G. Jebsen Center for Genetic Epidemiology, Department of Public Health and Nursing, Faculty of Medicine and Health Sciences, NTNU, Norwegian University of Science and Technology, Trondheim, Norway

[6] Department of Endocrinology, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway

[7] HUNT Research Centre, Department of Public Health and Nursing, NTNU, Norwegian University of Science and Technology, Trondheim, Norway

***Corresponding author**

Email: xiao-mei.mai@ntnu.no

Short title: Hours lying down and incident diabetes

Word count: Abstract:284; text: 3659 (including Tables)

Abstract

Objective: We aimed to examine relationship between hours lying down per day and risk of diabetes in young and middle-aged adults, and to assess if leisure-time physical activity and body mass index (BMI) modified this relationship.

Design: A population-based prospective cohort study.

Setting: Nord-Trøndelag, Norway.

Participants: The cohort included 17058 diabetes-free adults, at age of 20-55 years in 1995–1997, who were followed up to 2006–2008.

Primary outcome measures: Incident diabetes was defined by self-report of diabetes or non-fasting glucose levels greater than 11 mmol/L at the follow-up.

Methods: Multivariable logistic regression models were used to obtain odds ratios (OR) with 95% confidence intervals (CI) for risk of diabetes by the categories of hours lying down.

Results: 362 individuals (2.1%) developed diabetes during an average 11-year follow-up. Individuals who reported lying down ≥9 h/day had an adjusted OR of 1.35 (95% CI 1.01, 1.80) for incident diabetes compared with those lying down 8 h/day; the positive association was present for non-autoimmune diabetes (OR 1.41, 95% CI 1.05, 1.89) but not for autoimmune diabetes (OR 0.53, 95% CI 0.12, 2.47). Lying down ≤7 h/day was not associated with the risk of diabetes. In analysis stratified by physical activity, the ORs associated with lying down ≥9 h/day were 1.41 (95% CI 1.05, 1.90) and 0.90 (95% CI 0.23, 3.55) respectively among the less active and highly active individuals ($P_{interaction} = 0.048$). There was little evidence that BMI modified the association between hours lying down and risk of diabetes ($P_{interaction} = 0.62$).

Conclusions: Prolonged hours lying down per day was associated with an increased risk of diabetes in young and middle-aged adults. The positive association appeared to be modified by physical activity but not by BMI.

Article summary

Strengths and limitations of this study

- This study of young and middle-aged adults from Central Norway is one of the first population-based studies to provide an insight into potential long-term influence of hours spent lying down on diabetes risk.
- We had comprehensive information on potential confounding factors and we were able to distinguish between non-autoimmune and autoimmune diabetes.
- The size of the population was large, but stratified analysis by leisure-time physical activity showed imprecise results especially in the highly active group.
- We had no information available to separate hours lying down during the day from the night's sleep.

Background

The increasing prevalence of diabetes and its continuous inclusion in health policies indicate the significant impact of the disease on populations globally. Research shows a close association of diabetes with onset of cardiovascular diseases, a leading cause of morbidity and mortality in diabetic patients, and there has been a considerable increase in healthcare expenditures on diabetes over the years [1-3]. Therefore, the need for effective preventive measures has inspired research to look into potential health implications of various lifestyle factors.

A sedentary lifestyle refers to prolonged time spent in behaviours characterized by low muscle movement, which is linked to loss of metabolic health and chronic diseases [4 5]. As such, markers of sedentary behaviours, including total sitting and TV watching time, have shown compelling evidence of a positive association with the development of diabetes [6-8].

Lying down is characterized with very low energy expenditure. It may be used as another marker of sedentary behaviour and pose an independent health risk [9]. The detrimental effect of total time spent lying down on cardiovascular health has been highlighted in large prospective cohort studies [10 11]. Higher mortality from cardiovascular diseases was observed among adults who reported prolonged hours lying down per day, even in physically active individuals [10]. Although small-scaled experimental studies showed that prolonged bed rest was positively associated with muscle atrophy and insulin resistance [12-14], research on potential long-term effect of total hours lying down on diabetes risk at population level has been limited. In addition, it remains unknown if other lifestyle factors, such as physical activity and obesity, have any influence on the relationship. These lifestyle factors have shown to modify the association between total sitting time and diabetes risk [15-17].

The aim of this large prospective cohort study was to investigate the relation between hours lying down per day and risk of diabetes in young and middle-aged adults in an 11-year follow-up in Norway. Two specific research objectives were undertaken: 1) If hours lying down per day were associated with the risk of diabetes independently of total sitting time and other risk factors; 2) If leisure-time physical activity or obesity modified the association of hours lying down with the risk of diabetes.

Methods

Study population

The study population was derived from the HUNT study—a large population-based health study conducted in Nord-Trøndelag in Norway [18]. The HUNT study was conducted in three series. At each survey, health related information of participants was collected by means of well-structured questionnaires and a clinical examination. In the present study, we linked data from the HUNT2 survey (1995–1997) to HUNT3 survey (2006–2008) in an average 11-year follow up.

Among 65215 adults who participated in HUNT2, 40330 were at 20 to 55 years of age. The upper age limit was set because we were particularly interested in identifying lifestyle factors for prevention of diabetes in young and middle-aged adults. 25616 (64%) of the 40330 adults participated in HUNT3, of which 25282 were diabetes-free at baseline, i.e. they reported no diabetes and had a non-fasting blood glucose measurement less than 11 mmol/L in HUNT2. Among the 25282 diabetes-free adults (study cohort), 17058 (analysis cohort) had complete information on hours spent lying down per day and leisure-time physical activity in HUNT2 as well as information on diabetes in HUNT3. In general, the study and analysis cohorts showed comparable distribution of the baseline variables (Table S1).

Main variables

Participants answered a question “Do you have, or have you had diabetes?” in both HUNT2 and HUNT3. Among the diabetes-free adults at baseline, incident diabetes cases were identified by self-reporting of diabetes in HUNT3 and/or a non-fasting blood glucose measurement in HUNT3 exceeding 11 mmol/L. Self-reported incident cases were further ascertained by reported age of diagnosis falling between HUNT2 and HUNT3. Individuals without incident diabetes were those

who reported no diabetes in HUNT3 and had non-fasting blood glucose measurement in HUNT3 less than 11mmol/L.

Information on hours lying down per day was obtained from the question "How many hours do you usually spend lying down during a 24 hour period?" in the HUNT2 questionnaire. The mean and median value of the hours lying down per day in the study cohort was 8 hours. Finer categories of hours lying down were initially generated as ≤6, 7, 8, 9 and ≥10 h/day. To increase statistical precision, categories were collapsed into ≤7, 8 and ≥9 h/day in main analysis using 8 h/day as the reference category.

Leisure-time physical activity at baseline was classified into four groups based on a combination of hours of light (no sweat/not out of breath) and vigorous activity (sweat/out of breath) per week: inactive (no activity, or ≤2 h light activity only), low (≥3 h light activity only, or ≤2 h light activity and <1 h vigorous activity), moderate (≥3 h light activity and <1 h vigorous activity or 1-2 h vigorous activity regardless of light activity) and high activity (≥3 h vigorous activity regardless of light activity) [19]. For analysis stratified by leisure-time physical activity, the categories were collapsed into two groups labelled less active (inactive, low and moderate activity) and highly active (high activity).

Height and weight were measured by trained staff during the clinical examination at HUNT2. Body mass index (BMI) was estimated by weight divided by squared value of height and categorized as underweight or normal (<25.0 kg/m^2), overweight (25.0–29.9 kg/m^2), and obese (≥30.0 kg/m^2) in accordance with WHO recommendation. Data on BMI were collapsed into two groups, non-obese (underweight or normal & overweight) and obese for analysis stratified by BMI.

Other baseline variables

Other baseline variables were collected by questionnaires, including sex, age (20–29, 30–39, 40–49, and 50–55 years), smoking status (never, ex-smoker, current smoker, and missing 0.6%), alcohol consumption per month (never, 1-4 times, ≥5 times, and missing 1.9%), family history of diabetes (yes, no, and missing 0.9%), chronic diseases (yes, no, and missing 2%), years of education (<10, 10–12, ≥13 years, and missing 0.5%), economic difficulties (yes, no, and missing 1%), time spent sitting every day (0-4, 5-7, ≥8 h, and missing 2.9%), and type of work (sedentary work, much walking or lifting, heavy physical work, and missing 5.4%). The following question was used to define chronic disease: "Do you suffer from any long-term illness or injury of a physical or physiological nature that impairs your functioning in your everyday life?" (Long-term means at least one year). Economic difficulties were defined as yes when participants reported having difficulties to acquire food or transport etc. because of cost. Several other baseline variables were also collected: sleep problems were obtained by question "During the last month have you woken too early and not been able to get back to sleep?" with four options (almost every night, often, occasionally, and never); information on anxiety or depression symptoms was collected as a score using the Hospital Anxiety and Depression Scale (HADS).

Statistical analysis

Baseline characteristics were presented by categories of hours lying down per day. Binary logistic regression analysis was performed to estimate crude odds ratio (OR) with 95% confidence interval (CI) for incident diabetes by categories of hours lying down, using 8 h/day as the reference. The adjusted ORs were obtained after adjustment for potential confounding factors in the main model, including sex, age, BMI, smoking status, alcohol intake per month, family

history of diabetes, chronic diseases, education, economic difficulties, total sitting time per day, leisure-time physical activity, and type of work [10 17]. Missing information of the covariates was included as a separate category in the analysis. Three sensitivity analyses were performed; 1) BMI, chronic diseases, total sitting time per day, leisure-time physical activity, and type of work were left out from the adjustment. This was because BMI and chronic diseases were also possible mediators, and because time used in total sitting, leisure physical activity, work and lying down were co-dependent in a day of 24 hours. 2) sleep problems, and anxiety and depression symptoms (HADS as a continuous value) were additionally included in the adjustment, and 3) based on the values of serum glutamic acid decarboxylase antibodies (GADA) measured in those who reported diabetes in HUNT3, we classified the incident cases as autoimmune diabetes with a value of GADA $\geq$0.08 [20] and the rest as non-autoimmune diabetes. We repeated the analysis in the main model with multinomial logistic regression.

The analysis on the relationship between hours lying down per day and risk of diabetes was stratified by leisure-time physical activity (less active vs. highly active) and BMI status (non-obese vs. obese). Potential statistical interaction was assessed in a likelihood ratio test including a product term of 1) categories of hours lying down x leisure-time physical activity, and 2) categories of hours lying down x BMI in the regression model. All analyses were conducted using STATA/IC 13.0 for Windows (College Station, TX, USA).

Patient and Public Involvement

Neither patients nor members of the public were involved in this study.

Results

The descriptive statistics for the baseline characteristics by categories of hours lying down in the analysis cohort are shown in Table S2.

A total of 362 (2.1%) individuals were identified with diabetes during the 11-year follow-up period. Lying down ≥9 h/day was associated with an increased diabetes incidence with an adjusted OR of 1.35 (95% CI 1.01, 1.80), whereas lying down ≤7 h/day was not associated with the risk of diabetes (Table 1). Finer categories of hours lying down seemed to show a dose-response relationship (Table S3). In the first sensitivity analysis, the OR associated with lying down ≥9 h/day was 1.44 (95% CI 1.09, 1.90). In the second sensitivity analysis, the corresponding OR was 1.37 (95% CI 1.03, 1.83). The association estimates between lying down ≤7 h/day and incident diabetes in both sensitivity analyses did not differ from those in the main analyses (data not presented). In the third sensitivity analysis lying down ≥9 h/day was associated with an increased risk of non-autoimmune diabetes (adjusted OR 1.41, 95% CI 1.05, 1.89), but not with the risk of autoimmune diabetes (Table 2); lying down ≤7 h/day was not associated with either type of diabetes.

Table 1. Hours lying down per day in relation to incidence of diabetes over an 11-year follow up (n=17058)

Hours lying down per day	Number of participants	Number of cases	Risk (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
≤7	6596	130	2.0	0.98 (0.77, 1.24)	0.93 (0.73, 1.18)
8	7480	151	2.0	1.00 (reference)	1.00 (reference)
≥9	2982	81	2.7	1.36 (1.03, 1.78)	1.35 (1.01, 1.80)

CI: confidence interval; OR: odds ratio

Adjusted OR obtained after adjustment for sex, age, body mass index, smoking status, alcohol intake per month, education, economic difficulties, chronic diseases, family history of diabetes, total sitting time, physical activity, and type of work

Table 2. Hours lying down per day in relation to incidence of autoimmune diabetes or non-autoimmune diabetes over an 11-year follow up (n=17058)

	Hours lying down per day	Number of participants	Number of cases	Risk (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
Autoimmune diabetes[a]	≤7	6596	7	0.1	0.72 (0.28, 1.86)	0.69 (0.26, 1.83)
	8	7480	11	0.2	1.00 (reference)	1.00 (reference)
	≥9	2982	2	0.1	0.46 (0.10, 2.07)	0.53 (0.12, 2.47)
Non-autoimmune diabetes[b]	≤7	6596	123	1.9	1.00 (0.78, 1.27)	0.95 (0.74, 1.22)
	8	7480	140	1.9	1.00 (reference)	1.00 (reference)
	≥9	2982	79	2.7	1.43 (1.08, 1.88)	1.41 (1.05, 1.89)

CI: confidence interval; OR: odds ratio

[a]Autoimmune diabetes was classified as incident diabetes cases with a value of glutamic acid decarboxylase antibodies (GADA) ≥0.08. The rest of the incident cases were classified as [b]non-autoimmune diabetes.

Adjusted OR obtained after adjustment for sex, age, body mass index, smoking status, alcohol intake per month, education, economic difficulties, chronic diseases, family history of diabetes, total sitting time, physical activity, and type of work

Among the less active individuals, lying down ≥9 h/day was associated with an increased risk of diabetes with an OR of 1.41 (95% CI 1.05, 1.90) (Table 3). This positive association appeared absent among the highly active individuals (OR = 0.90, 95% CI 0.23, 3.55). Lying down ≤7 h/day was not associated with the risk of diabetes in the less active individuals, but it was associated with a reduced risk in the highly active individuals (Table 3). A likelihood ratio test showed evidence of statistical interaction between hours lying down per day and leisure-time physical activity ($P_{for\ interaction} = 0.048$).

Table 3. Hours lying down per day in relation to incidence of diabetes over an 11-year follow up stratified by leisure-time physical activity (n=17058)

Hours lying down per day	Number of participants	Number of cases	Risk (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
Less active[a]					
≤7	5743	127	2.2	1.05 (0.82, 1.34)	1.00 (0.77, 1.28)
8	6534	138	2.1	1.00 (reference)	1.00 (reference)
≥9	2623	78	3.0	1.42 (1.07, 1.88)	1.41 (1.05, 1.90)
Highly active[b]					
≤7	853	3	0.4	0.25 (0.07, 0.89)	0.21 (0.05, 0.83)
8	946	13	1.4	1.00 (reference)	1.00 (reference)
≥9	359	3	0.8	0.60 (0.17, 2.13)	0.90 (0.23, 3.55)

CI: confidence interval; OR - odds ratio

[a]Less active refers to inactive and low to moderate physical activity. [b]Highly active refers to high levels of physical activity

Adjusted OR obtained after adjustment for sex, age, body mass index, smoking status, alcohol intake per month, education, economic difficulties, chronic diseases, family history of diabetes, total sitting time, physical activity, and type of work

Among the obese individuals, lying down ≥9 h/day was associated with an increased risk of diabetes (OR = 1.61, 95% CI 1.04, 2.49) (Table 4). It was also associated with an increased OR among the non-obese individuals (OR = 1.23, 95% CI 0.83, 1.82). There was little evidence of statistical interaction between hours lying down and BMI ($P_{\text{for interaction}} = 0.62$).

Table 4. Hours lying down per day in relation to incidence of diabetes over an 11-year follow up stratified by BMI status (n=17024 [c])

Hours lying down per day	Number of participants	Number of cases	Risk (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
Non-obese[a]					
≤7	5870	78	1.3	1.06 (0 .77, 1.44)	0.97 (0.71, 1.34)
8	6598	83	1.3	1.00 (reference)	1.00 (reference)
≥9	2583	39	1.5	1.20 (0.82, 1.77)	1.23 (0.83, 1.82)
Obese[b]					
≤7	718	51	7.1	0.90 (0.62, 1.32)	0.86 (0.58, 1.28)
8	871	68	7.8	1.00 (reference)	1.00 (reference)
≥9	384	42	10.9	1.45 (0.98, 2.17)	1.61 (1.04, 2.49)

BMI: body mass index; CI: confidence interval; OR: odds ratio

[a]Non-obese refers to BMI <30.0 kg/m^2. [b]Obese refers to BMI ≥30.0 kg/m^2. [c]34 participants are not included due to missing information on BMI

Adjusted OR obtained after adjustment for sex, age, body mass index, smoking status, alcohol intake per month, education, economic difficulties, chronic diseases, family history of diabetes, total sitting time, physical activity, and type of work

Discussion

We observed a 35% higher risk of incident diabetes in people reporting lying down ≥9 h/day compared with those lying down 8 h/day. Lying down ≤7 h/day was not associated with the diabetes risk. Stratified analysis showed that lying down ≥9 h/day was associated with diabetes risk in the less physically active group but not in the highly active group. There was little evidence that BMI modified the association.

Prolonged hours lying down as an independent risk factor for diabetes

Results of the present study support previous reports of the negative impact of a sedentary lifestyle on health. This is in accordance with a meta-analysis study in which a positive association was found between prolonged sitting behaviour and increased risk of diabetes [21]. The most recent studies also show consistent results on the detrimental effect of total sitting time on diabetes [6 17]. After adjustment for sitting time and other risk factors in the present study, lying down ≥9 h/day was independently associated with a moderate increase in diabetes risk. In a previous HUNT study, prolonged hours lying down was independently associated with mortality from all-cause and cardiovascular disease [10].

Skeletal muscles function as a key site for insulin-stimulated glucose disposal, and loss in muscles associated with sedentary behaviour may contribute to pathogenesis of diabetes in adults [22]. Studies have also observed rapid decrease of muscle glucose transporter (GLUT) proteins when muscles are not utilized [23]. Low levels and expression of the GLUT-proteins affect carbohydrate metabolism and contribute to insulin resistance in the skeletal muscles [23-25]. In addition, low energy expenditure associated with sedentary behaviour may have negative impact on lipid levels leading to lipids accumulation and insulin resistance [26 27]. In a broader perspective,

all these mechanisms may result in increased levels of glucose, lipids, and other metabolic markers that contribute to metabolic syndrome [28]. Prolonged sitting time has been strongly linked with metabolic impairment [28 29], which predisposes individuals to high diabetes risk in the long term. The energy expenditure associated with lying down is very low. Compared to sitting, there is a decrease in heart rate and respiratory quotient associated with lying down [30]. Therefore, a detrimental effect of longer hours lying down on risk of diabetes can be anticipated.

Influence of physical activity on the association

Our findings are consistent with previous studies in which physical activity affected the association between prolonged sitting time and incident diabetes or mortality [15 17 31], with a positive association remained in the inactive individuals but disappeared in the active individuals. Nevertheless, the potential adverse effect of prolonged lying down on mortality has been shown to exist among both active and inactive people in a previous HUNT study [10]. In the referred study [10] active individuals were categorized as those who reported moderate to high levels of physical activity, which may explain why harmful effect of longer hours lying down remained in the physically active group. Our study suggested that physical activity above a moderate level might have a modifying effect. In practice, moderate level of physical activity in the HUNT studies aligns with the physical activity recommendations for public health [31 32]. Ekleund *et al.* in their meta-analysis found physical activity beyond recommended levels being capable of cancelling out risk of mortality associated with prolonged sitting [31].

It is well documented that physical activity increases glucose uptake and improves glucose homeostasis and overall energy balance [33-36]. Highly active individuals engage in more vigorous activity compared to the less active individuals. High intensity training has been shown to

increase glucose uptake during and post exercise [25 37 38]. Engaging in vigorous physical activity also provides a better lipid profile that may help to prevent insulin resistance [39 40]. Therefore, highly active individuals may have an advantage with higher insulin sensitivity and glucose metabolism during longer hours lying down to prevent or delay the onset of diabetes. Less active individuals with little or no vigorous physical activity may have an excess metabolic risk from prolonged lying down.

Influence of obesity on the association

Studies suggest that sedentary behaviour and obesity may have a bidirectional relationship [41-43]. Obesity may be either a confounding factor or an intermediate factor in the context [44]. Adjustment for a potential intermediate factor would bias the association between sedentary behaviour and health outcome towards null [44]. Thus, if obesity is a mediator, the magnitude of association between longer hours lying down and risk of diabetes may have been underestimated in the main result (OR 1.35).

Similar to a previous HUNT study on total sitting time in relation to diabetes risk [17], there was little evidence of statistical interaction by BMI status in the present study. This was inconsistent with two other studies that reported an influence of BMI on the association of sitting time with diabetes risk [15 16]. However, the latter studies either used self-reported height and weight or conducted in post-menopausal women.

Strengths and weaknesses

This prospective cohort study of young and middle-aged adults from Central Norway is one of the first population-based studies to provide an insight into the potential long-term influence of hours spent lying down on diabetes risk. The distribution of baseline characteristics were similar

in the study and analysis cohorts. In addition, comprehensive information on potential confounding factors warranted more accurate estimate for the association.

There are several limitations with the study. Selection bias cannot completely be excluded as 64% of the young and middle-aged adults in HUNT2 were followed up in HUNT3. However, the participation rate did not differ substantially among adults who reported lying down ≤7, 8 and ≥9 h/day (66%, 68% and 61% respectively). The size of the population was large, but stratified analysis showed imprecise results especially in the highly physically active group. Self-reported information on hours lying down, diabetes and covariates are subject to misclassification that is likely to be non-differential in a prospective study. Moreover, we cannot rule out residual confounding due to unknown or unmeasured factors, for example the lack of dietary information. Finally, hours spent lying down per day in our study included periods of sleep. We did not have available information to separate hours lying down during the day from the night's sleep. Both short and long sleep have been reported to increase the risk of mortality or diabetes in previous studies [45 46]. The harm of short sleep may be explained by consequences of sleep problems per se, but explanations for the harm of long sleep are unknown [45 46]. Our data showed that adjustment for chronic diseases in the main analysis and additional adjustment for sleep problems and anxiety and depression symptoms in the sensitivity analysis did not change the observed associations between hours lying down and risk of diabetes. Although remaining speculative, very low energy expenditure was a likely explanation for the harm of prolonged hours lying down at both daytime and night's sleep.

Conclusions

Prolonged hours lying down per day was associated with an increased risk of diabetes in a young and middle-aged adult population. The positive association was present in the less physically

active individuals, but appeared absent among the highly active individuals. Obesity did not seem to affect the association.

List of abbreviations

HUNT: HelseUndersøkelsen i Nord-Trøndelag

BMI: Body Mass Index

Declarations

Acknowledgements: The HUNT Study is a collaboration between the HUNT Research Centre (Faculty of Medicine and Health Sciences, NTNU, Norwegian University of Science and Technology), the Nord-Trøndelag County Council, Central Norway Regional Health Authority, and the Norwegian Institute of Public Health.

Contributors: EOA and XMM contributed to the study design. EOA and XMM conducted statistical analysis and wrote the initial draft of the manuscript. YQS, TILN, BOÅ and EPS contributed to interpretation of results and critically revised the manuscript for important intellectual content. All authors approved the final version of the manuscript.

Funding: This work was supported by Department of Public Health and Nursing, NTNU [EOA] and The Norwegian Cancer Society [project ID 5769155-2015] [YQS] and The Research Council of Norway "Gaveforsterkning" [YQS].

Competing interests: None declared

Patient consent: All participants signed informed written consent upon participation in HUNT.

Ethics approval: The study was approved by the Norwegian Regional Committees for Medical and Health Research Ethics (2010/389/REK midt).

Data sharing statement: Data from the HUNT Study that is used in research projects will, when reasonably requested by others, be made available on request to the HUNT Data Access Committee (hunt@medisin.ntnu.no). The HUNT data access information describes the policy regarding data availability (https://www.ntnu.edu/hunt/data).

Exclusive Licence

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in BMJ Open and any other BMJ products and to exploit all rights, as set out in our licence.

References

1. Leon BM, Maddox TM. Diabetes and cardiovascular disease: Epidemiology, biological mechanisms, treatment recommendations and future research. *World Journal of Diabetes* 2015;6(13):1246-58. doi: 10.4239/wjd.v6.i13.1246
2. Tamayo T, Rosenbauer J, Wild SH, et al. Diabetes in Europe: An update. *Diabetes Research and Clinical Practice*;103(2):206-17. doi: 10.1016/j.diabres.2013.11.007
3. Sørensen M, Arneberg F, Line TM, et al. Cost of diabetes in Norway 2011. *Diabetes Research and Clinical Practice* 2016;122:124-32. doi: http://dx.doi.org/10.1016/j.diabres.2016.10.012
4. Wolfe RR. The underappreciated role of muscle in health and disease. *The American Journal of Clinical Nutrition* 2006;84(3):475-82. doi: 10.1093/ajcn/84.3.475
5. Steene-Johannessen J, Anderssen SA, Kolle E, et al. Low muscle fitness is associated with metabolic risk in youth. *Medicine and science in sports and exercise* 2009;41(7):1361-7. doi: 10.1249/MSS.0b013e31819aaae5 [published Online First: 2009/06/12]
6. van der Berg JD, Stehouwer CD, Bosma H, et al. Associations of total amount and patterns of sedentary behaviour with type 2 diabetes and the metabolic syndrome: The Maastricht Study. *Diabetologia* 2016;59(4):709-18. doi: 10.1007/s00125-015-3861-8 [published Online First: 2016/02/03]
7. Grontved A, Hu FB. Television viewing and risk of type 2 diabetes, cardiovascular disease, and all-cause mortality: a meta-analysis. *Jama* 2011;305(23):2448-55. doi: 10.1001/jama.2011.812 [published Online First: 2011/06/16]
8. Henson J, Dunstan DW, Davies MJ, et al. Sedentary behaviour as a new behavioural target in the prevention and treatment of type 2 diabetes. *Diabetes/metabolism research and reviews* 2016;32 Suppl 1:213-20. doi: 10.1002/dmrr.2759 [published Online First: 2016/01/28]
9. Ainsworth BE, Haskell WL, Whitt MC, et al. Compendium of physical activities: an update of activity codes and MET intensities. *Medicine and science in sports and exercise* 2000;32(9 Suppl):S498-504. [published Online First: 2000/09/19]
10. Holtermann A, Mork PJ, Nilsen TI. Hours lying down per day and mortality from all-causes and cardiovascular disease: the HUNT Study, Norway. *European journal of epidemiology* 2014;29(8):559-65. doi: 10.1007/s10654-014-9939-7 [published Online First: 2014/07/17]
11. McDermott MM, Guralnik JM, Ferrucci L, et al. Community walking speed, sedentary or lying down time, and mortality in peripheral artery disease. *Vasc Med* 2016;21(2):120-9. doi: 10.1177/1358863X15626521
12. Dirks ML, Wall BT, van de Valk B, et al. One Week of Bed Rest Leads to Substantial Muscle Atrophy and Induces Whole-Body Insulin Resistance in the Absence of Skeletal Muscle Lipid Accumulation. *Diabetes* 2016;65(10):2862-75. doi: 10.2337/db15-1661 [published Online First: 2016/07/01]
13. Kenny HC, Rudwill F, Breen L, et al. Bed rest and resistive vibration exercise unveil novel links between skeletal muscle mitochondrial function and insulin resistance. *Diabetologia* 2017;60(8):1491-501. doi: 10.1007/s00125-017-4298-z [published Online First: 2017/05/14]
14. Alibegovic AC, Hojbjerre L, Sonne MP, et al. Impact of 9 days of bed rest on hepatic and peripheral insulin action, insulin secretion, and whole-body lipolysis in healthy young male offspring of patients with type 2 diabetes. *Diabetes* 2009;58(12):2749-56. doi: 10.2337/db09-0369 [published Online First: 2009/09/02]

15. Petersen CB, Bauman A, Tolstrup JS. Total sitting time and the risk of incident diabetes in Danish adults (the DANHES cohort) over 5 years: a prospective study. *British journal of sports medicine* 2016;50(22):1382-87. doi: 10.1136/bjsports-2015-095648 [published Online First: 2016/11/03]
16. Manini TM, Lamonte MJ, Seguin RA, et al. Modifying effect of obesity on the association between sitting time and incident diabetes in post-menopausal women. *Obesity (Silver Spring, Md)* 2014;22(4):1133-41. doi: 10.1002/oby.20620
17. Åsvold BO, Midthjell K, Krokstad S, et al. Prolonged sitting may increase diabetes risk in physically inactive individuals: an 11 year follow-up of the HUNT Study, Norway. *Diabetologia* 2017:1-6. doi: 10.1007/s00125-016-4193-z
18. Krokstad S, Langhammer A, Hveem K, et al. Cohort Profile: the HUNT Study, Norway. *International journal of epidemiology* 2013;42(4):968-77. doi: 10.1093/ije/dys095 [published Online First: 2012/08/11]
19. Jiang L, Sun YQ, Brumpton BM, et al. Prolonged Sitting, Its Combination With Physical Inactivity and Incidence of Lung Cancer: Prospective Data From the HUNT Study. *Frontiers in oncology* 2019;9:101. doi: 10.3389/fonc.2019.00101 [published Online First: 2019/03/13]
20. Sorgjerd EP, Skorpen F, Kvaloy K, et al. Time dynamics of autoantibodies are coupled to phenotypes and add to the heterogeneity of autoimmune diabetes in adults: the HUNT study, Norway. *Diabetologia* 2012;55(5):1310-8. doi: 10.1007/s00125-012-2463-y [published Online First: 2012/02/03]
21. Wilmot EG, Edwardson CL, Achana FA, et al. Sedentary time in adults and the association with diabetes, cardiovascular disease and death: systematic review and meta-analysis. *Diabetologia* 2012;55(11):2895-905. doi: 10.1007/s00125-012-2677-z
22. DeFronzo RA, Tripathy D. Skeletal muscle insulin resistance is the primary defect in type 2 diabetes. *Diabetes care* 2009;32 Suppl 2:S157-63. doi: 10.2337/dc09-S302 [published Online First: 2009/11/13]
23. Tremblay MS, Colley RC, Saunders TJ, et al. Physiological and health implications of a sedentary lifestyle. *Applied physiology, nutrition, and metabolism = Physiologie appliquee, nutrition et metabolisme* 2010;35(6):725-40. doi: 10.1139/h10-079 [published Online First: 2010/12/18]
24. Bergouignan A, Rudwill F, Simon C, et al. Physical inactivity as the culprit of metabolic inflexibility: evidence from bed-rest studies. *Journal of applied physiology (Bethesda, Md : 1985)* 2011;111(4):1201-10. doi: 10.1152/japplphysiol.00698.2011 [published Online First: 2011/08/13]
25. Richter EA, Hargreaves M. Exercise, GLUT4, and skeletal muscle glucose uptake. *Physiological reviews* 2013;93(3):993-1017. doi: 10.1152/physrev.00038.2012 [published Online First: 2013/08/01]
26. Kelley DE, Goodpaster BH. Skeletal muscle triglyceride. An aspect of regional adiposity and insulin resistance. *Diabetes care* 2001;24(5):933-41. [published Online First: 2001/05/12]
27. Corcoran MP, Lamon-Fava S, Fielding RA. Skeletal muscle lipid deposition and insulin resistance: effect of dietary fatty acids and exercise. *Am J Clin Nutr* 2007;85(3):662-77. doi: 10.1093/ajcn/85.3.662 [published Online First: 2007/03/09]
28. Edwardson CL, Gorely T, Davies MJ, et al. Association of Sedentary Behaviour with Metabolic Syndrome: A Meta-Analysis. *PLoS ONE* 2012;7(4):e34916. doi: 10.1371/journal.pone.0034916
29. Dunstan DW, Kingwell BA, Larsen R, et al. Breaking Up Prolonged Sitting Reduces Postprandial Glucose and Insulin Responses. *Diabetes care* 2012;35(5):976-83. doi: 10.2337/dc11-1931
30. Miles-Chan JL, Sarafian D, Montani JP, et al. Sitting comfortably versus lying down: Is there really a difference in energy expenditure? *Clin Nutr* 2014;33(1):175-78. doi: 10.1016/j.clnu.2013.11.009

31. Ekelund U, Steene-Johannessen J, Brown WJ. Does physical activity attenuate, or even eliminate, the detrimental association of sitting time with mortality? A harmonised meta-analysis of data from more than 1 million men and women (vol 388, pg 1302, 2016). *Lancet* 2016;388(10051):E6-E6.
32. WHO. Global recommendations on physical activity for health, 2010.
33. Horsch A, Wobmann M, Kriemler S, et al. Impact of physical activity on energy balance, food intake and choice in normal weight and obese children in the setting of acute social stress: a randomized controlled trial. *BMC Pediatrics* 2015;15:12. doi: 10.1186/s12887-015-0326-7
34. van Baak MA. Physical activity and energy balance. *Public health nutrition* 1999;2(3a):335-9. [published Online First: 1999/12/28]
35. Sylow L, Kleinert M, Richter EA, et al. Exercise-stimulated glucose uptake - regulation and implications for glycaemic control. *Nature reviews Endocrinology* 2017;13(3):133-48. doi: 10.1038/nrendo.2016.162 [published Online First: 2016/11/04]
36. Rottensteiner M, Leskinen T, Niskanen E, et al. Physical activity, fitness, glucose homeostasis, and brain morphology in twins. *Medicine and science in sports and exercise* 2015;47(3):509-18. doi: 10.1249/mss.0000000000000437 [published Online First: 2014/07/09]
37. Adams OP. The impact of brief high-intensity exercise on blood glucose levels. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy* 2013;6:113-22. doi: 10.2147/DMSO.S29222
38. Gibala MJ, Little JP, Macdonald MJ, et al. Physiological adaptations to low-volume, high-intensity interval training in health and disease. *The Journal of physiology* 2012;590(5):1077-84. doi: 10.1113/jphysiol.2011.224725 [published Online First: 2012/02/01]
39. Zheng S, Xu H, Zhou H, et al. Associations of lipid profiles with insulin resistance and beta cell function in adults with normal glucose tolerance and different categories of impaired glucose regulation. *PLoS One* 2017;12(2):e0172221. doi: 10.1371/journal.pone.0172221 [published Online First: 2017/02/16]
40. Kwon H-J, Lee H-J. Effect of vigorous physical activity on blood lipid and glucose. *Journal of Exercise Rehabilitation* 2017;13(6):653-58. doi: 10.12965/jer.1735150.575
41. Pedisic Z, Grunseit A, Ding D, et al. High sitting time or obesity: Which came first? Bidirectional association in a longitudinal study of 31,787 Australian adults. *Obesity (Silver Spring)* 2014;22(10):2126-30. doi: 10.1002/oby.20817 [published Online First: 2014/06/20]
42. Bullock VE, Griffiths P, Sherar LB, et al. Sitting time and obesity in a sample of adults from Europe and the USA. *Annals of human biology* 2017;44(3):230-36. doi: 10.1080/03014460.2016.1232749 [published Online First: 2016/09/09]
43. Heinonen I, Helajärvi H, Pahkala K, et al. Sedentary behaviours and obesity in adults: the Cardiovascular Risk in Young Finns Study. *BMJ Open* 2013;3(6)
44. Hamilton MT, Hamilton DG, Zderic TW. Sedentary behavior as a mediator of type 2 diabetes. *Medicine and sport science* 2014;60:11-26. doi: 10.1159/000357332
45. Gallicchio L, Kalesan B. Sleep duration and mortality: a systematic review and meta-analysis. *Journal of sleep research* 2009;18(2):148-58. doi: 10.1111/j.1365-2869.2008.00732.x [published Online First: 2009/08/04]
46. Shan Z, Ma H, Xie M, et al. Sleep Duration and Risk of Type 2 Diabetes: A Meta-analysis of Prospective Studies. *Diabetes care* 2015;38(3):529.

Additional files

Additional file 1: Table S1. Baseline characteristics of the study cohort and analysis cohort

Additional file 2: Table S2. Baseline characteristics of analysis cohort stratified by hours lying down per day

Additional file 3: Table S3. Finer categories of hours lying down per day in relation to incidence of diabetes over an 11-year follow up

Table S1. Baseline characteristics of the study cohort and analysis cohort

Characteristics	Study cohort (n=25282)		Analysis cohort (n=17058)	
	n	%	n	%
Sex				
Male	11252	44.5	7724	45.3
Female	14030	55.5	9334	54.7
Age (years)				
20−29	3988	15.8	2954	17.3
30−39	7553	29.9	5363	31.4
40−49	9796	38.7	6343	37.2
50−55	3945	15.6	2398	14.1
BMI (kg/m^2)				
<25.0	11656	46.1	8012	46.9
25−29.9	10462	41.4	7039	41.3
≥30.0	3114	12.3	1973	11.6
Missing	50	0.2	34	0.2
Smoking status				
Never	11494	45.5	8171	47.9
Ex-smoker	6326	25.0	4303	25.2
Current	7277	28.8	4483	26.3
Missing	185	0.7	101	0.6
Alcohol intake per month				
Never	6913	27.3	4427	26.0
1−4 times	14220	56.3	9863	57.8
≥5 times	3398	13.4	2447	14.4
Missing	751	3.0	321	1.9
Family history of diabetes				
Yes	3272	12.9	2407	14.1
No	18360	72.6	14,492	85.0
Missing	3650	14.5	159	0.9
Chronic diseases				
Yes	4191	16.6	2680	15.7
No	20354	80.5	14,044	82.3
Missing	737	2.9	334	2.0
Education (years)				
<10	5036	19.9	2864	16.8
10−12	13466	53.3	9155	53.7
≥ 13	6559	25.9	4949	29.0
Missing	221	0.9	90	0.5
Economic difficulties				
Yes	7068	27.9	5484	32.1
No	14505	57.4	11,412	66.9
Missing	3709	14.7	162	1.0
Sitting time, hours/day				
0−4	6553	25.9	4937	28.9
5−7	6275	24.8	4956	29.1

≥8	8068	31.9	6676	39.1
Missing	4386	17.4	489	2.9
Type of work				
Mostly sedentary work	6890	27.3	4949	29.0
Much walking or lifting at work	13848	54.8	9290	54.5
Heavy physical work	2843	11.2	1903	11.2
Missing	1701	6.7	916	5.4

BMI: body mass index; n: number of participants; %: column percentage

Table S2. Baseline characteristics of analysis cohort stratified by hours lying down per day (n=17058)

Characteristics	Hours lying down per day					
	≤7 n=6596		8 n=7480		≥9 n=2982	
	n	%	n	%	n	%
Sex						
Male	3606	54.7	3113	41.6	1005	33.7
Female	2990	45.3	4367	58.4	1977	66.3
Age (years)						
20−29	866	13.1	1307	17.5	781	26.2
30−39	2326	35.3	2218	29.7	819	27.5
40−49	2518	38.2	2856	38.2	969	32.5
50−55	886	13.4	1099	14.7	413	13.8
BMI (kg/m^2)						
<25.0	2959	44.9	3611	48.3	1442	48.4
25.0−29.9	2911	44.1	2987	39.9	1141	38.3
≥30.0	718	10.9	871	11.6	384	12.9
Missing	8	0.1	11	0.1	15	0.5
Smoking status						
Never	3008	45.6	3703	49.5	1460	49.0
Ex-smoker	1709	25.9	1893	25.3	701	23.5
Current	1843	27.9	1842	24.6	798	26.8
Missing	36	0.5	42	0.6	23	0.8
Alcohol intake per month						
Never	1624	24.6	1933	25.8	870	29.2
1−4 times	3813	57.8	4383	58.6	1667	55.9
≥5 times	1041	15.8	1034	13.8	372	12.5
Missing	118	1.8	130	1.7	73	2.4
Family history of diabetes						
Yes	918	13.9	1053	14.1	436	14.6
No	5606	85.0	6367	85.1	2519	84.5
Missing	72	1.1	60	0.8	27	0.9
Chronic diseases						
Yes	983	14.9	1067	14.3	630	21.1
No	5511	83.6	6264	83.7	2269	76.1
Missing	102	1.5	149	2.0	83	2.8
Education (years)						
<10	1047	15.9	1203	16.1	614	20.6
10−12	3612	54.8	3947	52.8	1596	53.5
≥ 13	1899	28.8	2297	30.7	753	25.3

Missing	38	0.6	33	0.4	19	0.6
Economic difficulties						
Yes	2224	33.7	2256	30.2	1004	33.7
No	4319	65.5	5149	68.8	1944	65.2
Missing	53	0.8	75	1.0	34	1.1
Sitting time, hours/day						
0−4	1904	28.9	2158	28.9	875	29.3
5−7	1818	27.6	2123	28.4	1015	34.0
≥8	2700	40.9	2996	40.1	980	32.9
Missing	174	2.6	203	2.7	112	3.8
Leisure-time physical activity						
Inactive	1665	25.2	1868	25.0	836	28.0
Low	1652	25.0	1906	25.5	788	26.4
Moderate	2426	36.8	2760	36.9	999	33.5
High	853	12.9	946	12.6	359	12.0
Type of work						
Mostly sedentary work	2072	31.4	2194	29.3	683	22.9
Much walking or lifting at work	3469	52.6	4108	54.9	1713	57.4
Heavy physical work	800	12.1	810	10.8	293	9.8
Missing	255	3.9	368	4.9	293	9.8

BMI: body mass index; n: number of participants; %: column percentage

Table S3. Finer categories of hours lying down per day in relation to incidence of diabetes over an 11-year follow up (n=17058)

Hours lying down per day	Number of participants	Number of cases	Risk (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
≤6	1174	22	1.8	0.93 (0.59, 1.46)	0.80 (0.50, 1.28)
7	5422	108	2.0	0.99 (0.77, 1.27)	0.96 (0.74, 1.24)
8	7480	151	2.0	1.00 (reference)	1.00 (reference)
9	2171	57	2.6	1.31 (0.96, 1.78)	1.34 (0.97, 1.85)
≥10	811	24	3.0	1.48 (0.96, 2.29)	1.38 (0.87, 2.19)

CI: confidence interval; OR: odds ratio

Adjusted OR obtained after adjustment for sex, age, body mass index, smoking status, alcohol intake per month, education, economic difficulties, chronic diseases, family history of diabetes, total sitting time, physical activity, and type of work

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	6-9
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7 & 8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8 & 9
		(*b*) Describe any methods used to examine subgroups and interactions	9
		(*c*) Explain how missing data were addressed	8 & 9
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	6 & 15
		(*e*) Describe any sensitivity analyses	9 & 10

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	6,8 & 9
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	6 & 10
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	10
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10 to13
		(*b*) Report category boundaries when continuous variables were categorized	7 & 8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12 & 13
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	17-18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Hours lying down per day, as a proxy for sedentary behaviour, and risk of diabetes in young and middle-aged adults in Norway: an 11-year follow-up of the HUNT Study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-035010.R1
Article Type:	Original research
Date Submitted by the Author:	19-Feb-2020
Complete List of Authors:	Asante, Ernest; Norwegian University of Science and Technology, Dept. of Public Health and Nursing Sun, Yi-Qian; Norwegian University of Science and Technology, Dept. of Clinical and Molecular Medicine; TkMidt-Center for Oral Health Services and Research Nilsen, Tom; Norwegian University of Science and Technology, Department of Public Health and Nursing; St. Olavs Hospital, Trondheim University Hospital, Clinic of Anesthesia and Intensive Care Åsvold, Bjørn; Norwegian University of Science and Technology, K.G. Jebsen Center for Genetic Epidemiology, Dept. of Public Health and Nursing; St. Olavs Hospital, Trondheim University Hospital, Department of Endocrinology Sørgjerd, Elin; The Norwegian University of Science and Technology, HUNT Research Centre, Department of public health and Nursing Mai, Xiao-Mei; Norwegian University of Science and Technology, Dept. of Public Health and Nursing
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Diabetes and endocrinology, Public health
Keywords:	General diabetes < DIABETES & ENDOCRINOLOGY, EPIDEMIOLOGY, PUBLIC HEALTH

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Hours lying down per day, as a proxy for sedentary behaviour, and risk of diabetes in young and middle-aged adults in Norway: an 11-year follow-up of the HUNT Study

Ernest O. Asante (Asante_Ernest@outlook.com)[1], Yi-Qian Sun (yi-qian.sun@ntnu.no)[2,3], Tom IL Nilsen (tom.nilsen@ntnu.no)[1,4], Bjørn O. Åsvold (bjorn.o.asvold@ntnu.no)[5,6,7], Elin P. Sørgjerd (elin.p.sorgjerd@ntnu.no)[7], Xiao-Mei Mai (xiao-mei.mai@ntnu.no)[1*]

[1] Department of Public Health and Nursing, Faculty of Medicine and Health Sciences, NTNU, Norwegian University of Science and Technology, Trondheim, Norway.

[2] Department of Clinical and Molecular Medicine, Faculty of Medicine and Health Sciences, NTNU, Norwegian University of Science and Technology, Trondheim, Norway.

[3] Center for Oral Health Services and Research, Mid-Norway (TkMidt), Trondheim, Norway

[4] Clinic of Anesthesia and Intensive Care, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway

[5] K.G. Jebsen Center for Genetic Epidemiology, Department of Public Health and Nursing, Faculty of Medicine and Health Sciences, NTNU, Norwegian University of Science and Technology, Trondheim, Norway

[6] Department of Endocrinology, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway

[7] HUNT Research Centre, Department of Public Health and Nursing, NTNU, Norwegian University of Science and Technology, Trondheim, Norway

***Corresponding author**

Email: xiao-mei.mai@ntnu.no

Short title: Hours lying down and incident diabetes

Word count: Abstract: 264; text: 3791 (including Tables)

Abstract

Objective: We aimed to examine relationship between hours lying down per day, as a proxy for sedentary behaviour, and risk of diabetes in young and middle-aged adults, and to assess if leisure-time physical activity and body mass index (BMI) modified this relationship.

Design: A population-based prospective cohort study.

Setting: Nord-Trøndelag, Norway.

Participants: The cohort included 17058 diabetes-free adults, at age of 20-55 years in 1995–1997, who were followed up to 2006–2008.

Primary outcome measures: Incident diabetes was defined by self-report of diabetes or non-fasting glucose levels greater than 11 mmol/L at the follow-up.

Methods: Multivariable logistic regression models were used to obtain odds ratios (OR) with 95% confidence intervals (CI) for risk of diabetes by the categories of hours lying down (≤7, 8 and ≥9 h/day).

Results: 362 individuals (2.1%) developed diabetes during an average 11-year follow-up. Individuals who reported lying down ≥9 h/day had an adjusted OR of 1.35 (95% CI 1.01, 1.80) for incident diabetes compared with those lying down 8 h/day. Lying down ≤7 h/day was not associated with the risk of diabetes. In analysis stratified by physical activity, the ORs associated with lying down ≥9 h/day were 1.41 (95% CI 1.05, 1.90) and 0.90 (95% CI 0.23, 3.55) respectively among the less active and highly active individuals ($P_{\text{interaction}} = 0.048$). There was little evidence that the association differed by BMI status ($P_{\text{interaction}} = 0.62$).

Conclusions: Prolonged hours lying down per day was associated with an increased risk of diabetes in young and middle-aged adults. The positive association appeared to be modified by physical activity but not by BMI.

Article summary

Strengths and limitations of this study

- This study of young and middle-aged adults from Central Norway is one of the first population-based studies to provide an insight into potential long-term influence of hours spent lying down on diabetes risk.
- We had comprehensive information on potential confounding factors.
- The size of the population was large, but stratified analysis by leisure-time physical activity showed imprecise result in the highly active group.
- We had no information available to separate hours lying down during the day from the night's sleep.

Background

The increasing prevalence of diabetes and its continuous inclusion in health policies indicate the significant impact of the disease on populations globally. Research shows a close association of diabetes with onset of cardiovascular diseases, a leading cause of morbidity and mortality in diabetic patients, and there has been a considerable increase in healthcare expenditures on diabetes over the years [1-3]. Therefore, the need for effective preventive measures has inspired research to look into potential health implications of various lifestyle factors.

A sedentary lifestyle refers to prolonged time spent in behaviours characterized by low muscle movement, which is linked to loss of metabolic health and chronic diseases [4 5]. As such, markers of sedentary behaviours, including total sitting and TV watching time, have shown compelling evidence of a positive association with the development of diabetes [6-8].

Lying down is characterized with very low energy expenditure. It may be used as an alternative marker for sedentary behaviour and pose an independent health risk [9]. The detrimental effect of total time spent lying down on cardiovascular health has been highlighted in large prospective cohort studies [10 11]. Higher mortality from cardiovascular diseases was observed among adults who reported prolonged hours lying down per day, even in physically active individuals [10]. Although small-scaled experimental studies showed that prolonged bed rest was positively associated with muscle atrophy and insulin resistance [12-14], research on potential long-term effect of total hours lying down on diabetes risk at population level has been limited. In addition, it remains unknown if other lifestyle factors such as physical activity and obesity modify the association. These lifestyle factors have shown to modify the association between total sitting time and diabetes risk [15-17].

The aim of this large prospective cohort study was to investigate the relation between hours lying down per day, as a proxy for sedentary behaviour, and risk of diabetes in young and middle-aged adults in an 11-year follow-up in Norway. Two specific research objectives were undertaken: 1) If longer hours lying down per day were positively associated with the risk of diabetes independently of total sitting time and other risk factors; 2) If leisure-time physical activity or obesity modified the association.

Methods

Study population

The study population was derived from the HUNT study—a large population-based health study conducted in Nord-Trøndelag in Norway [18]. The HUNT study was conducted in three series. At each survey, health related information of participants was collected by well-structured questionnaires and a clinical examination. In the present study, we linked data from the HUNT2 survey (1995–1997) to HUNT3 survey (2006–2008) in an average 11-year follow up.

Among 65215 adults who participated in HUNT2, 40330 were at 20 to 55 years of age. The upper age limit was set to 55 years because we were particularly interested in identifying lifestyle factors for prevention of diabetes in young and middle-aged adults. 25616 (64%) of the 40330 adults participated in HUNT3, of which 25282 were diabetes-free at baseline, i.e. they reported no diabetes and had a non-fasting blood glucose measurement less than 11 mmol/L in HUNT2. Among the 25282 diabetes-free adults (study cohort), 17058 (analysis cohort) had complete information on hours spent lying down per day and leisure-time physical activity in HUNT2 as well as information on diabetes in HUNT3. In general, the study and analysis cohorts showed comparable distribution of the baseline variables (Table S1).

Main variables

Participants answered a question “Do you have, or have you had diabetes?” in both HUNT2 and HUNT3. Among the diabetes-free adults at baseline, incident diabetes cases were identified by self-reporting of diabetes in HUNT3 and/or a non-fasting blood glucose measurement in HUNT3 exceeding 11 mmol/L. Self-reported incident cases were further ascertained by reported age of diagnosis falling between HUNT2 and HUNT3. Individuals without incident diabetes were those

who reported no diabetes in HUNT3 and had non-fasting blood glucose measurement in HUNT3 less than 11mmol/L. Based on serum glutamic acid decarboxylase antibodies (GADA) measured in HUNT3, we classified the incident cases as autoimmune diabetes with an index value of GADA ≥0.08 [19], type 2 diabetes with GADA <0.08 and an unknown type due to lack of measurement on GADA.

Information on hours lying down per day was obtained from the question "How many hours do you usually spend lying down during a 24 hour period?" in the HUNT2 questionnaire, in which night's sleep and siesta were specified. The mean and median value of the hours lying down per day in the study cohort was 8 hours. Finer categories of hours lying down were initially generated as ≤6, 7, 8, 9 and ≥10 h/day. To increase statistical precision, categories were collapsed into ≤7, 8 and ≥9 h/day in main analysis using 8 h/day as the reference category.

Leisure-time physical activity at baseline was classified into four groups based on a combination of hours of light (no sweat/not out of breath) and vigorous activity (sweat/out of breath) per week: inactive (no activity, or ≤2 h light activity only), low (≥3 h light activity only, or ≤2 h light activity and <1 h vigorous activity), moderate (≥3 h light activity and <1 h vigorous activity or 1-2 h vigorous activity regardless of light activity) and high activity (≥3 h vigorous activity regardless of light activity) [20]. For analysis stratified by leisure-time physical activity, the categories were collapsed into two groups labelled less active (inactive, low and moderate activity) and highly active (high activity).

Height and weight were measured by trained staff during the clinical examination at HUNT2. Body mass index (BMI) was estimated by weight divided by squared value of height and categorized as underweight or normal weight (<25.0 kg/m^2), overweight (25.0–29.9 kg/m^2), and obese (≥30.0 kg/m^2) in accordance with WHO recommendation. Data on BMI were collapsed

into two groups labelled as non-obese (underweight or normal & overweight) and obese for analysis stratified by BMI.

Other baseline variables

Other baseline variables were collected by questionnaires, including sex, age (20–29, 30–39, 40–49, and 50–55 years), smoking status (never, ex-smoker, current smoker, and missing 0.6%), alcohol consumption per month (never, 1-4 times, ≥5 times, and missing 1.9%), family history of diabetes (yes, no, and missing 0.9%), chronic diseases (yes, no, and missing 2%), years of education (<10, 10–12, ≥13 years, and missing 0.5%), economic difficulties (yes, no, and missing 1%), time spent sitting every day (0-4, 5-7, ≥8 h, and missing 2.9%), and type of work (sedentary work, much walking or lifting, heavy physical work, and missing 5.4%). The following question was used to define chronic disease: "Do you suffer from any long-term illness or injury of a physical or physiological nature that impairs your functioning in your everyday life?" (Long-term means at least one year). Economic difficulties were defined as yes when participants reported having difficulties to acquire food or transport etc. because of cost. Several other baseline variables were also collected: sleep problems were obtained by question "During the last month have you woken too early and not been able to get back to sleep?" with four options (almost every night, often, occasionally, and never); information on anxiety or depression symptoms was collected as a score using the Hospital Anxiety and Depression Scale (HADS).

Statistical analysis

Baseline characteristics were presented by categories of hours lying down per day (≤7, 8 and ≥9 h/day). In main analysis, logistic regression model was used to estimate crude odds ratio (OR)

with 95% confidence interval (CI) for incident diabetes by categories of hours lying down using 8 h/day as the reference. The adjusted ORs were obtained after adjustment for potential confounding factors including sex, age, BMI, smoking status, alcohol intake per month, family history of diabetes, chronic diseases, education, economic difficulties, total sitting time per day, leisure-time physical activity, and type of work [10 17]. Missing information of the covariates was included as a separate category in the analysis. Three sensitivity analyses were performed; 1) BMI, chronic diseases, total sitting time per day, leisure-time physical activity, and type of work were left out from the adjustment. This was because BMI and chronic diseases were also possible mediators, and time used in total sitting, leisure physical activity, work and lying down were co-dependent in a day of 24 hours. 2) sleep problems, and anxiety and depression symptoms (HADS as a continuous value) were additionally included in the adjustment. 3) we performed analyses using the finer categories of hours lying down and cubic spline regression model to verify the findings from the main analysis. We also calculated the ORs for autoimmune and type 2 diabetes by the three categories of hours lying down using multinomial logistic regression.

The analysis on the relationship between hours lying down per day and risk of diabetes was stratified by leisure-time physical activity (less active vs. highly active) and BMI status (non-obese vs. obese). Potential statistical interaction was assessed in a likelihood ratio test including a product term of 1) categories of hours lying down x leisure-time physical activity, and 2) categories of hours lying down x BMI in the regression model. All analyses were conducted using STATA/IC 13.0 for Windows (College Station, TX, USA).

Patient and Public Involvement

There was no patient or public involvement in the design or data analysis of this study.

Results

The descriptive statistics for the baseline characteristics by categories of hours lying down in the analysis cohort are shown in Table S2.

A total of 362 (2.1%) individuals were identified with diabetes during the 11-year follow-up period, including 20 with autoimmune diabetes, 307 with type 2 diabetes and 35 with an unknown type due to lack of measurement on GADA. Lying down ≥9 h/day was associated with an increased diabetes incidence with an adjusted OR of 1.35 (95% CI 1.01, 1.80), whereas lying down ≤7 h/day was not associated with the risk of diabetes in the main analysis (Table 1). In the first sensitivity analysis, the OR associated with lying down ≥9 h/day was 1.44 (95% CI 1.09, 1.90). In the second sensitivity analysis, the corresponding OR was 1.37 (95% CI 1.03, 1.83). The association estimates between lying down ≤7 h/day and incident diabetes in both sensitivity analyses did not differ from that in the main analysis (data not presented). Results using the finer categories of hours lying down and the cubic spline regression model were consistent with those from the main analysis (Table S3 and Table S4). Lying down ≥9 h/day was associated with an increased risk for type 2 diabetes (Table 2), but the estimated OR for autoimmune diabetes was imprecise due to few cases. Lying down ≤7 h/day was not associated with either type of diabetes.

Table 1. Hours lying down per day in relation to incidence of diabetes over an 11-year follow up (n=17058)

Hours lying down per day	Number of participants	Number of cases	Risk (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
≤7	6596	130	2.0	0.98 (0.77, 1.24)	0.93 (0.73, 1.18)
8	7480	151	2.0	1.00 (reference)	1.00 (reference)
≥9	2982	81	2.7	1.36 (1.03, 1.78)	1.35 (1.01, 1.80)

CI: confidence interval; OR: odds ratio

Adjusted OR obtained after adjustment for sex, age, body mass index, smoking status, alcohol intake per month, education, economic difficulties, chronic diseases, family history of diabetes, total sitting time, physical activity, and type of work

Table 2. Hours lying down per day in relation to incidence of autoimmune diabetes or type 2 diabetes over an 11-year follow up (n=17058[c])

	Hours lying down per day	Number of participants	Number of cases	Risk (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
Autoimmune diabetes[a]	≤7	6596	7	0.1	0.72 (0.28, 1.86)	0.69 (0.26, 1.83)
	8	7480	11	0.2	1.00 (reference)	1.00 (reference)
	≥9	2982	2	0.1	0.46 (0.10, 2.07)	0.53 (0.12, 2.47)
Type 2 diabetes[b]	≤7	6596	112	1.7	1.05 (0.81, 1.36)	0.99 (0.76, 1.30)
	8	7480	121	1.6	1.00 (reference)	1.00 (reference)
	≥9	2982	74	2.5	1.55 (1.15, 2.07)	1.54 (1.13, 2.09)

CI: confidence interval; OR: odds ratio

[a]Autoimmune diabetes: incident diabetes cases with an index value of glutamic acid decarboxylase antibodies (GADA) ≥0.08. [b]Type 2 diabetes: incident diabetes cases with GADA <0.08. [c]Data not presented for 35 incident diabetes cases with an unknown type due to lack of measurement on GADA

Adjusted OR obtained after adjustment for sex, age, body mass index, smoking status, alcohol intake per month, education, economic difficulties, chronic diseases, family history of diabetes, total sitting time, physical activity, and type of work

Among the less active individuals, lying down ≥9 h/day was associated with an increased risk of diabetes with an OR of 1.41 (95% CI 1.05, 1.90) (Table 3). This positive association appeared absent among the highly active individuals (OR = 0.90, 95% CI 0.23, 3.55). Lying down ≤7 h/day was not associated with the risk of diabetes in the less active individuals, but it was associated with a reduced risk in the highly active individuals (Table 3). A likelihood ratio test showed evidence of statistical interaction between hours lying down per day and leisure-time physical activity ($P_{for\ interaction} = 0.048$).

Table 3. Hours lying down per day in relation to incidence of diabetes over an 11-year follow up stratified by leisure-time physical activity (n=17058)

Hours lying down per day	Number of participants	Number of cases	Risk (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
Less active[a]					
≤7	5743	127	2.2	1.05 (0.82, 1.34)	1.00 (0.77, 1.28)
8	6534	138	2.1	1.00 (reference)	1.00 (reference)
≥9	2623	78	3.0	1.42 (1.07, 1.88)	1.41 (1.05, 1.90)
Highly active[b]					
≤7	853	3	0.4	0.25 (0.07, 0.89)	0.21 (0.05, 0.83)
8	946	13	1.4	1.00 (reference)	1.00 (reference)
≥9	359	3	0.8	0.60 (0.17, 2.13)	0.90 (0.23, 3.55)

CI: confidence interval; OR - odds ratio

[a]Less active refers to inactive and low to moderate physical activity. [b]Highly active refers to high levels of physical activity

Adjusted OR obtained after adjustment for sex, age, body mass index, smoking status, alcohol intake per month, education, economic difficulties, chronic diseases, family history of diabetes, total sitting time, and type of work

Among the obese individuals, lying down ≥9 h/day was associated with an increased risk of diabetes (OR = 1.61, 95% CI 1.04, 2.49) (Table 4). It was also associated with an increased OR among the non-obese individuals (OR = 1.23, 95% CI 0.83, 1.82). There was little evidence of statistical interaction between hours lying down and BMI ($P_{\text{for interaction}} = 0.62$).

Table 4. Hours lying down per day in relation to incidence of diabetes over an 11-year follow up stratified by BMI status (n=17024 [c])

Hours lying down per day	Number of participants	Number of cases	Risk (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
Non-obese[a]					
≤7	5870	78	1.3	1.06 (0 .77, 1.44)	0.97 (0.71, 1.34)
8	6598	83	1.3	1.00 (reference)	1.00 (reference)
≥9	2583	39	1.5	1.20 (0.82, 1.77)	1.23 (0.83, 1.82)
Obese[b]					
≤7	718	51	7.1	0.90 (0.62, 1.32)	0.86 (0.58, 1.28)
8	871	68	7.8	1.00 (reference)	1.00 (reference)
≥9	384	42	10.9	1.45 (0.98, 2.17)	1.61 (1.04, 2.49)

BMI: body mass index; CI: confidence interval; OR: odds ratio

[a]Non-obese refers to BMI <30.0 kg/m^2. [b]Obese refers to BMI ≥30.0 kg/m^2. [c]34 participants are not included due to missing information on BMI

Adjusted OR obtained after adjustment for sex, age, smoking status, alcohol intake per month, education, economic difficulties, chronic diseases, family history of diabetes, total sitting time, physical activity, and type of work

Discussion

We observed a 35% higher risk of incident diabetes in people reporting lying down ≥9 h/day compared with those lying down 8 h/day. Lying down ≤7 h/day was not associated with the diabetes risk. Stratified analysis showed that lying down ≥9 h/day was associated with diabetes risk in the less physically active group but not in the highly active group. There was little evidence that BMI modified the association.

Prolonged hours lying down as an independent risk factor for diabetes

Results of the present study are in accordance with a meta-analysis study in which a positive association was found between prolonged sitting behaviour and increased risk of diabetes [21]. The more recent studies have also demonstrated a positive association between total sitting time and diabetes risk [6 17]. After adjustment for sitting time and other risk factors in the present study, lying down ≥9 h/day was independently associated with a moderate increase in diabetes risk. In a previous HUNT study, prolonged hours lying down was independently associated with mortality from all-cause and cardiovascular disease [10].

Skeletal muscles function as a key site for insulin-stimulated glucose disposal, and loss in muscles associated with sedentary behaviour may contribute to pathogenesis of diabetes in adults [22]. Studies have also observed rapid decrease of muscle glucose transporter (GLUT) proteins when muscles are not utilized [23]. Low levels and expression of the GLUT-proteins affect carbohydrate metabolism and contribute to insulin resistance in the skeletal muscles [23-25]. In addition, low energy expenditure associated with sedentary behaviour may have negative impact on lipid levels leading to lipids accumulation and insulin resistance [26 27]. In a broader perspective, all these mechanisms may result in increased levels of glucose, lipids, and other metabolic

markers that contribute to metabolic syndrome [28]. Prolonged sitting time has been strongly linked with metabolic impairment [28 29], which predisposes individuals to high diabetes risk in the long term. The energy expenditure associated with lying down is very low. Compared to sitting, there is a decrease in heart rate and respiratory quotient associated with lying down [30]. Therefore, a detrimental effect of longer hours lying down on risk of diabetes can be anticipated.

Influence of physical activity on the association

Our findings are consistent with previous studies in which physical activity modified the association between prolonged sitting time and incident diabetes or mortality [15 17 31], with a positive association remained in the inactive individuals but disappeared in the active individuals. Nevertheless, the potential adverse effect of prolonged lying down on mortality has been shown to exist among both active and inactive people in a previous HUNT study [10]. In the referred study [10] active individuals were categorized as those who reported moderate to high levels of physical activity, which may explain why harmful effect of longer hours lying down remained in the physically active group. Our study suggested that high levels of physical activity might have an interaction with prolonged hours lying down on the risk of diabetes. In practice, moderate level of physical activity in the HUNT studies aligns with the physical activity recommendations for public health [31 32]. Ekelund *et al.* in their meta-analysis found physical activity beyond recommended levels being capable of cancelling out the risk of death associated with prolonged sitting [31].

It is well documented that physical activity increases glucose uptake and improves glucose homeostasis and overall energy balance [33-36]. Highly active individuals engage in more vigorous activity compared to the less active individuals. High intensity training has been shown to

increase glucose uptake during and post exercise [25 37 38]. Engaging in vigorous physical activity also provides a better lipid profile that may help to prevent insulin resistance [39 40]. Therefore, highly active individuals may have an advantage with higher insulin sensitivity and glucose metabolism during longer hours lying down to prevent or delay the onset of diabetes. Less active individuals with little or no vigorous physical activity may have an excess metabolic risk from prolonged lying down.

Influence of obesity on the association

Studies suggest that sedentary behaviour and obesity may have a bidirectional relationship [41-43]. Obesity may be either a confounding factor or an intermediate factor in the context [44]. Adjustment for a potential intermediate factor would bias the association between sedentary behaviour and health outcome towards null [44]. Thus, if obesity is a mediator, the magnitude of association between longer hours lying down and risk of diabetes may have been underestimated in the main result (OR 1.35).

Similar to a previous HUNT study on total sitting time in relation to diabetes risk [17], there was little evidence of statistical interaction by BMI status in the present study. This was inconsistent with two other studies that reported an interaction between BMI and sitting time on risk of diabetes [15 16]. However, the latter studies either used self-reported height and weight or conducted in post-menopausal women.

Strengths and weaknesses

This prospective cohort study of young and middle-aged adults from Central Norway is one of the first population-based studies to provide an insight into the potential long-term influence of hours spent lying down on diabetes risk. The distribution of baseline characteristics was similar

in the study and analysis cohorts. In addition, comprehensive information on potential confounding factors warranted more accurate estimate for the association.

There are several limitations with the study. Selection bias cannot completely be excluded as 64% of the young and middle-aged adults in HUNT2 were followed up in HUNT3. However, the participation rate did not differ substantially among adults who reported lying down ≤7, 8 and ≥9 h/day (66%, 68% and 61% respectively). The size of the population was large, but stratified analysis showed imprecise result in the highly physically active group. Self-reported information on hours lying down, diabetes and covariates are subject to misclassification that is likely to be non-differential in a prospective study. Moreover, we cannot rule out residual confounding due to unknown or unmeasured factors, for example the lack of dietary information. We are also unable to conclude if prolonged hours lying down was associated with an increased risk of autoimmune diabetes due to few cases. Finally, hours spent lying down per day in our study included night's sleep. We did not have information on duration of night's sleep specifically. Both short and long sleep have been reported to increase mortality and risk of diabetes in previous studies [45 46]. The harm of short sleep may be explained by consequences of sleep problems per se; the harm of long sleep is suggested to be explained by chronic diseases and depression [45 46]. Our data showed that adjustment for chronic diseases in the main analysis and additional adjustment for sleep problems, and anxiety and depression symptoms in the sensitivity analysis did not change the observed association between prolonged hours lying down and risk of diabetes. In addition, we did not observe that shorter hours lying down per day were associated with an increased risk of diabetes. All these suggested that our exposure variable was less likely to be a proxy for sleep duration.

Conclusions

Prolonged hours lying down per day, as a proxy for sedentary behaviour, was associated with an increased risk of diabetes in a young and middle-aged adult population. The positive association was present in the less physically active individuals, but it appeared absent among the highly active individuals. The association did not differ by BMI status.

List of abbreviations

HUNT: Helseundersøkelsen i Nord-Trøndelag

BMI: Body Mass Index

Declarations

Acknowledgements: The HUNT Study is a collaboration between the HUNT Research Centre (Faculty of Medicine and Health Sciences, NTNU, Norwegian University of Science and Technology), the Nord-Trøndelag County Council, Central Norway Regional Health Authority, and the Norwegian Institute of Public Health.

Contributors: EOA and XMM contributed to the study design. EOA and XMM conducted statistical analysis and wrote the initial draft of the manuscript. YQS, TILN, BOÅ and EPS contributed to interpretation of results and critically revised the manuscript for important intellectual content. All authors approved the final version of the manuscript.

Funding: This work was supported by Department of Public Health and Nursing, NTNU [EOA] and The Norwegian Cancer Society [project ID 5769155-2015] [YQS] and The Research Council of Norway "Gaveforsterkning" [YQS].

Competing interests: None declared

Patient consent: All participants signed informed written consent upon participation in HUNT.

Ethics approval: The study was approved by the Norwegian Regional Committees for Medical and Health Research Ethics (2010/389/REK midt).

Data sharing statement: Data from the HUNT Study that is used in research projects will, when reasonably requested by others, be made available on request to the HUNT Data Access Committee (hunt@medisin.ntnu.no). The HUNT data access information describes the policy regarding data availability (https://www.ntnu.edu/hunt/data).

Exclusive Licence

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in BMJ Open and any other BMJ products and to exploit all rights, as set out in our licence.

References

1. Leon BM, Maddox TM. Diabetes and cardiovascular disease: Epidemiology, biological mechanisms, treatment recommendations and future research. *World Journal of Diabetes* 2015;6(13):1246-58. doi: 10.4239/wjd.v6.i13.1246
2. Tamayo T, Rosenbauer J, Wild SH, et al. Diabetes in Europe: An update. *Diabetes Research and Clinical Practice*;103(2):206-17. doi: 10.1016/j.diabres.2013.11.007
3. Sørensen M, Arneberg F, Line TM, et al. Cost of diabetes in Norway 2011. *Diabetes Research and Clinical Practice* 2016;122:124-32. doi: http://dx.doi.org/10.1016/j.diabres.2016.10.012
4. Wolfe RR. The underappreciated role of muscle in health and disease. *The American Journal of Clinical Nutrition* 2006;84(3):475-82. doi: 10.1093/ajcn/84.3.475
5. Steene-Johannessen J, Anderssen SA, Kolle E, et al. Low muscle fitness is associated with metabolic risk in youth. *Medicine and science in sports and exercise* 2009;41(7):1361-7. doi: 10.1249/MSS.0b013e31819aaae5 [published Online First: 2009/06/12]
6. van der Berg JD, Stehouwer CD, Bosma H, et al. Associations of total amount and patterns of sedentary behaviour with type 2 diabetes and the metabolic syndrome: The Maastricht Study. *Diabetologia* 2016;59(4):709-18. doi: 10.1007/s00125-015-3861-8 [published Online First: 2016/02/03]
7. Grontved A, Hu FB. Television viewing and risk of type 2 diabetes, cardiovascular disease, and all-cause mortality: a meta-analysis. *Jama* 2011;305(23):2448-55. doi: 10.1001/jama.2011.812 [published Online First: 2011/06/16]
8. Henson J, Dunstan DW, Davies MJ, et al. Sedentary behaviour as a new behavioural target in the prevention and treatment of type 2 diabetes. *Diabetes/metabolism research and reviews* 2016;32 Suppl 1:213-20. doi: 10.1002/dmrr.2759 [published Online First: 2016/01/28]
9. Ainsworth BE, Haskell WL, Whitt MC, et al. Compendium of physical activities: an update of activity codes and MET intensities. *Medicine and science in sports and exercise* 2000;32(9 Suppl):S498-504. [published Online First: 2000/09/19]
10. Holtermann A, Mork PJ, Nilsen TI. Hours lying down per day and mortality from all-causes and cardiovascular disease: the HUNT Study, Norway. *European journal of epidemiology* 2014;29(8):559-65. doi: 10.1007/s10654-014-9939-7 [published Online First: 2014/07/17]
11. McDermott MM, Guralnik JM, Ferrucci L, et al. Community walking speed, sedentary or lying down time, and mortality in peripheral artery disease. *Vasc Med* 2016;21(2):120-9. doi: 10.1177/1358863X15626521
12. Dirks ML, Wall BT, van de Valk B, et al. One Week of Bed Rest Leads to Substantial Muscle Atrophy and Induces Whole-Body Insulin Resistance in the Absence of Skeletal Muscle Lipid Accumulation. *Diabetes* 2016;65(10):2862-75. doi: 10.2337/db15-1661 [published Online First: 2016/07/01]
13. Kenny HC, Rudwill F, Breen L, et al. Bed rest and resistive vibration exercise unveil novel links between skeletal muscle mitochondrial function and insulin resistance. *Diabetologia* 2017;60(8):1491-501. doi: 10.1007/s00125-017-4298-z [published Online First: 2017/05/14]
14. Alibegovic AC, Hojbjerre L, Sonne MP, et al. Impact of 9 days of bed rest on hepatic and peripheral insulin action, insulin secretion, and whole-body lipolysis in healthy young male offspring of patients with type 2 diabetes. *Diabetes* 2009;58(12):2749-56. doi: 10.2337/db09-0369 [published Online First: 2009/09/02]

15. Petersen CB, Bauman A, Tolstrup JS. Total sitting time and the risk of incident diabetes in Danish adults (the DANHES cohort) over 5 years: a prospective study. *British journal of sports medicine* 2016;50(22):1382-87. doi: 10.1136/bjsports-2015-095648 [published Online First: 2016/11/03]
16. Manini TM, Lamonte MJ, Seguin RA, et al. Modifying effect of obesity on the association between sitting time and incident diabetes in post-menopausal women. *Obesity (Silver Spring, Md)* 2014;22(4):1133-41. doi: 10.1002/oby.20620
17. Åsvold BO, Midthjell K, Krokstad S, et al. Prolonged sitting may increase diabetes risk in physically inactive individuals: an 11 year follow-up of the HUNT Study, Norway. *Diabetologia* 2017:1-6. doi: 10.1007/s00125-016-4193-z
18. Krokstad S, Langhammer A, Hveem K, et al. Cohort Profile: the HUNT Study, Norway. *International journal of epidemiology* 2013;42(4):968-77. doi: 10.1093/ije/dys095 [published Online First: 2012/08/11]
19. Sorgjerd EP, Skorpen F, Kvaloy K, et al. Time dynamics of autoantibodies are coupled to phenotypes and add to the heterogeneity of autoimmune diabetes in adults: the HUNT study, Norway. *Diabetologia* 2012;55(5):1310-8. doi: 10.1007/s00125-012-2463-y [published Online First: 2012/02/03]
20. Jiang L, Sun YQ, Brumpton BM, et al. Prolonged Sitting, Its Combination With Physical Inactivity and Incidence of Lung Cancer: Prospective Data From the HUNT Study. *Frontiers in oncology* 2019;9:101. doi: 10.3389/fonc.2019.00101 [published Online First: 2019/03/13]
21. Wilmot EG, Edwardson CL, Achana FA, et al. Sedentary time in adults and the association with diabetes, cardiovascular disease and death: systematic review and meta-analysis. *Diabetologia* 2012;55(11):2895-905. doi: 10.1007/s00125-012-2677-z
22. DeFronzo RA, Tripathy D. Skeletal muscle insulin resistance is the primary defect in type 2 diabetes. *Diabetes care* 2009;32 Suppl 2:S157-63. doi: 10.2337/dc09-S302 [published Online First: 2009/11/13]
23. Tremblay MS, Colley RC, Saunders TJ, et al. Physiological and health implications of a sedentary lifestyle. *Applied physiology, nutrition, and metabolism = Physiologie appliquee, nutrition et metabolisme* 2010;35(6):725-40. doi: 10.1139/h10-079 [published Online First: 2010/12/18]
24. Bergouignan A, Rudwill F, Simon C, et al. Physical inactivity as the culprit of metabolic inflexibility: evidence from bed-rest studies. *Journal of applied physiology (Bethesda, Md : 1985)* 2011;111(4):1201-10. doi: 10.1152/japplphysiol.00698.2011 [published Online First: 2011/08/13]
25. Richter EA, Hargreaves M. Exercise, GLUT4, and skeletal muscle glucose uptake. *Physiological reviews* 2013;93(3):993-1017. doi: 10.1152/physrev.00038.2012 [published Online First: 2013/08/01]
26. Kelley DE, Goodpaster BH. Skeletal muscle triglyceride. An aspect of regional adiposity and insulin resistance. *Diabetes care* 2001;24(5):933-41. [published Online First: 2001/05/12]
27. Corcoran MP, Lamon-Fava S, Fielding RA. Skeletal muscle lipid deposition and insulin resistance: effect of dietary fatty acids and exercise. *Am J Clin Nutr* 2007;85(3):662-77. doi: 10.1093/ajcn/85.3.662 [published Online First: 2007/03/09]
28. Edwardson CL, Gorely T, Davies MJ, et al. Association of Sedentary Behaviour with Metabolic Syndrome: A Meta-Analysis. *PLoS ONE* 2012;7(4):e34916. doi: 10.1371/journal.pone.0034916
29. Dunstan DW, Kingwell BA, Larsen R, et al. Breaking Up Prolonged Sitting Reduces Postprandial Glucose and Insulin Responses. *Diabetes care* 2012;35(5):976-83. doi: 10.2337/dc11-1931
30. Miles-Chan JL, Sarafian D, Montani JP, et al. Sitting comfortably versus lying down: Is there really a difference in energy expenditure? *Clin Nutr* 2014;33(1):175-78. doi: 10.1016/j.clnu.2013.11.009

31. Ekelund U, Steene-Johannessen J, Brown WJ. Does physical activity attenuate, or even eliminate, the detrimental association of sitting time with mortality? A harmonised meta-analysis of data from more than 1 million men and women (vol 388, pg 1302, 2016). *Lancet* 2016;388(10051):E6-E6.
32. WHO. Global recommendations on physical activity for health, 2010.
33. Horsch A, Wobmann M, Kriemler S, et al. Impact of physical activity on energy balance, food intake and choice in normal weight and obese children in the setting of acute social stress: a randomized controlled trial. *BMC Pediatrics* 2015;15:12. doi: 10.1186/s12887-015-0326-7
34. van Baak MA. Physical activity and energy balance. *Public health nutrition* 1999;2(3a):335-9. [published Online First: 1999/12/28]
35. Sylow L, Kleinert M, Richter EA, et al. Exercise-stimulated glucose uptake - regulation and implications for glycaemic control. *Nature reviews Endocrinology* 2017;13(3):133-48. doi: 10.1038/nrendo.2016.162 [published Online First: 2016/11/04]
36. Rottensteiner M, Leskinen T, Niskanen E, et al. Physical activity, fitness, glucose homeostasis, and brain morphology in twins. *Medicine and science in sports and exercise* 2015;47(3):509-18. doi: 10.1249/mss.0000000000000437 [published Online First: 2014/07/09]
37. Adams OP. The impact of brief high-intensity exercise on blood glucose levels. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy* 2013;6:113-22. doi: 10.2147/DMSO.S29222
38. Gibala MJ, Little JP, Macdonald MJ, et al. Physiological adaptations to low-volume, high-intensity interval training in health and disease. *The Journal of physiology* 2012;590(5):1077-84. doi: 10.1113/jphysiol.2011.224725 [published Online First: 2012/02/01]
39. Zheng S, Xu H, Zhou H, et al. Associations of lipid profiles with insulin resistance and beta cell function in adults with normal glucose tolerance and different categories of impaired glucose regulation. *PLoS One* 2017;12(2):e0172221. doi: 10.1371/journal.pone.0172221 [published Online First: 2017/02/16]
40. Kwon H-J, Lee H-J. Effect of vigorous physical activity on blood lipid and glucose. *Journal of Exercise Rehabilitation* 2017;13(6):653-58. doi: 10.12965/jer.1735150.575
41. Pedisic Z, Grunseit A, Ding D, et al. High sitting time or obesity: Which came first? Bidirectional association in a longitudinal study of 31,787 Australian adults. *Obesity (Silver Spring)* 2014;22(10):2126-30. doi: 10.1002/oby.20817 [published Online First: 2014/06/20]
42. Bullock VE, Griffiths P, Sherar LB, et al. Sitting time and obesity in a sample of adults from Europe and the USA. *Annals of human biology* 2017;44(3):230-36. doi: 10.1080/03014460.2016.1232749 [published Online First: 2016/09/09]
43. Heinonen I, Helajärvi H, Pahkala K, et al. Sedentary behaviours and obesity in adults: the Cardiovascular Risk in Young Finns Study. *BMJ Open* 2013;3(6)
44. Hamilton MT, Hamilton DG, Zderic TW. Sedentary behavior as a mediator of type 2 diabetes. *Medicine and sport science* 2014;60:11-26. doi: 10.1159/000357332
45. Gallicchio L, Kalesan B. Sleep duration and mortality: a systematic review and meta-analysis. *Journal of sleep research* 2009;18(2):148-58. doi: 10.1111/j.1365-2869.2008.00732.x [published Online First: 2009/08/04]
46. Shan Z, Ma H, Xie M, et al. Sleep Duration and Risk of Type 2 Diabetes: A Meta-analysis of Prospective Studies. *Diabetes care* 2015;38(3):529.

Additional files

Additional file 1: Table S1. Baseline characteristics of the study cohort and analysis cohort

Additional file 2: Table S2. Baseline characteristics of analysis cohort stratified by hours lying down per day

Additional file 3: Table S3. Finer categories of hours lying down per day in relation to incidence of diabetes over an 11-year follow up

Additional file 4: Table S4. Estimated odds ratio from the cubic spline regression model for incidence of diabetes by hours lying down per day

Table S1. Baseline characteristics of the study cohort and analysis cohort

Characteristics	Study cohort (n=25282)		Analysis cohort (n=17058)	
	n	%	n	%
Sex				
Male	11252	44.5	7724	45.3
Female	14030	55.5	9334	54.7
Age (years)				
20−29	3988	15.8	2954	17.3
30−39	7553	29.9	5363	31.4
40−49	9796	38.7	6343	37.2
50−55	3945	15.6	2398	14.1
BMI (kg/m^2)				
<25.0	11656	46.1	8012	46.9
25−29.9	10462	41.4	7039	41.3
≥30.0	3114	12.3	1973	11.6
Missing	50	0.2	34	0.2
Smoking status				
Never	11494	45.5	8171	47.9
Ex-smoker	6326	25.0	4303	25.2
Current	7277	28.8	4483	26.3
Missing	185	0.7	101	0.6
Alcohol intake per month				
Never	6913	27.3	4427	26.0
1−4 times	14220	56.3	9863	57.8
≥5 times	3398	13.4	2447	14.4
Missing	751	3.0	321	1.9
Family history of diabetes				
Yes	3272	12.9	2407	14.1
No	18360	72.6	14,492	85.0
Missing	3650	14.5	159	0.9
Chronic diseases				
Yes	4191	16.6	2680	15.7
No	20354	80.5	14,044	82.3
Missing	737	2.9	334	2.0
Education (years)				
<10	5036	19.9	2864	16.8
10−12	13466	53.3	9155	53.7
≥ 13	6559	25.9	4949	29.0
Missing	221	0.9	90	0.5
Economic difficulties				
Yes	7068	27.9	5484	32.1
No	14505	57.4	11,412	66.9
Missing	3709	14.7	162	1.0
Sitting time, hours/day				
0−4	6553	25.9	4937	28.9
5−7	6275	24.8	4956	29.1

≥8	8068	31.9	6676	39.1
Missing	4386	17.4	489	2.9
Type of work				
Mostly sedentary work	6890	27.3	4949	29.0
Much walking or lifting at work	13848	54.8	9290	54.5
Heavy physical work	2843	11.2	1903	11.2
Missing	1701	6.7	916	5.4

BMI: body mass index; n: number of participants; %: column percentage

Table S2. Baseline characteristics of analysis cohort stratified by hours lying down per day (n=17058)

Characteristics	Hours lying down per day					
	≤7 n=6596		8 n=7480		≥9 n=2982	
	n	%	n	%	n	%
Sex						
Male	3606	54.7	3113	41.6	1005	33.7
Female	2990	45.3	4367	58.4	1977	66.3
Age (years)						
20–29	866	13.1	1307	17.5	781	26.2
30–39	2326	35.3	2218	29.7	819	27.5
40–49	2518	38.2	2856	38.2	969	32.5
50–55	886	13.4	1099	14.7	413	13.8
BMI (kg/m^2)						
<25.0	2959	44.9	3611	48.3	1442	48.4
25.0–29.9	2911	44.1	2987	39.9	1141	38.3
≥30.0	718	10.9	871	11.6	384	12.9
Missing	8	0.1	11	0.1	15	0.5
Smoking status						
Never	3008	45.6	3703	49.5	1460	49.0
Ex-smoker	1709	25.9	1893	25.3	701	23.5
Current	1843	27.9	1842	24.6	798	26.8
Missing	36	0.5	42	0.6	23	0.8
Alcohol intake per month						
Never	1624	24.6	1933	25.8	870	29.2
1–4 times	3813	57.8	4383	58.6	1667	55.9
≥5 times	1041	15.8	1034	13.8	372	12.5
Missing	118	1.8	130	1.7	73	2.4
Family history of diabetes						
Yes	918	13.9	1053	14.1	436	14.6
No	5606	85.0	6367	85.1	2519	84.5
Missing	72	1.1	60	0.8	27	0.9
Chronic diseases						
Yes	983	14.9	1067	14.3	630	21.1
No	5511	83.6	6264	83.7	2269	76.1
Missing	102	1.5	149	2.0	83	2.8
Education (years)						
<10	1047	15.9	1203	16.1	614	20.6
10–12	3612	54.8	3947	52.8	1596	53.5
≥ 13	1899	28.8	2297	30.7	753	25.3

Missing	38	0.6	33	0.4	19	0.6
Economic difficulties						
Yes	2224	33.7	2256	30.2	1004	33.7
No	4319	65.5	5149	68.8	1944	65.2
Missing	53	0.8	75	1.0	34	1.1
Sitting time, hours/day						
0–4	1904	28.9	2158	28.9	875	29.3
5–7	1818	27.6	2123	28.4	1015	34.0
≥8	2700	40.9	2996	40.1	980	32.9
Missing	174	2.6	203	2.7	112	3.8
Leisure-time physical activity						
Inactive	1665	25.2	1868	25.0	836	28.0
Low	1652	25.0	1906	25.5	788	26.4
Moderate	2426	36.8	2760	36.9	999	33.5
High	853	12.9	946	12.6	359	12.0
Type of work						
Mostly sedentary work	2072	31.4	2194	29.3	683	22.9
Much walking or lifting at work	3469	52.6	4108	54.9	1713	57.4
Heavy physical work	800	12.1	810	10.8	293	9.8
Missing	255	3.9	368	4.9	293	9.8

BMI: body mass index; n: number of participants; %: column percentage

Table S3. Finer categories of hours lying down per day in relation to incidence of diabetes over an 11-year follow up (n=17058)

Hours lying down per day	Number of participants	Number of cases	Risk (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
≤6	1174	22	1.8	0.93 (0.59, 1.46)	0.80 (0.50, 1.28)
7	5422	108	2.0	0.99 (0.77, 1.27)	0.96 (0.74, 1.24)
8	7480	151	2.0	1.00 (reference)	1.00 (reference)
9	2171	57	2.6	1.31 (0.96, 1.78)	1.34 (0.97, 1.85)
≥10	811	24	3.0	1.48 (0.96, 2.29)	1.38 (0.87, 2.19)

CI: confidence interval; OR: odds ratio

Adjusted OR obtained after adjustment for sex, age, body mass index, smoking status, alcohol intake per month, education, economic difficulties, chronic diseases, family history of diabetes, total sitting time, physical activity, and type of work

Table S4. Estimated odds ratio from the cubic spline regression model for incidence of diabetes by hours lying down per day (n=17058)

Hours lying down per day	Adjusted OR (95% CI)
5	0.91 (0.61, 1.37)
6	0.84 (0.64, 1.10)
7	0.83 (0.67, 1.02)
8	1.00 (reference)
9	1.14 (1.00, 1.29)
10	1.19 (0.87, 1.63)
11	1.22 (0.71, 2.11)

CI: confidence interval; OR: odds ratio

Adjusted OR obtained after adjustment for sex, age, body mass index, smoking status, alcohol intake per month, education, economic difficulties, chronic diseases, family history of diabetes, total sitting time, physical activity, and type of work

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	6-9
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8 & 9
		(*b*) Describe any methods used to examine subgroups and interactions	9
		(*c*) Explain how missing data were addressed	8 & 9
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	6 & 18
		(*e*) Describe any sensitivity analyses	9

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11
		(b) Indicate number of participants with missing data for each variable of interest	6,8 & 9
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	6 & 11
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	11
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-14
		(*b*) Report category boundaries when continuous variables were categorized	7 & 8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-14
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	17-18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.