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Does the risk of chronic low back pain depend on age at menarche or menopause? A population-based cross-sectional and cohort study: the Trøndelag Health Study

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Abstract

Objective In most population-based studies of low back pain (LBP) women have a higher risk than men, possibly reflecting hormonal influences. The aim of this study was to explore the associations between age at menarche and menopause and risk of chronic LBP.

Design Population-based cross-sectional and cohort study designs.

Setting The HUNT2 and HUNT3 surveys of Nord-Trøndelag County in Norway.

Main outcome measure Chronic LBP, defined as LBP persisting at least 3 months continuously during the last year.

Participants The cross-sectional study of the association in HUNT2 between age at menarche and prevalence of chronic LBP comprised 27697 women aged 20-69 years, including 7300 women with LBP. In the cohort study, 11659 women without chronic LBP at baseline in HUNT2 were available for analysis. In total, 2353 women reported LBP at follow-up 11 years later in HUNT3. Altogether 11332 women aged 40-69 years were included in the cross-sectional study of age at menopause or premenopausal status, with 3439 women reporting chronic LBP. The cohort study included 7893 women without LBP at baseline, of whom 1100 developed LBP.

Methods Associations between age at menarche or age at menopause and risk of chronic LBP were examined by generalised linear modelling.

Results A U-shaped association was indicated between age at menarche and risk of chronic LBP, both in the cross-sectional and cohort studies. Age at menarche ≤11 years was associated with an increased risk of chronic LBP (relative risk (RR) 1.32, 95% CI 1.15 to 1.52, vs. age 14 years at menarche), after adjustment for relevant risk factors. No association was established between age at menopause and risk of LBP. Being premenopausal had no influence on risk.

Conclusions In contrast to results for age at menopause, the association with age at menarche suggests that hormonal factors affect the risk of LBP.

Strengths and limitations of this study

-The study included data collected using both a cross-sectional and a cohort design, with a long follow-up period of 11 years.

- The information on age at menarche and menopause made it possible to carry out analyses with a detailed categorisation.

-The information about back pain was self-reported in a questionnaire.

-No information was available on pain intensity.

INTRODUCTION

Low back pain (LBP) constitutes a major problem for the individuals affected,[1] and the disorder entails large annual expenses for society.[2] To obtain insight into the etiology it is important to determine potential risk factors for LBP. In most population-based studies, women have a higher risk of LBP than men,[3] a tendency which may reflect hormonal differences.[4]

Women who experience early menarche or late menopause have generally been exposed to endogenous oestrogen for a long time. Oestrogen is known to be important in reducing osteoporosis and fracture rates[5] and may in this way potentially also reduce the risk of LBP. On the other hand, higher levels of oestrogen may increase the risk of LBP during and after pregnancy,[6] possibly through the involvement of the hormone relaxin. The greater risk of LBP observed in women using hormone therapy[4] or oral contraceptives[4] may also be related to oestrogen levels.[6]

There are very few epidemiological studies of associations between age at menarche or menopause and risk of LBP. A large population-based cross-sectional study in the Netherlands found an increase in the risk of combined chronic LBP and upper extremity pain among women with an early menarche[4] but results were equivocal for those with LBP only. No association was found in a smaller Swedish study.[7] A study in the United States[8] found a higher risk of LBP among women with menopause before age 40 years, but essentially no association with age at menopause after that early threshold.

In a large-scale population-based Norwegian study, we previously found an increase in risk of chronic LBP among women having experienced at least one delivery, but no further increase with subsequent deliveries.[9] Moreover, the risk depended on age at first delivery.[9] Data from the same surveys have also been used to study associations between chronic LBP and body mass index (BMI),[10] lipid levels[11] and physical activity in leisure time.[12] The aim of the present study was to investigate the relationships between age at menarche and menopause and risk of chronic LBP, considering cross-sectional and 11-year follow-up data.

METHODS

Collection of information

In the former Nord-Trøndelag County in Norway the two health surveys HUNT2 and HUNT3 were conducted in 1995 to 1997 and 2006 to 2008.[13] In the present work cross-sectional data from the HUNT2 survey are combined with follow-up data from the HUNT3 survey.

All residents of this county aged 20 years and above were invited to take part in the HUNT2 survey. They were requested to complete a questionnaire on health status, and they were invited to a clinical consultation, including measurement of height and weight. In the HUNT3 survey 11 years later, similar information was collected by questionnaires and a clinical examination.

One question in the HUNT2 and HUNT3 questionnaires was expressed in this way: "During the last year, have you suffered from pain and/or stiffness in your muscles and joints that has lasted for at least 3 consecutive months?" Each participant answering yes was given the following question: "Where did you have these complaints?" Several body regions were listed. Individuals answering yes to the first question and including the lower back as a relevant region were regarded as having chronic LBP.[14]

Women participating in HUNT2 gave information on age at menarche by answering the question "How old were you when you started menstruating?". They were also asked the question "Do you still menstruate?" Those aged ≥40 years indicating "yes" were regarded as premenopausal. The women who indicated "no" answered the following question: "How old were you when you stopped menstruating?" This was regarded as age at menopause.

The participants also gave information regarding physical activity in leisure time, smoking, duration of education and childbirths. In addition, they provided information used for computing Hospital Anxiety and Depression Scale (HADS) scores.[15]

Study design

Age at menarche

The target population of the HUNT2 study comprised 37 503 women in the age range 20-69 years. Of these, a total of 28 520 women participated in HUNT2 (figure 1).[16] Information about age at menarche in HUNT2 and about presence or absence of chronic LBP was

collected from 27 697 women, corresponding to an overall participation rate of 74%. This data set formed the basis of the cross-sectional study of associations with age at menarche.

The 20 397 women who reported absence of chronic LBP in HUNT2 were included in the cohort considered in the prospective study of association between age at menarche and risk of chronic LBP. Information about residence status was obtained from national registries and linked using the unique Norwegian personal identification numbers. During the 11-year follow-up period, 712 women in this cohort died and 1266 individuals left the county of Nord-Trøndelag (figure 1). A total of 6760 women in the cohort residing in Nord-Trøndelag at the time of HUNT3 did not participate or did not supply information about chronic LBP. The remaining 11 659 women could be included in the analysis of risk of LBP after the 11-year follow-up period, representing 63% of the remaining women resident in the county, and 57% of the original cohort.

Age at menopause

Only women in the age range 40-69 years were included in the study of age at menopause. The target population of the HUNT2 study comprised 20 765 women in this interval. Of these, a total of 17 568 women participated in HUNT2 (figure 2).[16] Women who were pregnant when the questionnaire was filled in were excluded. Information about age at menopause or premenopausal status in HUNT2 as well as presence or absence of chronic LBP was collected from 14 269 women, corresponding to a participation rate of 69%. At this stage, 2937 women were excluded because of surgery involving hysterectomy or removal of both ovaries, leaving 11 332 women included in the cross-sectional study (figure 2).

A total of 7893 women who reported absence of chronic LBP in HUNT2, were included in the prospective study of associations between age at menopause and risk of LBP. During the 11-year follow-up period, 339 women in this cohort died, 198 individuals left the county and 1962 women residing in Nord-Trøndelag at the time of HUNT3 did not participate or did not supply information about chronic LBP. Thus, a total of 5394 women were available for analysis of risk of LBP after the follow-up period, representing 73% of the remaining women resident in the county, and 68% of the original cohort.

Variables

Age at menarche reported in HUNT2 was categorised into seven groups: ≤11, 12, 13, 14, 15, 16, ≥17 years. Women aged 14 years at menarche were considered the reference group. Age at menopause was categorized into seven groups: ≤40, 41-43, 44-46, 47-49, 50-52, 53-55, ≥56 years. The premenopausal women were regarded as a separate reference group. In additional analyses, testing the linear or quadratic effects of the two study variables, these variables were regarded as continuous.

BMI, defined as weight/height^2 and computed in kg/m^2, was subdivided into three groups: <25, 25-29.9, ≥30. Categories of education were defined according to duration, ≤9, 10-12, and ≥13 years. Cigarette smoking was described using the categories current daily smoking, previous daily smoking and never daily smoking. For physical activity in leisure time, including going to work, one category comprised those engaged in light activity only or hard physical activity (leading to sweating or being out of breath) <1 hour per week. Other categories represented hard physical activity 1-2 and ≥3 hours per week. The information about physical activity collected in HUNT2 was verified by a reliability and validity study of a subsample.[17] A particular variable was defined to take into account both nulliparity and age at first delivery among parous women. Categories of age at first delivery were: ≤19, 20-24, 25-29, 30-34, ≥35 years. Five categories were introduced for total HADS scores: 0-4, 5-9, 10-14, 15-19 and ≥20.

Statistical analyses

Associations between the study variables age at menarche or menopause and prevalence or risk of chronic LBP were assessed by generalised linear modelling for binomial observations with a log link, with adjustment for potential confounders. Initial analyses involved adjustment for age only, and adjustment was then added for other relevant risk factors for LBP, as BMI,[10] physical activity in leisure time,[12] education and smoking, nulliparity and age at first delivery.[9] The effect of age was modelled by a cubic polynomial. In the main analyses, all other variables adjusted for were regarded as categorical.

Separate tests were carried out for interaction between each factor adjusted for and study variables showing an association with risk of chronic LBP. The effect of age at menarche was then modelled by a quadratic polynomial.

Because information on potential confounders was missing in a minor part of the data set, analyses involving more complete adjustment included a slightly lower number of individuals than the age-adjusted analyses. HADS scores could not be computed for 3178 (13%) of the 24 951 women included in cross-sectional analysis of relations with age at menarche with adjustment for other potential confounders. The corresponding proportion, 11%, in the prospective analysis was also rather high. For this reason, additional adjustment for HADS was only carried out in particular sensitivity analyses. At the same time, analyses were also performed without adjustment for HADS, including only women with known HADS scores, to evaluate the exact effect of the adjustment.

To assess potential effects of differential participation, participation rates in HUNT3 were computed among the women reporting LBP in HUNT2 and those not reporting LBP, within broad categories of age at menarche or menopause.

All statistical analyses were carried out using IBM SPSS version 26 (IBM Corp., Armonk, New York).

Public and patient involvement

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

RESULTS

Age at menarche

Women in HUNT2 with a late menarche tended to have a low BMI and an education of short duration (table 1). Daily current smoking was more common among those with an early menarche. Nulliparity showed a weak inverse relationship with age at menarche (table 1).

Among the 27 697 women in the cross-sectional study of the association between age at menarche and prevalence of chronic LBP, 7300 women (26%) reported chronic LBP in HUNT2 (figure 1). In the prospective study with 11 659 women available for analysis of risk of LBP at end of follow-up, 2353 women (20%) reported chronic LBP at end of follow-up in HUNT3.

Table 1 Relationships at baseline in HUNT2 between age at menarche and menopause and other potential risk factors

	Age at menarche (year)*				Age at menopause (year)†				
	≤ 11	12-13	14-15	≥ 16	≤ 46	47-49	50-52	≥ 53	Pre-meno-pausal
Age in HUNT2‡ (year)	41.1	41.8	45.9	47.6	55.9	56.3	58.4	60.2	45.8
BMI‡ (kg/m^2)	27.1	26.0	25.5	24.9	26.6	26.8	26.9	27.5	25.9
Physical activity per week§ (%)									
< 1hour hard	73	74	78	78	85	84	86	85	76
1-2 hours hard	19	19	16	15	11	12	11	11	18
≥ 3hours hard	8	7	6	7	4	4	4	4	6
Cigarette smoking§ (%)									
never	39	43	42	43	31	38	45	51	35
daily former	25	25	27	28	28	28	30	32	30
daily current	37	33	32	29	41	35	26	17	34
Education§ (year) (%)									
≤ 9	24	27	35	40	56	54	58	58	27
10-12	48	47	43	38	29	33	27	27	46
≥ 13	28	25	22	22	14	13	15	15	27
Nulliparity§ (%)	15	15	12	11	7	6	6	3	5
Age at first childbirth‡,¶ (year)	22.6	22.8	23.1	24.0	23.1	23.2	23.3	23.2	22.9
Number of women included	2288	12 176	9388	1099	1044	972	1579	826	5633

*Among women with information about chronic LBP, BMI, physical activity, education, smoking, nulliparity, age at first delivery and age at menarche.

†Among women with information about chronic LBP, BMI, physical activity, education, smoking, nulliparity, age at first delivery and age at menarche and menopause.

‡Mean value within category of age at menarche or menopause.

§Percentages of risk factor categories within category of age at menarche or menopause.

¶Among women with at least 1 child.

BMI, body mass index; HUNT, Trøndelag Health Study; LBP, low back pain.

Table 2 Associations between age at menarche and prevalence of chronic LBP in HUNT2 in cross-sectional analysis

	Total number of women in category of age at menarche*	Number of women with chronic LBP (%)	RR (95% CI) with adjustment for age only	RR (95 % CI) with additional adjustment†
Number of women included			27 697	24 951
Age at menarche (year)				
≤ 11	2487	806 (32.4)	1.39 (1.30 -1.49)	1.33 (1.24-1.43)
12	5536	1499 (27.1)	1.17 (1.11-1.24)	1.13 (1.06-1.21)
13	7789	1953 (25.1)	1.08 (1.02-1.14)	1.07 (1.01-1.14)
14	6861	1713 (25.0)	1.00 (reference)	1.00 (reference)
15	3759	994 (26.4)	1.03 (0.96-1.10)	1.04 (0.97-1.12)
16	975	252 (25.8)	0.99 (0.89-1.11)	1.02 (0.91-1.15)
≥ 17	290	83 (28.6)	1.12 (0.93-1.35)	1.31 (1.08-1.59)
P for categorical effect			< 0.001	< 0.001
P for linear trend			< 0.001	< 0.001
P for quadratic effect‡			< 0.001	< 0.001

*In analysis adjusted for age only.

†Adjustment for age, BMI, physical activity, education, smoking, nulliparity and age at first delivery.

‡In model also including linear effect.

BMI, body mass index; HUNT, Trøndelag Health Study; LBP, low back pain; RR, relative risk.

A U-shaped relationship between age at menarche and prevalence of chronic LBP was found in the cross-sectional study (table 2). This relationship was retained after adjustment for age, BMI, physical activity, education, smoking, nulliparity and age at first delivery. The prospective analysis revealed a similar U-shaped relationship between age at menarche and risk of chronic LBP, with an estimated 32% and 43% increased risk among women with menarche at age ≤11 years and ≥17 years, respectively, compared to those with age at menarche 14 years (table 3).

An interaction was observed between age at menarche and baseline age in the cross-sectional analysis (p=0.026). Definite U-shaped relationships between age at menarche and prevalence of chronic LBP were found among women in the two age intervals 20-39 years and 40-49 years in HUNT2 (supplemental table 1). Although a U-shaped relationship was still suggested among the oldest women aged 50-69 years (supplemental table 1), the association was much weaker. No interaction with baseline age was found in the prospective analyses of risk of LBP in HUNT3 (p=0.35; supplemental table 2).

In the cross-sectional analysis an interaction was also found between age at menarche and duration of education (p=0.031). The U-shaped relationship with age at menarche was most evident in women with 10-12 years of education, but estimates were also compatible with a relationship of this kind in the categories representing shorter or longer duration of education (supplemental table 3). In the prospective analysis no significant interaction between age at menarche and duration of education was observed (p=0.84; supplemental table 4).

Sensitivity analyses with additional adjustment for HADS revealed only minor changes in the association with age at menarche, both in the cross-sectional (supplemental table 5) and the prospective (supplemental table 6) situations.

Participation rates in HUNT3 depended only weakly on age at menarche, with slightly higher rates among women with a late menarche. Within broad categories of age at menarche, however, participation rates were quite similar among those reporting LBP in HUNT2 and those not reporting LBP. Among women with age at menarche ≤11 years, the two participation rates were 55% and 58%, respectively, among those with age at menarche 12-13 years 56% and 57%, among women with menarche 14-15 years 58% and 58%, and among women with age at menarche ≥16 years 59% and 61%.

Table 3 Associations between age at menarche and risk of chronic LBP in HUNT3 in prospective analysis

	Total number of women in category of age at menarche*	Number of women with chronic LBP (%)	RR (95% CI) with adjustment for age only	RR (95 % CI) with additional adjustment†
Number of women included			11 659	10 854
Age at menarche (year)				
≤ 11	930	236 (25.4)	1.34 (1.17-1.53)	1.32 (1.15-1.52)
12	2228	468 (21.0)	1.11 (1.00-1.24)	1.12 (1.00-1.25)
13	3340	641 (19.2)	1.01 (0.91-1.12)	1.01 (0.91-1.13)
14	3014	582 (19.3)	1.00 (reference)	1.00 (reference)
15	1600	314 (19.6)	1.01 (0.89-1.14)	1.02 (0.90-1.16)
16	421	82 (19.5)	1.00 (0.81-1.23)	1.01 (0.81-1.25)
≥ 17	126	30 (23.8)	1.24 (0.90-1.70)	1.43 (1.04-1.98)
P for categorical effect			0.001	0.002
P for linear trend			0.001	0.008
P for quadratic effect‡			0.001	< 0.001

*In analysis adjusted for age only.

†Adjustment for age, BMI, physical activity, education, smoking, nulliparity and age at first delivery.

‡In model also including linear effect.

BMI, body mass index; HUNT, Trøndelag Health Study; LBP, low back pain; RR, relative risk.

Age at menopause

Early menopause was primarily associated with daily current smoking and with nulliparity (table 1). Premenopausal women tended to have a relatively long duration of education and were engaged in more physical activity than postmenopausal women.

In the cross-sectional study of association between age at menopause and chronic LBP in HUNT2, 11 332 women were included, and a total of 3439 women (30%) reported chronic LBP (figure 2). In the prospective study among the remaining 5394 women who did not report chronic LBP in HUNT2, a total of 1100 women (20%) reported chronic LBP at end of follow-up in HUNT3.

No association between age at menopause and prevalence or risk of chronic LBP was observed, neither in the cross-sectional (table 4) nor in the prospective (table 5) data. Being premenopausal had no particular influence on prevalence or risk of chronic LBP. Additional adjustment for HADS in sensitivity analyses produced very similar estimates.

Participation rates in HUNT3 were somewhat higher for women with an older age at menopause. Yet within broad categories of age at menopause, participation rates were very similar for those reporting LBP in HUNT2 and those not reporting LBP. Premenopausal women represented an exception, with a participation rate equal to 65% among those reporting LBP, compared to 71% among those without LBP.

Table 4 Associations between age at menopause and prevalence of chronic LBP in cross-sectional analysis, among women at least 40 years old in HUNT2

	Total number of women in category of age at menopause	Number of women with chronic LBP (%)	RR (95% CI) with adjustment for age only	RR (95 % CI) with additional adjustment*
Number of women included			11 332	10 054
Age at menopause (year)				
≤ 40	263	90 (34.2)	1.10 (0.92-1.32)	1.08 (0.88-1.32)
41-43	269	88 (32.7)	1.06 (0.88-1.28)	1.05 (0.86-1.27)
44-46	743	260 (35.0)	1.12 (0.98-1.27)	1.06 (0.92-1.21)
47-49	1170	394 (33.7)	1.07 (0.96-1.20)	1.05 (0.93-1.18)
50-52	1859	601 (32.3)	1.01 (0.90-1.13)	1.03 (0.92-1.15)
53-55	818	290 (35.5)	1.09 (0.95-1.25)	1.06 (0.91-1.23)
≥ 56	182	46 (25.3)	0.78 (0.59-1.02)	0.79 (0.59-1.06)
Premenopausal	6028	1670 (27.7)	1.00 (reference)	1.00 (reference)
P for categorical effect			0.09	0.56
P for linear trend†			0.15	0.49

*Adjustment for age, BMI, physical activity, education, smoking, nulliparity, age at first delivery and age at menarche.

†Among postmenopausal women.

BMI, body mass index; HUNT, Trøndelag Health Study; LBP, low back pain; RR, relative risk.

Table 5 Associations between age at menopause and risk of chronic LBP in HUNT3 in prospective analysis, among women at least 40 years old in HUNT2

	Total number of women in category of age at menopause	Number of women with chronic LBP (%)	RR (95% CI) with adjustment for age only	RR (95 % CI) with additional adjustment*
Number of women included			5394	4941
Age at menopause (year)				
≤ 40	108	24 (22.2)	1.06 (0.73 -1.55)	1.05 (0.70-1.57)
41-43	102	26 (25.5)	1.21 (0.85 -1.73)	1.10 (0.74-1.62)
44-46	308	67 (21.8)	1.03 (0.80-1.34)	1.03 (0.79-1.34)
47-49	500	96 (19.2)	0.91 (0.73-1.15)	0.94 (0.74 -1.19)
50-52	841	155 (18.4)	0.87 (0.70 -1.09)	0.86 (0.68-1.09)
53-55	368	83 (22.6)	1.07 (0.82-1.40)	1.05 (0.79-1.40)
≥ 56	86	12 (14.0)	0.66 (0.38 -1.16)	0.68 (0.37 -1.26)
Premenopausal	3081	637 (20.7)	1.00 (reference)	1.00 (reference)
P categorical effect			0.33	0.59
P for linear trend†			0.11	0.31

*Adjustment for age, BMI, physical activity, education, smoking, nulliparity, age at first delivery and age at menarche.

†Among postmenopausal women.

BMI, body mass index; HUNT, Trøndelag Health Study; LBP, low back pain; RR, relative risk.

DISCUSSION

In this study an association was found between age at menarche and both prevalence and risk of LBP. The main feature was a decline in risk with increasing age at menarche, with relatively high risk estimates for ages ≤12 years, but little variation in risk for ages at menarche in the interval 13-16 years. However, the small group of women with a very late menarche, at an age ≥17 years, also showed a higher risk, and an overall relationship emerged that was approximately U-shaped. No association could be established between age at menopause and risk of LBP. Risk estimates were largely similar among pre- and postmenopausal women.

Strengths and limitations

Results in this study were based on cross-sectional and cohort data derived from surveys of the entire population in a Norwegian county. The similar results found with the two study designs provide additional support to the main findings. In principle, more weight should be attached to the cohort data, but the cross-sectional data set was considerably larger. The information on age at menarche referred anyhow to an event that mostly occurred a number of years before. In this situation the difference between the two study designs is probably less important.

Recall of age at menarche may be subject to error, but studies of validity[18] and reliability[19] indicate that the error is generally rather small. Minor random errors in reported age at menarche would in any case mainly be expected to attenuate the relationships observed. For menopause, the relevant event mostly occurred a relatively short time before data collection, improving the accuracy of the information. Recall of age at menopause is also regarded as fairly reliable.[20] However, reporting may be slightly biased, with women with an early menopause tending to overestimate their age at menopause and women with a late menopause reporting underestimates.[20] Also, the age specified when menstruation stopped may not represent the exact age at the final menstrual period, which requires a 12-month interval of amenorrhea before a strict assessment can be made.[21] In any case, neither

potential source of bias is likely to create an apparent lack of association with age at menopause, as observed in this study.

In the cohort data, no information was available on changes in potential risk factors or LBP status in the period between HUNT2 and HUNT3. Thus, women who were recorded as being premenopausal in HUNT2 may have been postmenopausal during part of the subsequent follow-up period. The self-reported information used to assess LBP was also incomplete in the sense that pain intensity was not recorded. Moreover, participation rates were rather low in the cohort study. However, a bias in relative risk estimates will only arise if participation rates differ between women with and without LBP in HUNT3 within categories of age at menarche or menopause. These rates are unknown, but LBP in HUNT3 was strongly associated with LBP in HUNT2, which was used to compare corresponding participation rates in HUNT3 for women with and without LBP in HUNT2. The fact that these rates were quite similar suggests that no major response bias has been introduced, except possibly for premenopausal women in the analyses involving menopausal status.

Age at menarche can be affected by various influences in childhood or puberty.[22] Information on body size or physical activity at those stages was not available in the present study, but adjustment was made in the statistical analysis for similar factors recorded much later in life. The population studied had a nearly uniform ethnic background and socioeconomic differences were generally small.[16] Socioeconomic status was taken into account by adjustment for duration of education. It is not possible to rule out potential confounding by other variables in the association between age at menarche and risk of LBP, but it seems unlikely that unknown factors should account entirely for the relationship observed.

Previous studies

To the best of our knowledge, the only other large study of relationships between age at menarche and occurrence of chronic LBP is the Dutch cross-sectional study of Wijnhoven et al.,[4] including 11 428 women in the age interval 20-59 years. Women with an age at menarche ≤11 years showed a greater prevalence of combined chronic LBP and upper extremity pain. Yet no definite relationship was demonstrated for prevalence of chronic LBP

without upper extremity pain, although risk estimates displayed a declining trend with increasing age at menarche. The top category represented ages at menarche ≥15 years. Overall, the results of Wijnhoven et al. may still be compatible with those obtained here. The much smaller Swedish study of Bergenudd et al.,[7] including 252 women, did not find any association between age at menarche and occurrence of back pain.

It is not clear whether LBP experienced during pregnancy represents the same medical disorder as LBP during other periods in a woman's life.[23, 24] Pelvic girdle pain in connection with pregnancy has often been combined with LBP in epidemiological studies. A large Norwegian study[25] found a pronounced inverse association between age at menarche and pelvic girdle syndrome in pregnancy. However, all women with an age at menarche >14 years were regarded as a single category. A small Swedish study of combined LBP and pelvic pain during pregnancy[26] found no association.

Age at menarche has also been considered as a potential risk factor in studies focusing on musculoskeletal disorders in a more general sense. One Norwegian study dealing with data from the same Nord-Trøndelag population[27] found an increased prevalence among women with age at menarche ≤12 years, while another study from a neighbouring county[28] found no association. Yet another study from Nord-Trøndelag[29] found an increased prevalence of headache for age at menarche ≤12 years.

Associations between age at menopause and LBP were examined in the relatively large cross-sectional study of Adera et al. in the United States, including 5325 women.[8] Compared to premenopausal women, considerably higher prevalence estimates of LBP were found among women with an age at menopause <30 and 30-39 years. However, it was not possible to distinguish between women with a natural menopause and those with medical procedures underlying the menopause. Thus these results cannot be expected to be similar to those in the present study. For ages at menopause 40-49 and ≥50 years the risk estimates were lower[8] and may be more consistent with our results. The Swedish study of Bergenudd et al.[7] did not show any association between age at menopause and back pain.

Several studies have compared prevalence of back pain more generally among pre- and postmenopausal women, not considering specific values of age at menopause. Some cross-sectional studies[30-32] found little evidence of any difference in prevalence. Other cross-

sectional studies,[33, 34] distinguishing between several stages of the menopausal transition, indicated a higher prevalence of LBP in postmenopausal phases. However, in some studies[33, 35] the prevalence decreased at the final postmenopausal stage, although prevalence estimates were higher in late perimenopausal or early postmenopausal periods. Still other studies recorded pain scores for general back pain[36] or LBP[37, 38] and found either an increasing trend in scores moving to later postmenopausal stages[36, 37] or essentially no difference between periods.[38]

If there is a short-term increase in risk of back pain during particular periods following menopause, the effect will not necessarily become apparent in analyses of associations with age at menopause such as those carried out in the present study. Most studies of back pain related to menopausal stages were based on information from less than 1000 women,[7, 30-33, 36-38] and the definitions of the medical condition considered varied widely. Chronic LBP as defined in our study[14] may represent a more serious disorder, involving a smaller proportion of the general female population. Some studies[33, 34, 37, 38] introduced no adjustment for the age when information was collected or only a crude adjustment. In analyses of risk related to menopause it may be particularly important to carry out accurate age adjustment.

A meta-analysis of studies of musculoskeletal pain[39] found an increased prevalence among peri- and postmenopausal women compared to premenopausal women. Restricting attention to moderate or severe pain, the prevalence also increased moving from the perimenopausal to the postmenopausal category.

Interpretation

It is well-known that the risks of breast cancer[40] and endometrial cancer[41] are inversely related to age at menarche. These relationships have mainly been explained in terms of a longer lifetime exposure to oestrogens among women with early menarche. This may also be a potential explanation of the increased risk of LBP seen in the present study in these women. The explanation is consistent with the increase in risk of LBP observed among women using hormone therapy or oral contraceptives,[4] and with the association found between risk of LBP and a woman's first childbirth.[9] This kind of hormonal influence may affect soft

tissues supporting the spine,[42] followed by laxity in joints and ligaments, leading to pain.[6] A hormonal effect may easily be attenuated in older age categories, in accordance with the interaction partly seen in the present study with baseline age.

Oestrogen loss may contribute to low bone mineral density (BMD) and development of osteoporosis.[5] This is consistent with indications that early menarche is associated with higher BMD[43] and a lower risk of vertebral fractures.[44] However, it is not clear what the relationship is between BMD and the overall risk of LBP.[45] If LBP is associated with high BMD,[46] this could explain the part of the association seen here in the lower half of the range for age at menarche, but this is not the case if LBP is associated with low BMD,[45] or if LBP is to some extent the cause of the high BMD.[46] Alternative explanations could involve hormonal effects on body size or growth during puberty, as suggested for relationships between age at menarche and cardiovascular disease.[47] Oestrogens may also play a role in modulation of pain[48] but it is difficult to state how this affects the experience of LBP.[49]

U-shaped relationships with age at menarche have previously been found for risk of cardiovascular disease[50] and diabetes.[51] A greater risk of disease among the relatively small group of women with age at menarche ≥16 years may possibly reflect underlying metabolic disorders associated with delayed onset of puberty.[51] It is not obvious how this would influence the risk of LBP, although the risk may in general depend on lipid levels.[11]

If the association between risk of LBP and age at menarche reflects effects of hormonal factors, the lack of association in this study with age at menopause or menopausal status may seem surprising. Perhaps changes in hormonal status when women are older must be present during a longer period of time before the risk of LBP is affected. This would accord with increased prevalence of LBP found by Adera et al.[8] among women with an age at menopause <40 years, when the menopause mostly must have been induced. In the present study, the great majority of the postmenopausal women must have experienced natural menopause.

The association found in this study with age at menarche may at least partly be consistent with a hormonal explanation of the general difference between men and women in risk of LBP. This difference has otherwise been explained in terms of childbearing, child care, heavier workloads, different distribution of muscle and bone mass and psychological

factors.[3] However, the present study does not lend support to a hypothesis involving a major additional increase in the risk difference after the menopausal phase.[52] Further studies are needed to investigate the nature of the risk difference and the influence of hormones on risk of LBP in both females and males.

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Contributors InH, IvH, KH, KS and J-AZ contributed to the study design. InH and IvH contributed to analysis and interpretation of data. InH wrote the paper. IvH, KH, KS and J-AZ all revised the manuscript. All authors discussed the results, commented on the manuscript and approved the paper.

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Competing interests None declared.

Ethics approval The work was approved by the Regional Committee for Medical and Health Research Ethics in Central Norway (approval number 2014/968/REK midt), and HUNT was also approved by the Norwegian Data Inspectorate. Each participant in the surveys signed a written informed consent regarding the collection and use of data for research purposes. The participants have given written informed consent.

Data sharing statement The data set analysed belongs to a third party, the HUNT study (the Trøndelag Health Study). The authors of the current manuscript are not affiliated with the project as such, but have been given permission to analyse the data after obtaining the necessary Norwegian permits. Because of the confidentiality requirements according to Norwegian law, a data set of this kind with information from a complete county at the individual level cannot be made public. However, research groups wishing to analyse data from the HUNT study may apply to the HUNT organisation (https://www.ntnu.edu/hunt) to get access to the data, after having obtained the permits needed according to Norwegian law.

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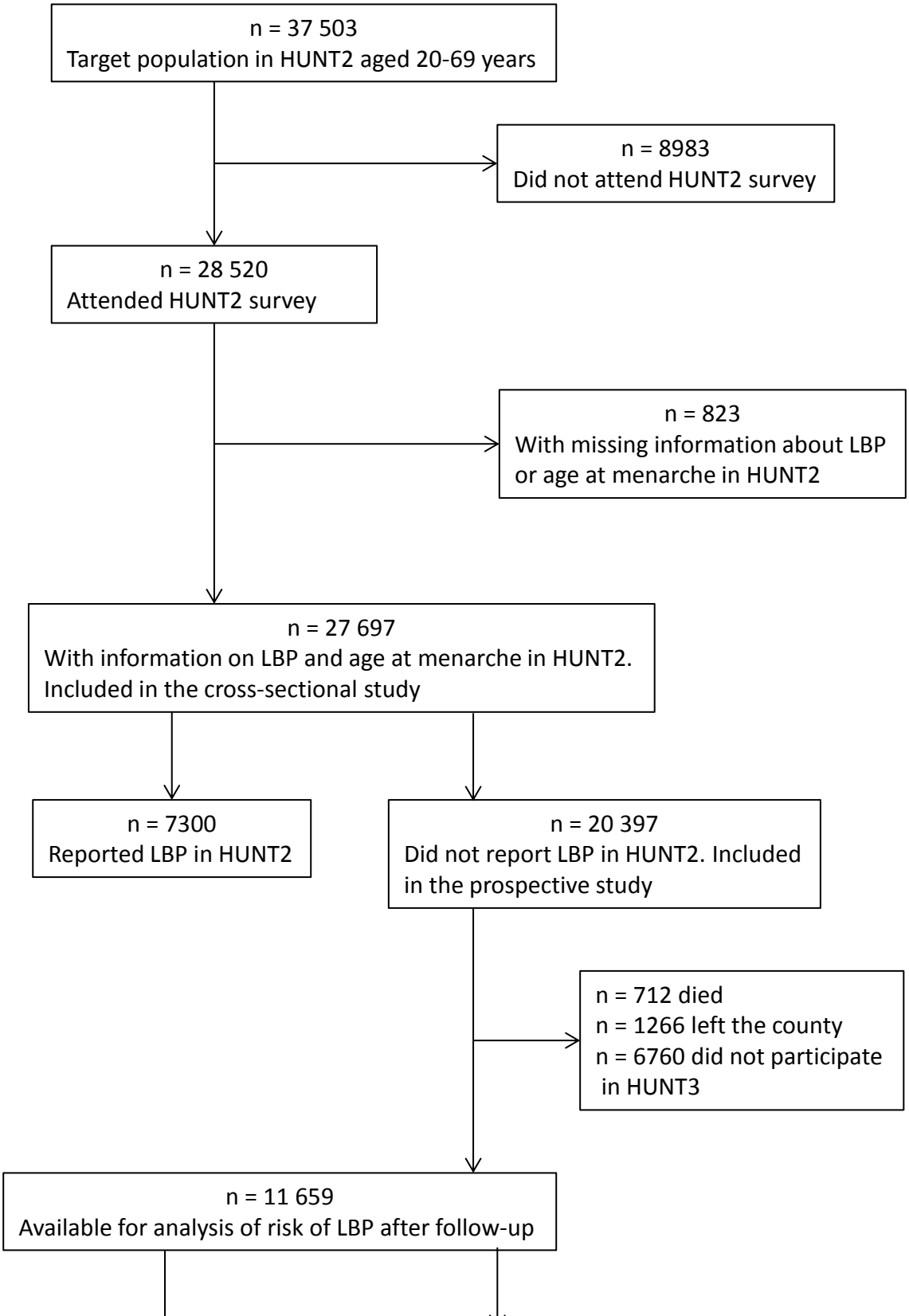
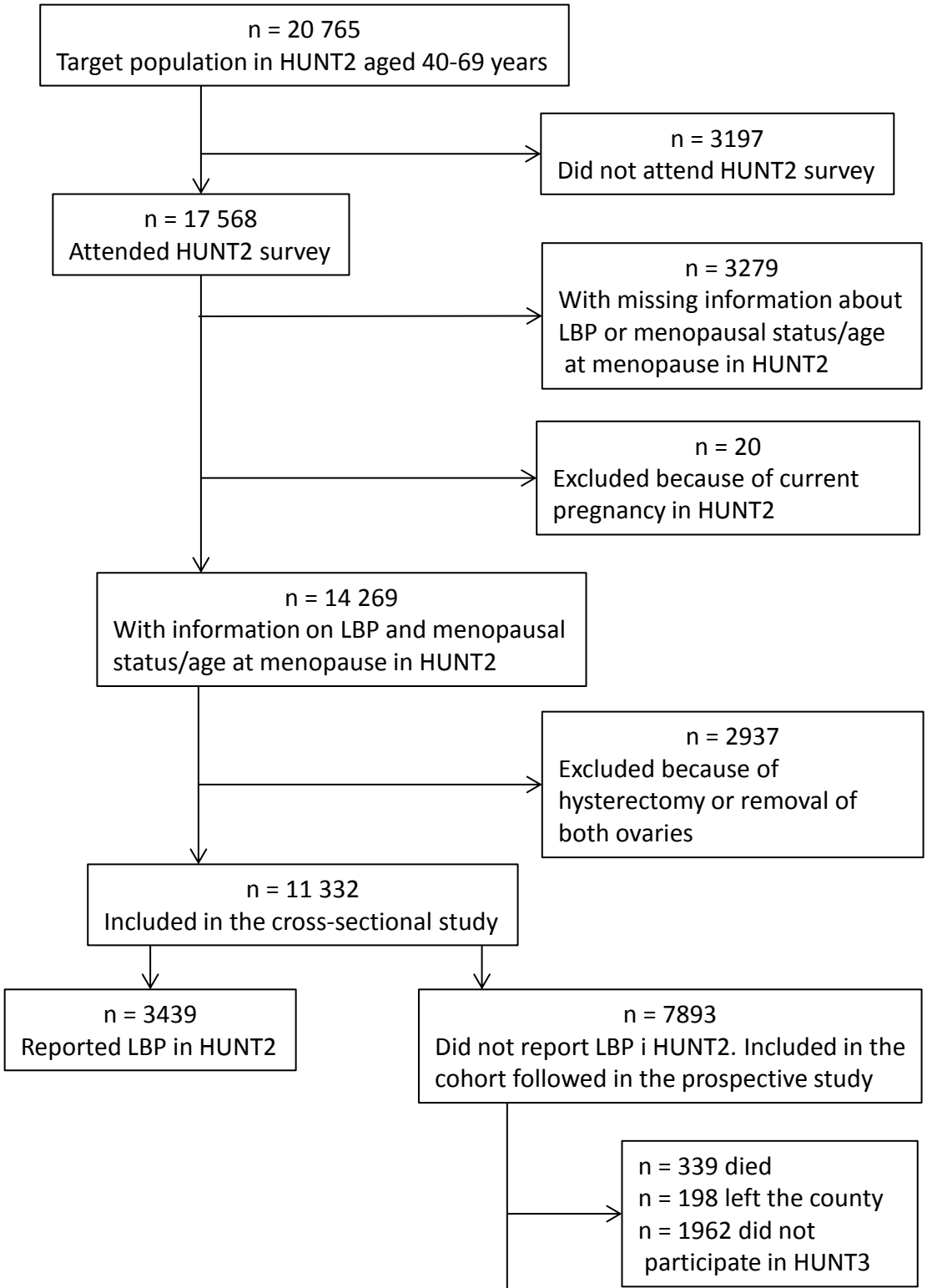
Legend for figures

Figure 1. Flow chart for the cross-sectional and prospective studies of age at menarche as a potential risk factor. HUNT, Trøndelag Health Study; LBP, low back pain.

Figure 2. Flow chart for the cross-sectional and prospective studies of age at menopause as a potential risk factor. HUNT, Trøndelag Health Study; LBP, low back pain.





Supplemental table 1 Associations between age at menarche and prevalence of chronic LBP in HUNT2 in cross-sectional analysis, in broad intervals of age

	Age 20-39 years RR (95% CI)*	Age 40-49 years RR (95% CI)*	Age 50-69 years RR (95% CI)*
Number of women included	10 298	6508	8145
Age at menarche (year)			
≤ 11	1.54 (1.34-1.77)	1.36 (1.19 -1.56)	1.18 (1.05-1.33)
12	1.16 (1.03-1.32)	1.14 (1.02-1.29)	1.12 (1.02-1.23)
13	1.09 (0.96-1.22)	1.11 (0.99-1.24)	1.06 (0.97-1.15)
14	1.00 (reference)	1.00 (reference)	1.00 (reference)
15	1.09 (0.93-1.29)	1.12 (0.98-1.28)	0.98 (0.89-1.08)
16	1.36 (1.07-1.74)	1.02 (0.80-1.30)	0.93 (0.78-1.09)
≥ 17	1.48 (0.97-2.26)	1.75 (1.22-2.51)	1.11 (0.85-1.45)
P for categorical effect	< 0.001	< 0.001	0.013
P for linear trend	< 0.001	0.009	< 0.001
P for quadratic effect†	< 0.001	0.001	0.21

*Adjustment for age, BMI, physical activity, education, smoking, nulliparity and age at first delivery.

†In model also including linear effect.

BMI, body mass index; HUNT, Trøndelag Health Study; LBP, low back pain; RR, relative risk.

Supplemental table 2 Associations between age at menarche and risk of chronic LBP in prospective analysis in HUNT3, in broad intervals of age in HUNT2

	Age 20-39 years	**Age 40-49 years**	**Age 50-69 years**
	RR (95% CI)*	**RR (95% CI)***	**RR (95 % CI)***
Number of women included	4254	3144	3456
Age at menarche (year)			
≤ 11	1.34 (1.06-1.68)	1.33 (1.05 -1.68)	1.30 (1.00-1.69)
12	1.15 (0.95-1.38)	0.99 (0.80-1.21)	1.24 (1.02-1.51)
13	1.01 (0.85-1.21)	1.01 (0.84-1.22)	1.03 (0.86-1.24)
14	1.00 (reference)	1.00 (reference)	1.00 (reference)
15	1.20 (0.96-1.51)	0.96 (0.76-1.21)	0.95 (0.77-1.18)
16	1.13 (0.75-1.71)	0.79 (0.51-1.21)	1.08 (0.78-1.49)
≥ 17	1.60 (0.94-2.75)	1.16 (0.53-2.53)	1.54 (0.97-2.46)
P for categorical effect	0.10	0.19	0.08
P for linear trend	0.46	0.048	0.06
P for quadratic effect†	0.002	0.32	0.019

*Adjustment for age, BMI, physical activity, education, smoking, nulliparity and age at first delivery.

†In model also including linear effect.

BMI, body mass index; HUNT, Trøndelag Health Study; LBP, low back pain; RR, relative risk.

Supplemental table 3 Associations between age at menarche and prevalence of chronic LBP in HUNT2 in cross-sectional analysis, by duration of education

	Education ≤ 9 years	Education 10-12 years	Education ≥ 13 years
	RR (95% CI)*	RR (95% CI)*	RR (95 % CI)*
Number of women included	7597	11 361	5993
Age at menarche (year)			
≤ 11	1.16 (1.03-1.31)	1.56 (1.40 -1.73)	1.22 (1.02-1.45)
12	1.13 (1.03-1.24)	1.16 (1.05-1.28)	1.10 (0.94-1.29)
13	1.06 (0.97-1.16)	1.10 (1.01-1.21)	1.04 (0.90-1.21)
14	1.00 (reference)	1.00 (reference)	1.00 (reference)
15	0.99 (0.89-1.10)	1.12 (1.00-1.26)	1.01 (0.84-1.22)
16	0.95 (0.80-1.13)	1.00 (0.80-1.24)	1.32 (1.01-1.73)
≥ 17	1.42 (1.10-1.84)	1.30 (0.95-1.77)	0.99 (0.56-1.75)
P for categorical effect	0.008	< 0.001	0.21
P for linear trend	0.006	< 0.001	0.19
P for quadratic effect†	0.06	< 0.001	0.048

*Adjustment for age, BMI, physical activity, education, smoking, nulliparity and age at first delivery.

†In model also including linear effect.

BMI, body mass index; HUNT, Trøndelag Health Study; LBP, low back pain; RR, relative risk.

Supplemental table 4 Associations between age at menarche and risk of chronic LBP in prospective analysis in HUNT3, by duration of education recorded in HUNT2

	Education ≤ 9 years	**Education 10-12 years**	**Education ≥ 13 years**
	RR (95% CI)*	**RR (95% CI)***	**RR (95 % CI)***
Number of women included	2957	4997	2900
Age at menarche (year)			
≤ 11	1.31 (0.98-1.74)	1.28 (1.05-1.56)	1.36 (1.04-1.79)
12	1.08 (0.88-1.33)	1.15 (0.98-1.34)	1.05 (0.81-1.35)
13	1.10 (0.91-1.32)	1.01 (0.87-1.17)	0.92 (0.72-1.16)
14	1.00 (reference)	1.00 (reference)	1.00 (reference)
15	1.13 (0.91-1.39)	1.05 (0.86-1.27)	0.77 (0.56-1.06)
16	0.95 (0.65-1.37)	1.14 (0.83-1.57)	0.87 (0.50-1.50)
≥ 17	1.75 (1.07-2.85)	0.95 (0.50-1.79)	1.87 (1.06-3.29)
P for categorical effect	0.29	0.21	0.012
P for linear trend	0.61	0.06	0.031
P for quadratic effect[b]	0.08	0.06	0.015

*Adjustment for age, BMI, physical activity, education, smoking, nulliparity and age at first delivery.

†In model also including linear effect.

BMI, body mass index; HUNT, Trøndelag Health Study; LBP, low back pain; RR, relative risk.

Supplemental table 5 Associations between age at menarche and prevalence of chronic LBP in cross-sectional analysis in HUNT2, with and without adjustment for HADS

	With standard adjustment*	With standard adjustment* among individuals with known HADS score	With standard adjustment*and adjustment for HADS score
	RR (95% CI)	RR (95% CI)	RR (95 % CI)
Number of women included	24 951	21 773	21 773
Age at menarche (year)			
≤ 11	1.33 (1.24-1.43)	1.31 (1.21 -1.42)	1.27 (1.18-1.37)
12	1.13 (1.06-1.21)	1.13 (1.05-1.21)	1.12 (1.05-1.19)
13	1.07 (0.01-1.14)	1.07 (1.00-1.14)	1.07 (1.00-1.14)
14	1.00 (reference)	1.00 (reference)	1.00 (reference)
15	1.04 (0.97-1.12)	1.05 (0.97-1.13)	1.02 (0.95-1.10)
16	1.02 (0.91-1.15)	1.07 (0.94-1.21)	1.05 (0.92-1.19)
≥ 17	1.31 (1.08-1.59)	1.34 (1.08-1.65)	1.28 (1.04-1.57)
P for categorical effect	< 0.001	< 0.001	< 0.001
P for linear trend	< 0.001	< 0.001	< 0.001
P for quadratic effect†	< 0.001	< 0.001	< 0.001

*Adjustment for age, BMI, physical activity, education, smoking, nulliparity and age at first delivery.

†In model also including linear effect.

BMI, body mass index; HADS, Hospital Anxiety and Depression Scale; HUNT, Trøndelag Health Study; LBP, low back pain; RR, relative risk.

Supplemental table 6 Associations between age at menarche and risk of chronic LBP in prospective analysis in HUNT3, with and without adjustment for HADS

	With standard adjustment*	With standard adjustment* among individuals with known HADS score	With standard adjustment* and adjustment for HADS score
	RR (95% CI)	RR (95% CI)	RR (95 % CI)
Number of women included	10 854	9666	9666
Age at menarche (year)			
≤ 11	1.32 (1.15-1.52)	1.37 (1.18 -1.59)	1.36 (1.17-1.57)
12	1.12 (1.00-1.25)	1.16 (1.03-1.31)	1.15 (1.02-1.30)
13	1.01 (0.91-1.13)	1.04 (0.92-1.16)	1.04 (0.93-1.16)
14	1.00 (reference)	1.00 (reference)	1.00 (reference)
15	1.02 (0.90-1.16)	1.05 (0.92-1.21)	1.04 (0.91-1.20)
16	1.01 (0.81-1.25)	1.07 (0.85-1.36)	1.07 (0.84-1.35)
≥ 17	1.43 (1.04-1.98)	1.31 (0.89-1.92)	1.25 (0.85-1.83)
P for categorical effect	0.002	0.002	0.003
P for linear trend	0.008	0.004	0.003
P for quadratic effect†	< 0.001	0.001	0.001

*****Adjustment for age, BMI, physical activity, education, smoking, nulliparity and age at first delivery.

†In model also including linear effect.

BMI, body mass index; HADS, Hospital Anxiety and Depression Scale; HUNT, Trøndelag Health Study; LBP, low back pain; RR, relative risk.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5, 6
Objectives	3	State specific objectives, including any prespecified hypotheses	3, 5
Methods			
Study design	4	Present key elements of study design early in the paper	3, 6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	6, 7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8, 9
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	8
Bias	9	Describe any efforts to address potential sources of bias	17
Study size	10	Explain how the study size was arrived at	6, 7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	8,9
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 (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	7 9-16
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	17, 18
Outcome data	15*	Report numbers of outcome events or summary measures over time	11,13,15,16 Table 2-5

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 (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9, 12 Table 2-4 Supplemental table 1-6
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12
Discussion			
Key results	18	Summarise key results with reference to study objectives	12, 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, 18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18-20
Generalisability	21	Discuss the generalisability (external validity) of the study results	20-22
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	17

*Give information separately for exposed and unexposed groups.

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 http://www.strobe-statement.org.

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Does the risk of chronic low back pain depend on age at menarche or menopause? A population-based cross-sectional and cohort study: the Trøndelag Health Study

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Does the risk of chronic low back pain depend on age at menarche or menopause? A population-based cross-sectional and cohort study: the Trøndelag Health Study

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Abstract

Objective In most population-based studies of low back pain (LBP) women have a higher risk than men, possibly reflecting hormonal influences. The aim of this study was to explore the associations between age at menarche and menopause and risk of chronic LBP.

Design Population-based cross-sectional and cohort study designs.

Setting The HUNT2 and HUNT3 surveys of Nord-Trøndelag County in Norway.

Main outcome measure Prevalence or risk of chronic LBP, defined as LBP persisting at least 3 months continuously during the last year.

Participants Associations between age at menarche and prevalence of chronic LBP were examined in cross-sectional data from HUNT2, comprising 27697 women aged 20-69 years, with 7300 women reporting LBP. The corresponding cohort data included 11659 women without chronic LBP at baseline in HUNT2, with 2353 women reporting LBP at follow-up 11 years later in HUNT3. The cross-sectional data on age at menopause or premenopausal status included 11332 women aged 40-69 years, with 3439 women reporting chronic LBP. The corresponding cohort data included 7893 women without LBP at baseline, of whom 1100 developed LBP.

Methods Associations between age at menarche or age at menopause and risk of chronic LBP were examined by generalised linear modelling.

Results A U-shaped association was indicated between age at menarche and risk of chronic LBP, both in the cross-sectional and cohort studies. Age at menarche ≤11 years was associated with an increased risk of chronic LBP (relative risk (RR) 1.32, 95% CI 1.15 to 1.52, vs. age 14 years at menarche), after adjustment for relevant risk factors. No association was established between age at menopause and risk of LBP. Being premenopausal had no influence on risk.

Conclusions In contrast to results for age at menopause, the association with age at menarche suggests that hormonal factors affect the risk of LBP.

Strengths and limitations of this study

-The study included data collected using both a cross-sectional and a cohort design, with a long follow-up period of 11 years.

- The information on age at menarche and menopause made it possible to carry out analyses with a detailed categorisation.

-The information about back pain was self-reported in a questionnaire.

-No information was available on pain intensity.

INTRODUCTION

Low back pain (LBP) constitutes a major problem for the individuals affected,[1] and the disorder entails large annual expenses for society.[2] To obtain insight into the etiology it is important to determine potential risk factors for LBP. In most population-based studies, women have a higher risk of LBP than men,[3] a tendency which may reflect hormonal differences.[4]

Women who experience early menarche or late menopause have generally been exposed to endogenous oestrogen for a long time. Oestrogen is known to be important in reducing osteoporosis and fracture rates[5] and may in this way potentially also reduce the risk of LBP. On the other hand, higher levels of oestrogen may increase the risk of LBP during and after pregnancy,[6] possibly through the involvement of the hormone relaxin. The greater risk of LBP observed in women using hormone therapy[4] or oral contraceptives[4] may also be related to oestrogen levels.[6]

There are very few epidemiological studies of associations between age at menarche or menopause and risk of LBP. A large population-based cross-sectional study in the Netherlands found an increase in the risk of combined chronic LBP and upper extremity pain among women with an early menarche[4] but results were equivocal for those with LBP only. No association was found in a smaller Swedish study.[7] A study in the United States[8] found a higher risk of LBP among women with menopause before age 40 years, but essentially no association with age at menopause after that early threshold.

In a large-scale population-based Norwegian study, we previously found an increase in risk of chronic LBP among women having experienced at least one delivery, but no further increase with subsequent deliveries.[9] Moreover, the risk depended on age at first delivery.[9] Data from the same surveys have also been used to study associations between chronic LBP and body mass index (BMI),[10] lipid levels[11] and physical activity in leisure time.[12] The aim of the present study was to investigate the relationships between age at menarche and menopause and risk of chronic LBP, considering cross-sectional and 11-year follow-up data.

METHODS

Collection of information

In the former Nord-Trøndelag County in Norway the two health surveys HUNT2 and HUNT3 were conducted in 1995 to 1997 and 2006 to 2008.[13] In the present work cross-sectional data from the HUNT2 survey are combined with follow-up data from the HUNT3 survey.

All residents of this county aged 20 years and above were invited to take part in the HUNT2 survey. They were requested to complete a questionnaire on health status, and they were invited to a clinical examination, including measurement of height and weight. In the HUNT3 survey 11 years later, similar information was collected by questionnaires and an examination.

One question in the HUNT2 and HUNT3 questionnaires was expressed in this way: "During the last year, have you suffered from pain and/or stiffness in your muscles and joints that has lasted for at least 3 consecutive months?" Each participant answering yes was given the following question: "Where did you have these complaints?" Several body regions were listed. Individuals answering yes to the first question and including the lower back as a relevant region were regarded as having chronic LBP.[14]

Women participating in HUNT2 gave information on age at menarche by answering the question "How old were you when you started menstruating?". They were also asked the question "Do you still menstruate?" Those aged ≥40 years indicating "yes" were regarded as premenopausal. The women who indicated "no" answered the following question: "How old were you when you stopped menstruating?" This was regarded as age at menopause.

The participants also gave information regarding physical activity in leisure time, smoking, duration of education and childbirths. In addition, they provided information used for computing Hospital Anxiety and Depression Scale (HADS) scores.[15]

Study design

Age at menarche

The target population of the HUNT2 study comprised 37 503 women in the age range 20-69 years. Of these, a total of 28 520 women participated in HUNT2 (figure 1).[16] Information about age at menarche in HUNT2 and about presence or absence of chronic LBP was collected from 27 697 women, corresponding to an overall participation rate of 74%. This data set formed the basis of the cross-sectional study of associations with age at menarche.

The 20 397 women who reported absence of chronic LBP in HUNT2 were included in the cohort considered in the prospective study of association between age at menarche and risk of chronic LBP. Information about residence status was obtained from national registries and linked using the unique Norwegian personal identification numbers. During the 11-year follow-up period, 712 women in this cohort died and 1266 individuals left the county of Nord-Trøndelag (figure 1). A total of 6760 women in the cohort residing in Nord-Trøndelag at the time of HUNT3 did not participate or did not supply information about chronic LBP. The remaining 11 659 women could be included in the analysis of risk of LBP after the 11-year follow-up period, representing 63% of the remaining women resident in the county, and 57% of the original cohort.

Age at menopause

Only women in the age range 40-69 years in HUNT2 were included in the study of age at menopause. The target population of the HUNT2 study comprised 20 765 women in this interval. Of these, a total of 17 568 women participated in HUNT2 (figure 2).[16] Women who were pregnant when the questionnaire was filled in were excluded. Information about age at menopause or premenopausal status in HUNT2 as well as presence or absence of chronic LBP was collected from 14 269 women, corresponding to a participation rate of 69%. At this stage, 2937 women were excluded because of surgery involving hysterectomy or removal of both ovaries, leaving 11 332 women included in the cross-sectional study (figure 2).

A total of 7893 women who reported absence of chronic LBP in HUNT2, were included in the prospective study of associations between age at menopause and risk of LBP. During the 11-year follow-up period, 339 women in this cohort died, 198 individuals left the county and 1962 women residing in Nord-Trøndelag at the time of HUNT3 did not participate or did not supply information about chronic LBP. Thus, a total of 5394 women were available for analysis of risk of LBP after the follow-up period, representing 73% of the remaining women resident in the county, and 68% of the original cohort.

Variables

Age at menarche reported in HUNT2 was categorised into seven groups: ≤11, 12, 13, 14, 15, 16, ≥17 years. Women aged 14 years at menarche were considered the reference group. Age at menopause was categorised into seven groups: ≤40, 41-43, 44-46, 47-49, 50-52, 53-55, ≥56 years. The premenopausal women were regarded as a separate reference group. In additional analyses, testing the linear or quadratic effects of the two study variables, these variables were regarded as continuous.

BMI, defined as weight/height^2 and computed in kg/m^2, was subdivided into three groups: <25, 25-29.9, ≥30. Categories of education were defined according to duration, ≤9, 10-12, and ≥13 years. Cigarette smoking was described using the categories current daily smoking, previous daily smoking and never daily smoking. For physical activity in leisure time, including going to work, one category comprised those engaged in light activity only or hard physical activity (leading to sweating or being out of breath) <1 hour per week. Other categories represented hard physical activity 1-2 and ≥3 hours per week. The information about physical activity collected in HUNT2 was verified by a reliability and validity study of a subsample.[17] A particular variable was defined to take into account both nulliparity and age at first delivery among parous women. Categories of age at first delivery were: ≤19, 20-24, 25-29, 30-34, ≥35 years. Five categories were introduced for total HADS scores: 0-4, 5-9, 10-14, 15-19 and ≥20.

Statistical analyses

Associations between the study variables age at menarche or menopause and prevalence or risk of chronic LBP were assessed by generalised linear modelling for binomial observations with a log link, with adjustment for potential confounders. Initial analyses involved adjustment for age only, and adjustment was then added for other factors known to be risk factors for LBP, as BMI,[10] physical activity in leisure time,[12] education and smoking, nulliparity and age at first delivery.[9] The non-linear effect of age[10] was modelled by a cubic polynomial. In the main analyses, all other variables adjusted for were regarded as categorical.

Separate tests were carried out for interaction between each factor adjusted for and study variables showing an association with risk of chronic LBP. To obtain more powerful

interaction tests, the effect of age at menarche was then modelled by a quadratic polynomial depending on scores representing the successive categories.

Because information on potential confounders was missing in a minor part of the data set, analyses involving more complete adjustment included a slightly lower number of individuals than the age-adjusted analyses. HADS scores, representing important psychological factors, could not be computed for 3178 (13%) of the 24 951 women included in cross-sectional analysis of relations with age at menarche with adjustment for other potential confounders. The corresponding proportion, 11%, in the prospective analysis was also rather high. For this reason, additional adjustment for HADS was only carried out in particular sensitivity analyses. At the same time, analyses were also performed without adjustment for HADS, including only women with known HADS scores, to evaluate the exact effect of the adjustment.

To assess potential effects of differential participation, participation rates in HUNT3 were computed among the women reporting LBP in HUNT2 and those not reporting LBP, within broad categories of age at menarche or menopause.

All statistical analyses were carried out using IBM SPSS version 26 (IBM Corp., Armonk, New York).

Public and patient involvement

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

RESULTS

Age at menarche

Women in HUNT2 with a late menarche tended to have a low BMI and an education of short duration (table 1). Daily current smoking was more common among those with an early menarche. Nulliparity showed a weak inverse relationship with age at menarche (table 1).

Among the 27 697 women in the cross-sectional study of the association between age at menarche and prevalence of chronic LBP, 7300 women (26%) reported chronic LBP in

HUNT2 (figure 1). In the prospective study with 11 659 women available for analysis of risk of LBP at end of follow-up, 2353 women (20%) reported chronic LBP at end of follow-up in HUNT3.

Table 1 Baseline mean values and category percentages for potential confounders, by age at menarche and menopause

	Age at menarche (year)*				Age at menopause (year)†				
	≤ 11	12-13	14-15	≥ 16	≤ 46	47-49	50-52	≥ 53	Pre-menopausal
Number of women included	2288	12 176	9388	1099	1044	972	1579	826	5633
Age in HUNT2‡ (year)	41.1	41.8	45.9	47.6	55.9	56.3	58.4	60.2	45.8
BMI‡ (kg/m^2)	27.1	26.0	25.5	24.9	26.6	26.8	26.9	27.5	25.9
Physical activity per week§ (%)									
< 1 hour hard	73	74	78	78	85	84	86	85	76
1-2 hours hard	19	19	16	15	11	12	11	11	18
≥ 3 hours hard	8	7	6	7	4	4	4	4	6
Cigarette smoking§ (%)									
never	39	43	42	43	31	38	45	51	35
daily former	25	25	27	28	28	28	30	32	30
daily current	37	33	32	29	41	35	26	17	34
Education§ (year) (%)									
≤ 9	24	27	35	40	56	54	58	58	27
10-12	48	47	43	38	29	33	27	27	46
≥ 13	28	25	22	22	14	13	15	15	27
Nulliparity§ (%)	15	15	12	11	7	6	6	3	5
Age at first childbirth‡,¶ (year)	22.6	22.8	23.1	24.0	23.1	23.2	23.3	23.2	22.9

*Among women with information about chronic LBP, BMI, physical activity, education, smoking, nulliparity, age at first delivery and age at menarche.

†Among women with information about chronic LBP, BMI, physical activity, education, smoking, nulliparity, age at first delivery and age at menarche and menopause.

‡Mean value within category of age at menarche or menopause.

§Percentages of categories for potential confounder within category of age at menarche or menopause.

¶Among women with at least 1 child.

BMI, body mass index; HUNT, Trøndelag Health Study; LBP, low back pain.

Table 2 Associations between age at menarche and prevalence of chronic LBP in HUNT2 in cross-sectional analysis

	Total number of women in category of age at menarche*	Number of women with chronic LBP (%)	RR (95% CI) with adjustment for age only	RR (95 % CI) with additional adjustment†
Number of women included			27 697	24 951
Age at menarche (year)				
≤ 11	2487	806 (32.4)	1.39 (1.30 -1.49)	1.33 (1.24-1.43)
12	5536	1499 (27.1)	1.17 (1.11-1.24)	1.13 (1.06-1.21)
13	7789	1953 (25.1)	1.08 (1.02-1.14)	1.07 (1.01-1.14)
14	6861	1713 (25.0)	1.00 (reference)	1.00 (reference)
15	3759	994 (26.4)	1.03 (0.96-1.10)	1.04 (0.97-1.12)
16	975	252 (25.8)	0.99 (0.89-1.11)	1.02 (0.91-1.15)
≥ 17	290	83 (28.6)	1.12 (0.93-1.35)	1.31 (1.08-1.59)
P for categorical effect			< 0.001	< 0.001
P for linear trend			< 0.001	< 0.001
P for quadratic effect‡			< 0.001	< 0.001

*In analysis adjusted for age only.

†Adjustment for age, BMI, physical activity, education, smoking, nulliparity and age at first delivery.

‡In model also including linear effect.

BMI, body mass index; HUNT, Trøndelag Health Study; LBP, low back pain; RR, relative risk.

A U-shaped relationship between age at menarche and prevalence of chronic LBP was suggested in the cross-sectional study (table 2). This relationship was retained after adjustment for age, BMI, physical activity, education, smoking, nulliparity and age at first delivery. The prospective analysis revealed a similar U-shaped relationship between age at menarche and risk of chronic LBP, with an estimated 32% and 43% increased risk among women with menarche at age ≤11 years and ≥17 years, respectively, compared to those with age at menarche 14 years (table 3).

An interaction was observed between age at menarche and baseline age in the cross-sectional analysis (p=0.026). Definite U-shaped relationships between age at menarche and prevalence of chronic LBP were found among women in the two age intervals 20-39 years and 40-49 years in HUNT2 (supplemental table 1). Although a U-shaped relationship was still suggested among the oldest women aged 50-69 years (supplemental table 1), the association was much weaker. No interaction with baseline age was found in the prospective analyses of risk of chronic LBP in HUNT3 (p=0.35; supplemental table 2).

In the cross-sectional analysis an interaction was also found between age at menarche and duration of education (p=0.031). The U-shaped relationship with age at menarche was most evident in women with 10-12 years of education, but estimates were also compatible with a relationship of this kind in the categories representing shorter or longer duration of education (supplemental table 3). In the prospective analysis no significant interaction between age at menarche and duration of education was observed (p=0.84; supplemental table 4).

Sensitivity analyses with additional adjustment for HADS revealed only minor changes in the association with age at menarche, both in the cross-sectional (supplemental table 5) and the prospective (supplemental table 6) situations.

Participation rates in HUNT3 depended only weakly on age at menarche, with slightly higher rates among women with a late menarche. Within broad categories of age at menarche, however, participation rates were quite similar among those reporting LBP in HUNT2 and those not reporting LBP. Among women with age at menarche ≤11 years, the two participation rates were 55% and 58%, respectively, among those with age at menarche 12-13 years 56% and 57%, among women with menarche 14-15 years 58% and 58%, and among women with age at menarche ≥16 years 59% and 61%.

Table 3 Associations between age at menarche and risk of chronic LBP in HUNT3 in prospective analysis

	Total number of women in category of age at menarche*	Number of women with chronic LBP (%)	RR (95% CI) with adjustment for age only	RR (95 % CI) with additional adjustment†
Number of women included			11 659	10 854
Age at menarche (year)				
≤ 11	930	236 (25.4)	1.34 (1.17-1.53)	1.32 (1.15-1.52)
12	2228	468 (21.0)	1.11 (1.00-1.24)	1.12 (1.00-1.25)
13	3340	641 (19.2)	1.01 (0.91-1.12)	1.01 (0.91-1.13)
14	3014	582 (19.3)	1.00 (reference)	1.00 (reference)
15	1600	314 (19.6)	1.01 (0.89-1.14)	1.02 (0.90-1.16)
16	421	82 (19.5)	1.00 (0.81-1.23)	1.01 (0.81-1.25)
≥ 17	126	30 (23.8)	1.24 (0.90-1.70)	1.43 (1.04-1.98)
P for categorical effect			0.001	0.002
P for linear trend			0.001	0.008
P for quadratic effect‡			0.001	< 0.001

*In analysis adjusted for age only.

†Adjustment for age, BMI, physical activity, education, smoking, nulliparity and age at first delivery.

‡In model also including linear effect.

BMI, body mass index; HUNT, Trøndelag Health Study; LBP, low back pain; RR, relative risk.

Age at menopause

Early menopause was primarily associated with daily current smoking and with nulliparity (table 1). Premenopausal women tended to have a relatively long duration of education and were engaged in more physical activity than postmenopausal women.

In the cross-sectional study of association between age at menopause and chronic LBP in HUNT2, 11 332 women were included, and a total of 3439 women (30%) reported chronic LBP (figure 2). In the prospective study among the remaining 5394 women who did not report chronic LBP in HUNT2, a total of 1100 women (20%) reported chronic LBP at end of follow-up in HUNT3.

No association between age at menopause and prevalence or risk of chronic LBP was observed, neither in the cross-sectional (table 4) nor in the prospective (table 5) data. Being premenopausal had no particular influence on prevalence or risk of chronic LBP. Additional adjustment for HADS in sensitivity analyses produced very similar estimates.

Participation rates in HUNT3 were somewhat higher for women with an older age at menopause. Yet within broad categories of age at menopause, participation rates were very similar for those reporting LBP in HUNT2 and those not reporting LBP. Premenopausal women represented an exception, with a participation rate equal to 65% among those reporting LBP, compared to 71% among those without LBP.

Table 4 Associations between age at menopause and prevalence of chronic LBP in cross-sectional analysis, among women at least 40 years old in HUNT2

	Total number of women in category of age at menopause	Number of women with chronic LBP (%)	RR (95% CI) with adjustment for age only	RR (95 % CI) with additional adjustment*
Number of women included			11 332	10 054
Age at menopause (year)				
≤ 40	263	90 (34.2)	1.10 (0.92-1.32)	1.08 (0.88-1.32)
41-43	269	88 (32.7)	1.06 (0.88-1.28)	1.05 (0.86-1.27)
44-46	743	260 (35.0)	1.12 (0.98-1.27)	1.06 (0.92-1.21)
47-49	1170	394 (33.7)	1.07 (0.96-1.20)	1.05 (0.93-1.18)
50-52	1859	601 (32.3)	1.01 (0.90-1.13)	1.03 (0.92-1.15)
53-55	818	290 (35.5)	1.09 (0.95-1.25)	1.06 (0.91-1.23)
≥ 56	182	46 (25.3)	0.78 (0.59-1.02)	0.79 (0.59-1.06)
Premenopausal	6028	1670 (27.7)	1.00 (reference)	1.00 (reference)
P for categorical effect			0.09	0.56
P for linear trend†			0.15	0.49

*Adjustment for age, BMI, physical activity, education, smoking, nulliparity, age at first delivery and age at menarche.

†Among postmenopausal women.

BMI, body mass index; HUNT, Trøndelag Health Study; LBP, low back pain; RR, relative risk.

Table 5 Associations between age at menopause and risk of chronic LBP in HUNT3 in prospective analysis, among women at least 40 years old in HUNT2

	Total number of women in category of age at menopause	Number of women with chronic LBP (%)	RR (95% CI) with adjustment for age only	RR (95 % CI) with additional adjustment*
Number of women included			5394	4941
Age at menopause (year)				
≤ 40	108	24 (22.2)	1.06 (0.73-1.55)	1.05 (0.70-1.57)
41-43	102	26 (25.5)	1.21 (0.85-1.73)	1.10 (0.74-1.62)
44-46	308	67 (21.8)	1.03 (0.80-1.34)	1.03 (0.79-1.34)
47-49	500	96 (19.2)	0.91 (0.73-1.15)	0.94 (0.74-1.19)
50-52	841	155 (18.4)	0.87 (0.70-1.09)	0.86 (0.68-1.09)
53-55	368	83 (22.6)	1.07 (0.82-1.40)	1.05 (0.79-1.40)
≥ 56	86	12 (14.0)	0.66 (0.38-1.16)	0.68 (0.37-1.26)
Premenopausal	3081	637 (20.7)	1.00 (reference)	1.00 (reference)
P categorical effect			0.33	0.59
P for linear trend†			0.11	0.31

*Adjustment for age, BMI, physical activity, education, smoking, nulliparity, age at first delivery and age at menarche.

†Among postmenopausal women.

BMI, body mass index; HUNT, Trøndelag Health Study; LBP, low back pain; RR, relative risk.

DISCUSSION

In this study an association was found between age at menarche and both prevalence and risk of LBP. The main feature was a decline in risk with increasing age at menarche, with relatively high risk estimates for ages ≤12 years, but little variation in risk for ages at menarche in the interval 13-16 years. However, the small group of women with a very late menarche, at an age ≥17 years, also showed a higher risk, and an overall relationship emerged that was approximately U-shaped. No association could be established between age at menopause and risk of LBP. Risk estimates were largely similar among pre- and postmenopausal women.

Strengths and limitations

Results in this study were based on cross-sectional and cohort data derived from surveys of the entire population in a Norwegian county. The similar results found with the two study designs provide additional support to the main findings. In principle, more weight should be attached to the cohort data, but the cross-sectional data set was considerably larger. The information on age at menarche referred anyhow to an event that mostly occurred a number of years before. In this situation the difference between the two study designs is probably less important.

Recall of age at menarche may be subject to error, but studies of validity[18] and reliability[19] indicate that the error is generally rather small. Minor random errors in reported age at menarche would in any case mainly be expected to attenuate the relationships observed. For menopause, the relevant event mostly occurred a relatively short time before data collection, improving the accuracy of the information. Recall of age at menopause is also regarded as fairly reliable.[20] However, reporting may be slightly biased, with women with an early menopause tending to overestimate their age at menopause and women with a late menopause reporting underestimates.[20] Also, the age specified when menstruation stopped may not represent the exact age at the final menstrual period, which requires a 12-month interval of amenorrhea before a strict assessment can be made.[21] In any case, neither potential source of bias is likely to create an apparent lack of association with age at menopause, as observed in this study.

In the cohort data, no information was available on changes in potential risk factors or LBP status in the period between HUNT2 and HUNT3. Thus, women who were recorded as being premenopausal in HUNT2 may have been postmenopausal during part of the subsequent follow-up period. The self-reported information used to assess LBP was also incomplete in the sense that pain intensity was not recorded. Moreover, participation rates were rather low in the cohort study. However, a bias in relative risk estimates will only arise if participation rates differ between women with and without LBP in HUNT3 within categories of age at menarche or menopause. These rates are unknown, but LBP in HUNT3 was strongly associated with LBP in HUNT2, which was used to compare corresponding participation rates in HUNT3 for women with and without LBP in HUNT2. The fact that these rates were quite similar suggests that no major response bias has been introduced, except possibly for premenopausal women in the analyses involving menopausal status.

Age at menarche can be affected by various influences in childhood or puberty.[22] Information on body size or physical activity at those stages was not available in the present study, but adjustment was made in the statistical analysis for similar factors recorded much later in life. The population studied had a nearly uniform ethnic background and socioeconomic differences were generally small.[16] Socioeconomic status was taken into account by adjustment for duration of education. It is not possible to rule out potential confounding by other variables in the association between age at menarche and risk of LBP, but it seems unlikely that unknown factors should account entirely for the relationship observed.

Previous studies

To the best of our knowledge, the only other large study of relationships between age at menarche and occurrence of chronic LBP is the Dutch cross-sectional study of Wijnhoven et al.,[4] including 11 428 women in the age interval 20-59 years. Women with an age at menarche ≤11 years showed a greater prevalence of combined chronic LBP and upper extremity pain. Yet no definite relationship was demonstrated for prevalence of chronic LBP without upper extremity pain, although risk estimates displayed a declining trend with increasing age at menarche. The top category represented ages at menarche ≥15 years. Overall, the results of Wijnhoven et al. may still be compatible with those obtained here. The

much smaller Swedish study of Bergenudd et al.,[7] including 252 women, did not find any association between age at menarche and occurrence of back pain.

Pelvic girdle pain in connection with pregnancy has often been combined with LBP in epidemiological work. A large Norwegian study[23] found a pronounced inverse association between age at menarche and pelvic girdle syndrome in pregnancy. A small Swedish study of combined LBP and pelvic pain during pregnancy[24] found no association. It is not entirely clear, however, whether LBP experienced during pregnancy represents the same medical disorder as LBP during other periods in a woman's life.[25, 26]

Age at menarche has also been considered as a potential risk factor in studies focusing on musculoskeletal disorders in a more general sense. One Norwegian study dealing with data from the same Nord-Trøndelag population[27] found an increased prevalence of widespread musculoskeletal complaints among women with age at menarche ≤12 years, while another study from a neighbouring county[28] found no association. Yet another study from Nord-Trøndelag[29] found an increased prevalence of headache for age at menarche ≤12 years.

Associations between age at menopause and LBP were examined in the relatively large cross-sectional study of Adera et al. in the United States, including 5325 women.[8] Compared to premenopausal women, considerably higher prevalence estimates of LBP were found among women with an age at menopause <30 and 30-39 years. However, it was not possible to distinguish between women with a natural menopause and those with medical procedures underlying the menopause. Thus these results cannot be expected to be similar to those in the present study. For ages at menopause 40-49 and ≥50 years the risk estimates were lower[8] and may be more consistent with our results. The Swedish study of Bergenudd et al.[7] did not show any association between age at menopause and back pain.

Several studies have compared prevalence of back pain more generally among pre- and postmenopausal women, not considering specific values of age at menopause. Some cross-sectional studies[30-32] found little evidence of any difference in prevalence. Other cross-sectional studies,[33, 34] distinguishing between several stages of the menopausal transition, indicated a higher prevalence of LBP in postmenopausal phases. However, in some studies[33, 35] the prevalence decreased at the final postmenopausal stage, although prevalence estimates were higher in late perimenopausal or early postmenopausal periods.

Still other studies recorded pain scores for general back pain[36] or LBP[37, 38] and found either an increasing trend in scores moving to later postmenopausal stages[36, 37] or essentially no difference between periods.[38]

If there is a short-term increase in risk of back pain during particular periods following menopause, the effect will not necessarily become apparent in analyses of associations with age at menopause such as those carried out in the present study. Most studies of back pain related to menopausal stages were based on information from less than 1000 women,[7, 30-33, 36-38] and the definitions of the medical condition considered varied widely. Chronic LBP as defined in our study[14] may represent a more serious disorder, involving a smaller proportion of the general female population. Some studies[33, 34, 37, 38] introduced no adjustment for the age when information was collected or only a crude adjustment. In analyses of risk related to menopause, the study design often creates a strong association between age at menopause and attained age in the data available for analysis, and it may be particularly important to carry out accurate age adjustment.

A meta-analysis of studies of musculoskeletal pain[39] found an increased prevalence among peri- and postmenopausal women compared to premenopausal women. Restricting attention to moderate or severe pain, the prevalence also increased moving from the perimenopausal to the postmenopausal category.

Interpretation

It is well-known that the risks of breast cancer[40] and endometrial cancer[41] are inversely related to age at menarche. These relationships have mainly been explained in terms of a longer lifetime exposure to oestrogens among women with early menarche. This may also be a potential explanation of the increased risk of LBP seen in the present study in these women. The explanation is consistent with the increase in risk of LBP observed among women using hormone therapy or oral contraceptives,[4] and with the association found between risk of LBP and a woman's first childbirth.[9] This kind of hormonal influence may affect soft tissues supporting the spine,[42] followed by laxity in joints and ligaments, leading to pain.[6] A hormonal effect may easily be attenuated in older age categories, in accordance with the interaction partly seen in the present study with baseline age.

Oestrogen loss may contribute to low bone mineral density (BMD) and development of osteoporosis.[5] This is consistent with indications that early menarche is associated with higher BMD[43] and a lower risk of vertebral fractures.[44] However, it is not clear what the relationship is between BMD and the overall risk of LBP.[45] If LBP is associated with high BMD,[46] this could explain the part of the association seen here in the lower half of the range for age at menarche, but this is not the case if LBP is associated with low BMD,[45] or if LBP is to some extent the cause of the high BMD.[46] Alternative explanations could involve hormonal effects on body size or growth during puberty, as suggested for relationships between age at menarche and cardiovascular disease.[47] Oestrogens may also play a role in modulation of pain[48] but it is difficult to state how this affects the experience of LBP.[49]

U-shaped relationships with age at menarche have previously been found for risk of cardiovascular disease[50] and diabetes.[51] A greater risk of disease among the relatively small group of women with age at menarche ≥16 years may possibly reflect underlying metabolic disorders associated with delayed onset of puberty.[51] It is not obvious how this would influence the risk of LBP, although the risk may in general depend on lipid levels.[11]

If the association between risk of LBP and age at menarche reflects effects of hormonal factors, the lack of association in this study with age at menopause or menopausal status may seem surprising. Perhaps changes in hormonal status when women are older must be present during a longer period of time before the risk of LBP is affected. This would accord with increased prevalence of LBP found by Adera et al.[8] among women with an age at menopause <40 years, when the menopause mostly must have been induced. In the present study, the great majority of the postmenopausal women must have experienced natural menopause. It is also possible that the association found with age at menarche represents essential developmental factors which are not relevant to menopause. With a lack of association with age at menopause, a risk factor analyses of the total number of reproductive years, defined as the difference between ages at menopause and menarche, will mainly reflect associations with age at menarche only. For this reason the number of reproductive years was not considered as potential risk factor in our analysis.

The association found in this study with age at menarche may at least partly be consistent with a hormonal explanation of the general difference between men and women in risk of

LBP. This difference has otherwise been explained in terms of childbearing, child care, heavier workloads, different distribution of muscle and bone mass and psychological factors.[3] However, the present study does not lend support to a hypothesis involving a major additional increase in the risk difference after the menopausal phase.[52] Further studies are needed to investigate the nature of the risk difference and the influence of hormones on risk of LBP in both females and males.

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Contributors InH, IvH, KH, KS and J-AZ contributed to the study design. InH and IvH contributed to analysis and interpretation of data. InH wrote the paper. IvH, KH, KS and J-AZ all revised the manuscript. All authors discussed the results, commented on the manuscript and approved the paper.

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Competing interests None declared.

Ethics approval The work was approved by the Regional Committee for Medical and Health Research Ethics in Central Norway (approval number 2014/968/REK midt), and HUNT was also approved by the Norwegian Data Inspectorate. Each participant in the surveys signed a written informed consent regarding the collection and use of data for research purposes. The participants have given written informed consent.

Data sharing statement The data set analysed belongs to a third party, the HUNT study (the Trøndelag Health Study). The authors of the current manuscript are not affiliated with the project as such, but have been given permission to analyse the data after obtaining the necessary Norwegian permits. Because of the confidentiality requirements according to Norwegian law, a data set of this kind with information from a complete county at the individual level cannot be made public. However, research groups wishing to analyse data from the HUNT study may apply to the HUNT organisation (https://www.ntnu.edu/hunt) to get access to the data, after having obtained the permits needed according to Norwegian law.

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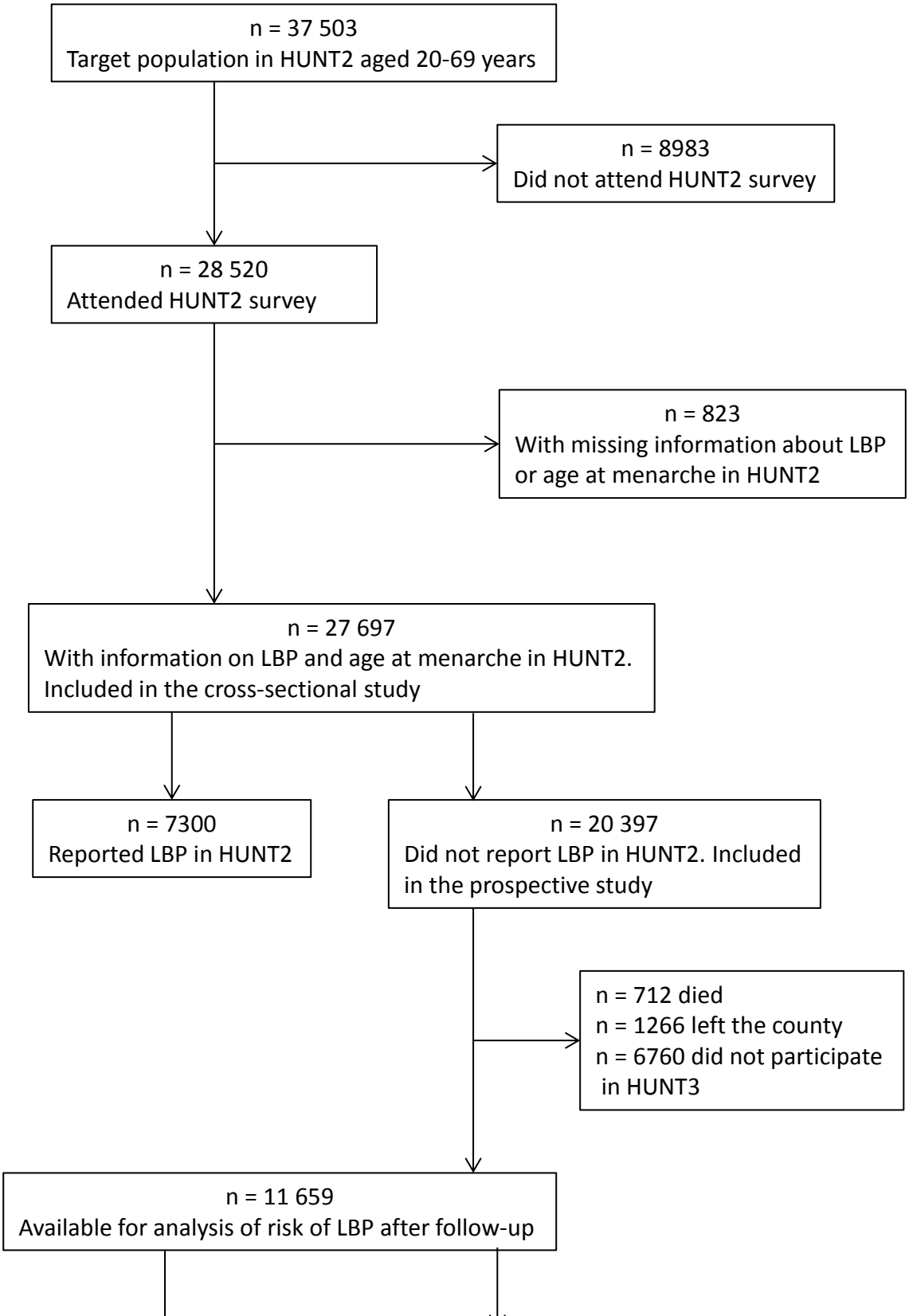
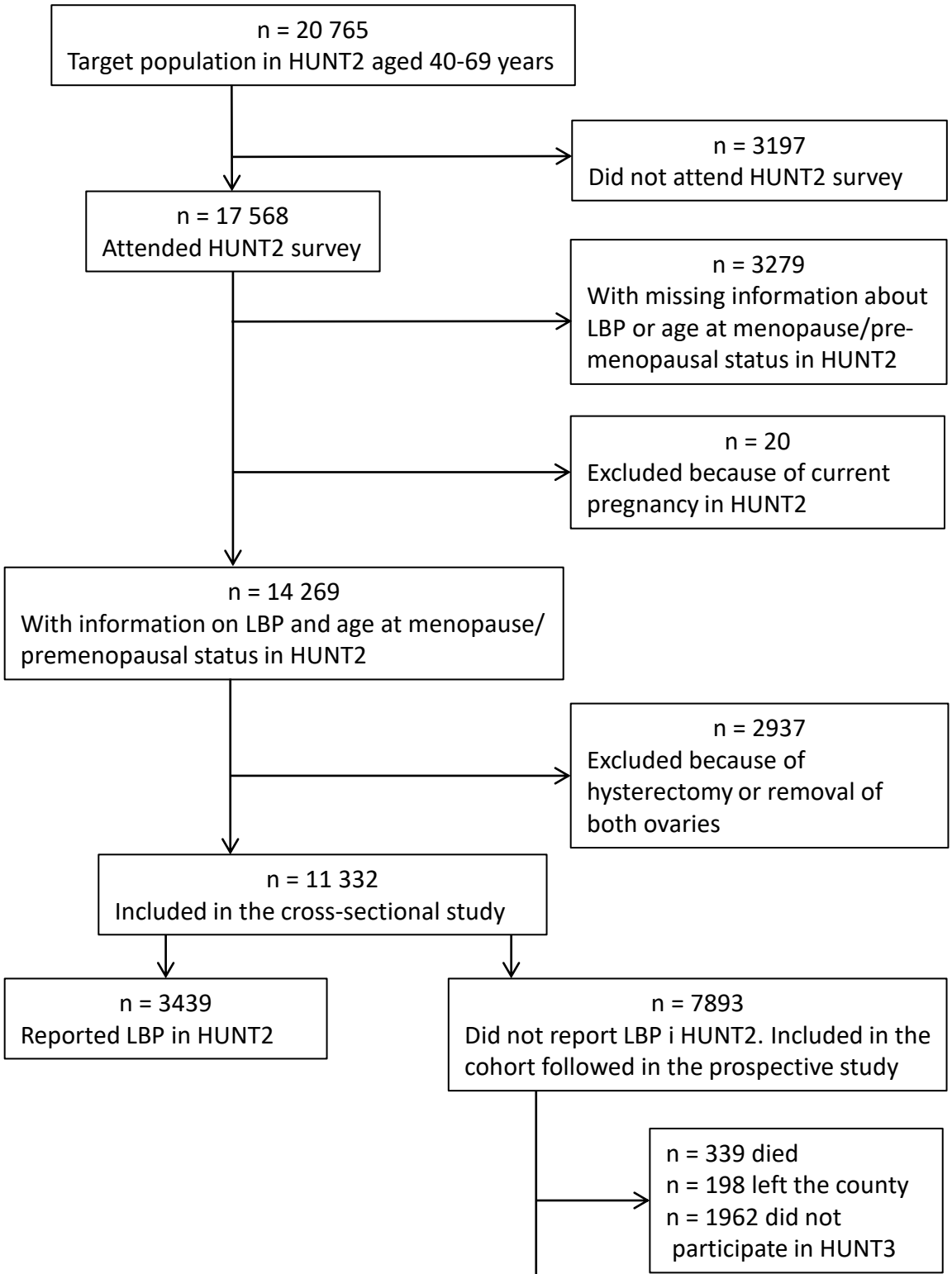
Legend for figures

Figure 1. Flow chart for the cross-sectional and prospective studies of age at menarche as a potential risk factor. HUNT, Trøndelag Health Study; LBP, low back pain.

Figure 2. Flow chart for the cross-sectional and prospective studies of age at menopause as a potential risk factor. HUNT, Trøndelag Health Study; LBP, low back pain.





Supplemental table 1 Associations between age at menarche and prevalence of chronic LBP in HUNT2 in cross-sectional analysis, in broad intervals of age

	Age 20-39 years	**Age 40-49 years**	**Age 50-69 years**
	RR (95% CI)*	**RR (95% CI)***	**RR (95% CI)***
Number of women included	10 298	6508	8145
Age at menarche (year)			
≤ 11	1.54 (1.34-1.77)	1.36 (1.19 -1.56)	1.18 (1.05-1.33)
12	1.16 (1.03-1.32)	1.14 (1.02-1.29)	1.12 (1.02-1.23)
13	1.09 (0.96-1.22)	1.11 (0.99-1.24)	1.06 (0.97-1.15)
14	1.00 (reference)	1.00 (reference)	1.00 (reference)
15	1.09 (0.93-1.29)	1.12 (0.98-1.28)	0.98 (0.89-1.08)
16	1.36 (1.07-1.74)	1.02 (0.80-1.30)	0.93 (0.78-1.09)
≥ 17	1.48 (0.97-2.26)	1.75 (1.22-2.51)	1.11 (0.85-1.45)
P for categorical effect	< 0.001	< 0.001	0.013
P for linear trend	< 0.001	0.009	< 0.001
P for quadratic effect†	< 0.001	0.001	0.21

*****Adjustment for age, BMI, physical activity, education, smoking, nulliparity and age at first delivery.

†In model also including linear effect.

BMI, body mass index; HUNT, Trøndelag Health Study; LBP, low back pain; RR, relative risk.

Supplemental table 2 Associations between age at menarche and risk of chronic LBP in prospective analysis in HUNT3, in broad intervals of age in HUNT2

	Age 20-39 years	**Age 40-49 years**	**Age 50-69 years**
	RR (95% CI)*	**RR (95% CI)***	**RR (95 % CI)***
Number of women included	4254	3144	3456
Age at menarche (year)			
≤ 11	1.34 (1.06-1.68)	1.33 (1.05 -1.68)	1.30 (1.00-1.69)
12	1.15 (0.95-1.38)	0.99 (0.80-1.21)	1.24 (1.02-1.51)
13	1.01 (0.85-1.21)	1.01 (0.84-1.22)	1.03 (0.86-1.24)
14	1.00 (reference)	1.00 (reference)	1.00 (reference)
15	1.20 (0.96-1.51)	0.96 (0.76-1.21)	0.95 (0.77-1.18)
16	1.13 (0.75-1.71)	0.79 (0.51-1.21)	1.08 (0.78-1.49)
≥ 17	1.60 (0.94-2.75)	1.16 (0.53-2.53)	1.54 (0.97-2.46)
P for categorical effect	0.10	0.19	0.08
P for linear trend	0.46	0.048	0.06
P for quadratic effect†	0.002	0.32	0.019

*Adjustment for age, BMI, physical activity, education, smoking, nulliparity and age at first delivery.

†In model also including linear effect.

BMI, body mass index; HUNT, Trøndelag Health Study; LBP, low back pain; RR, relative risk.

Supplemental table 3 Associations between age at menarche and prevalence of chronic LBP in HUNT2 in cross-sectional analysis, by duration of education

	Education ≤ 9 years	**Education 10-12 years**	**Education ≥ 13 years**
	RR (95% CI)*	**RR (95% CI)***	**RR (95 % CI)***
Number of women included	7597	11 361	5993
Age at menarche (year)			
≤ 11	1.16 (1.03-1.31)	1.56 (1.40 -1.73)	1.22 (1.02-1.45)
12	1.13 (1.03-1.24)	1.16 (1.05-1.28)	1.10 (0.94-1.29)
13	1.06 (0.97-1.16)	1.10 (1.01-1.21)	1.04 (0.90-1.21)
14	1.00 (reference)	1.00 (reference)	1.00 (reference)
15	0.99 (0.89-1.10)	1.12 (1.00-1.26)	1.01 (0.84-1.22)
16	0.95 (0.80-1.13)	1.00 (0.80-1.24)	1.32 (1.01-1.73)
≥ 17	1.42 (1.10-1.84)	1.30 (0.95-1.77)	0.99 (0.56-1.75)
P for categorical effect	0.008	< 0.001	0.21
P for linear trend	0.006	< 0.001	0.19
P for quadratic effect†	0.06	< 0.001	0.048

*Adjustment for age, BMI, physical activity, education, smoking, nulliparity and age at first delivery.

†In model also including linear effect.

BMI, body mass index; HUNT, Trøndelag Health Study; LBP, low back pain; RR, relative risk.

Supplemental table 4 Associations between age at menarche and risk of chronic LBP in prospective analysis in HUNT3, by duration of education recorded in HUNT2

	Education ≤ 9 years	**Education 10-12 years**	**Education ≥ 13 years**
	RR (95% CI)*	**RR (95% CI)***	**RR (95 % CI)***
Number of women included	2957	4997	2900
Age at menarche (year)			
≤ 11	1.31 (0.98-1.74)	1.28 (1.05-1.56)	1.36 (1.04-1.79)
12	1.08 (0.88-1.33)	1.15 (0.98-1.34)	1.05 (0.81-1.35)
13	1.10 (0.91-1.32)	1.01 (0.87-1.17)	0.92 (0.72-1.16)
14	1.00 (reference)	1.00 (reference)	1.00 (reference)
15	1.13 (0.91-1.39)	1.05 (0.86-1.27)	0.77 (0.56-1.06)
16	0.95 (0.65-1.37)	1.14 (0.83-1.57)	0.87 (0.50-1.50)
≥ 17	1.75 (1.07-2.85)	0.95 (0.50-1.79)	1.87 (1.06-3.29)
P for categorical effect	0.29	0.21	0.012
P for linear trend	0.61	0.06	0.031
P for quadratic effect[b]	0.08	0.06	0.015

*Adjustment for age, BMI, physical activity, education, smoking, nulliparity and age at first delivery.

†In model also including linear effect.

BMI, body mass index; HUNT, Trøndelag Health Study; LBP, low back pain; RR, relative risk.

Supplemental table 5 Associations between age at menarche and prevalence of chronic LBP in cross-sectional analysis in HUNT2, with and without adjustment for HADS

	With standard adjustment*	With standard adjustment* among individuals with known HADS score	With standard adjustment*and adjustment for HADS score
	RR (95% CI)	**RR (95% CI)**	**RR (95 % CI)**
Number of women included	24 951	21 773	21 773
Age at menarche (year)			
≤ 11	1.33 (1.24-1.43)	1.31 (1.21 -1.42)	1.27 (1.18-1.37)
12	1.13 (1.06-1.21)	1.13 (1.05-1.21)	1.12 (1.05-1.19)
13	1.07 (0.01-1.14)	1.07 (1.00-1.14)	1.07 (1.00-1.14)
14	1.00 (reference)	1.00 (reference)	1.00 (reference)
15	1.04 (0.97-1.12)	1.05 (0.97-1.13)	1.02 (0.95-1.10)
16	1.02 (0.91-1.15)	1.07 (0.94-1.21)	1.05 (0.92-1.19)
≥ 17	1.31 (1.08-1.59)	1.34 (1.08-1.65)	1.28 (1.04-1.57)
P for categorical effect	< 0.001	< 0.001	< 0.001
P for linear trend	< 0.001	< 0.001	< 0.001
P for quadratic effect†	< 0.001	< 0.001	< 0.001

*Adjustment for age, BMI, physical activity, education, smoking, nulliparity and age at first delivery.

†In model also including linear effect.

BMI, body mass index; HADS, Hospital Anxiety and Depression Scale; HUNT, Trøndelag Health Study; LBP, low back pain; RR, relative risk.

Supplemental table 6 Associations between age at menarche and risk of chronic LBP in prospective analysis in HUNT3, with and without adjustment for HADS

	With standard adjustment*	With standard adjustment* among individuals with known HADS score	With standard adjustment* and adjustment for HADS score
	RR (95% CI)	RR (95% CI)	RR (95 % CI)
Number of women included	10 854	9666	9666
Age at menarche (year)			
≤ 11	1.32 (1.15-1.52)	1.37 (1.18 -1.59)	1.36 (1.17-1.57)
12	1.12 (1.00-1.25)	1.16 (1.03-1.31)	1.15 (1.02-1.30)
13	1.01 (0.91-1.13)	1.04 (0.92-1.16)	1.04 (0.93-1.16)
14	1.00 (reference)	1.00 (reference)	1.00 (reference)
15	1.02 (0.90-1.16)	1.05 (0.92-1.21)	1.04 (0.91-1.20)
16	1.01 (0.81-1.25)	1.07 (0.85-1.36)	1.07 (0.84-1.35)
≥ 17	1.43 (1.04-1.98)	1.31 (0.89-1.92)	1.25 (0.85-1.83)
P for categorical effect	0.002	0.002	0.003
P for linear trend	0.008	0.004	0.003
P for quadratic effect†	< 0.001	0.001	0.001

*****Adjustment for age, BMI, physical activity, education, smoking, nulliparity and age at first delivery.

†In model also including linear effect.

BMI, body mass index; HADS, Hospital Anxiety and Depression Scale; HUNT, Trøndelag Health Study; LBP, low back pain; RR, relative risk.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5, 6
Objectives	3	State specific objectives, including any prespecified hypotheses	3, 5
Methods			
Study design	4	Present key elements of study design early in the paper	3, 6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	6, 7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8, 9
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	8
Bias	9	Describe any efforts to address potential sources of bias	17
Study size	10	Explain how the study size was arrived at	6, 7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	8,9
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 (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	7 9-16
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	17, 18
Outcome data	15*	Report numbers of outcome events or summary measures over time	11,13,15,16 Table 2-5

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 (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9, 12 Table 2-4 Supplemental table 1-6
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12
Discussion			
Key results	18	Summarise key results with reference to study objectives	12, 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, 18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18-20
Generalisability	21	Discuss the generalisability (external validity) of the study results	20-22
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	17

*Give information separately for exposed and unexposed groups.

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 http://www.strobe-statement.org.

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Does the risk of chronic low back pain depend on age at menarche or menopause? A population-based cross-sectional and cohort study: the Trøndelag Health Study

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Abstract

Objective In most population-based studies of low back pain (LBP) women have a higher risk than men, possibly reflecting hormonal influences. The aim of this study was to explore associations between age at menarche and menopause and risk of chronic LBP.

Design Population-based cross-sectional and cohort study designs.

Setting The HUNT2 and HUNT3 surveys of Nord-Trøndelag County in Norway.

Main outcome measure Prevalence or risk of chronic LBP, defined as LBP persisting at least 3 months continuously during last year.

Participants Associations between age at menarche and prevalence of chronic LBP were examined in cross-sectional data from HUNT2, comprising 27697 women aged 20-69 years, with 7300 women reporting LBP. The corresponding cohort data included 11659 women without LBP at baseline in HUNT2, with 2353 women reporting LBP at follow-up 11 years later in HUNT3. Cross-sectional data on age at menopause or premenopausal status included 11332 women aged 40-69 years, with 3439 women reporting chronic LBP. Corresponding cohort data included 7893 women without LBP at baseline, of whom 1100 developed LBP.

Methods Associations between age at menarche or menopause and risk of chronic LBP were examined by generalised linear modelling.

Results A U-shaped association was indicated between age at menarche and risk of chronic LBP, both in the cross-sectional and cohort studies. Age at menarche ≤11 years was associated with an increased risk of chronic LBP, with a relative risk (RR) of 1.32 (95% CI 1.15 to 1.52), compared to age 14 years at menarche, after relevant adjustments. Corresponding cross-sectional crude absolute risks were 32% and 25%, respectively. No association was established between age at menopause and risk of LBP. Being premenopausal had no influence on risk.

Conclusions In contrast to results for age at menopause, the association with age at menarche suggests that hormonal factors affect the risk of LBP.

Strengths and limitations of this study

-The study included data collected using both a cross-sectional and a cohort design, with a long follow-up period of 11 years.

-The information on age at menarche and menopause made it possible to carry out analyses with a detailed categorisation.

-The information about back pain was self-reported in a questionnaire.

-No information was available on pain intensity.

INTRODUCTION

Low back pain (LBP) constitutes a major problem for the individuals affected,[1] and the disorder entails large annual expenses for society.[2] To obtain insight into the etiology it is important to determine potential risk factors for LBP. In most population-based studies, women have a higher risk of LBP than men,[3] a tendency which may reflect hormonal differences.[4]

Women who experience early menarche or late menopause have generally been exposed to endogenous oestrogen for a long time. Oestrogen is known to be important in reducing osteoporosis and fracture rates[5] and may in this way potentially also reduce the risk of LBP. On the other hand, higher levels of oestrogen may increase the risk of LBP during and after pregnancy,[6] possibly through the involvement of the hormone relaxin. The greater risk of LBP observed in women using hormone therapy[4] or oral contraceptives[4] may also be related to oestrogen levels.[6]

There are very few epidemiological studies of associations between age at menarche or menopause and risk of LBP. A large population-based cross-sectional study in the Netherlands found an increase in the risk of combined chronic LBP and upper extremity pain among women with an early menarche[4] but results were equivocal for those with LBP only. No association was found in a smaller Swedish study.[7] A study in the United States[8] found a higher risk of LBP among women with menopause before age 40 years, but essentially no association with age at menopause after that early threshold.

In a large-scale population-based Norwegian study, we previously found an increase in risk of chronic LBP among women having experienced at least one delivery, but no further increase with subsequent deliveries.[9] Moreover, the risk depended on age at first delivery.[9] Data from the same surveys have also been used to study associations between chronic LBP and body mass index (BMI),[10] lipid levels[11] and physical activity in leisure time.[12] The aim of the present study was to investigate the relationships between age at menarche and menopause and risk of chronic LBP, considering cross-sectional and 11-year follow-up data.

METHODS

Collection of information

In the former Nord-Trøndelag County in Norway the two health surveys HUNT2 and HUNT3 were conducted in 1995 to 1997 and 2006 to 2008.[13] In the present work cross-sectional data from the HUNT2 survey are combined with follow-up data from the HUNT3 survey.

All residents of this county aged 20 years and above were invited to take part in the HUNT2 survey. They were requested to complete a questionnaire on health status, and they were invited to a clinical examination, including measurement of height and weight. In the HUNT3 survey 11 years later, similar information was collected by questionnaires and an examination.

One question in the HUNT2 and HUNT3 questionnaires was expressed in this way: "During the last year, have you suffered from pain and/or stiffness in your muscles and joints that has lasted for at least 3 consecutive months?" Each participant answering yes was given the following question: "Where did you have these complaints?" Several body regions were listed. Individuals answering yes to the first question and including the lower back as a relevant region were regarded as having chronic LBP.[14]

Women participating in HUNT2 gave information on age at menarche by answering the question "How old were you when you started menstruating?". They were also asked the question "Do you still menstruate?" Those aged ≥40 years indicating "yes" were regarded as premenopausal. The women who indicated "no" answered the following question: "How old were you when you stopped menstruating?" This was regarded as age at menopause.

The participants also gave information regarding physical activity in leisure time, smoking, duration of education and childbirths. In addition, they provided information used for computing Hospital Anxiety and Depression Scale (HADS) scores.[15]

Study design

Age at menarche

The target population of the HUNT2 study comprised 37 503 women in the age range 20-69 years. Of these, a total of 28 520 women participated in HUNT2 (figure 1).[16] Information about age at menarche and about presence or absence of chronic LBP in HUNT2 was collected from 27 697 women, corresponding to an overall participation rate of 74%. This data set formed the basis of the cross-sectional study of associations with age at menarche.

The 20 397 women who reported absence of chronic LBP in HUNT2 were included in the cohort considered in the prospective study of association between age at menarche and risk of chronic LBP. Information about residence status was obtained from national registries and linked using the unique Norwegian personal identification numbers. During the 11-year follow-up period, 712 women in this cohort died and 1266 individuals left the county of Nord-Trøndelag (figure 1). A total of 6760 women in the cohort residing in Nord-Trøndelag at the time of HUNT3 did not participate or did not supply information about chronic LBP. The remaining 11 659 women could be included in the analysis of risk of LBP after the 11-year follow-up period, representing 63% of the remaining women resident in the county, and 57% of the original cohort.

Age at menopause

Only women in the age range 40-69 years in HUNT2 were included in the study of age at menopause. The target population of the HUNT2 study comprised 20 765 women in this interval. Of these, a total of 17 568 women participated in HUNT2 (figure 2).[16] Women who were pregnant when the questionnaire was filled in were excluded. Information about age at menopause or premenopausal status in HUNT2 as well as presence or absence of chronic LBP was collected from 14 269 women, corresponding to a participation rate of 69%. At this stage, 2937 women were excluded because of surgery involving hysterectomy or removal of both ovaries, leaving 11 332 women included in the cross-sectional study (figure 2).

A total of 7893 women who reported absence of chronic LBP in HUNT2, were included in the prospective study of associations between age at menopause and risk of LBP. During the 11-year follow-up period, 339 women in this cohort died, 198 individuals left the county and 1962 women residing in Nord-Trøndelag at the time of HUNT3 did not participate or did not supply information about chronic LBP. Thus, a total of 5394 women were available for analysis of risk of LBP after the follow-up period, representing 73% of the remaining women resident in the county, and 68% of the original cohort.

Variables

Age at menarche reported in HUNT2 was categorised into seven groups: ≤11, 12, 13, 14, 15, 16, ≥17 years. Women aged 14 years at menarche were considered the reference group. Age at menopause was categorised into seven groups: ≤40, 41-43, 44-46, 47-49, 50-52, 53-55, ≥56 years. The premenopausal women were regarded as a separate reference group. In additional analyses, testing the linear or quadratic effects of the two study variables, these variables were regarded as continuous.

BMI, defined as weight/height^2 and computed in kg/m^2, was subdivided into three groups: <25, 25-29.9, ≥30. Categories of education were defined according to duration, ≤9, 10-12, and ≥13 years. Cigarette smoking was described using the categories current daily smoking, previous daily smoking and never daily smoking. For physical activity in leisure time, including going to work, one category comprised those engaged in light activity only or hard physical activity (leading to sweating or being out of breath) <1 hour per week. Other categories represented hard physical activity 1-2 and ≥3 hours per week. The information about physical activity collected in HUNT2 was verified by a reliability and validity study of a subsample.[17] A particular variable was defined to take into account both nulliparity and age at first delivery among parous women. Categories of age at first delivery were: ≤19, 20-24, 25-29, 30-34, ≥35 years. Five categories were introduced for total HADS scores: 0-4, 5-9, 10-14, 15-19 and ≥20.

Statistical analyses

Associations between the study variables age at menarche or menopause and prevalence or risk of chronic LBP were assessed by generalised linear modelling for binomial observations with a log link, with adjustment for potential confounders. Initial analyses involved adjustment for age only, and adjustment was then added for other factors known to be risk factors for LBP, as BMI,[10] physical activity in leisure time,[12] education and smoking, nulliparity and age at first delivery.[9] The non-linear effect of age[10] was modelled by a cubic polynomial. In the main analyses, all other variables adjusted for were regarded as categorical.

Separate tests were carried out for interaction between each factor adjusted for and study variables showing an association with risk of chronic LBP. To obtain more powerful

interaction tests, the effect of age at menarche was then modelled by a quadratic polynomial depending on scores representing the successive categories.

Because information on potential confounders was missing in a minor part of the data set, analyses involving more complete adjustment included a slightly lower number of individuals than the age-adjusted analyses. HADS scores, representing important psychological factors, could not be computed for 3178 (13%) of the 24 951 women included in cross-sectional analysis of relations with age at menarche with adjustment for other potential confounders. The corresponding proportion, 11%, in the prospective analysis was also rather high. For this reason, additional adjustment for HADS was only carried out in particular sensitivity analyses. At the same time, analyses were also performed without adjustment for HADS, including only women with known HADS scores, to evaluate the exact effect of the adjustment.

To assess potential effects of differential participation, participation rates in HUNT3 were computed among the women reporting LBP in HUNT2 and those not reporting LBP, within broad categories of age at menarche or menopause.

All statistical analyses were carried out using IBM SPSS version 26 (IBM Corp., Armonk, New York).

Public and patient involvement

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

RESULTS

Age at menarche

Women in HUNT2 with a late menarche tended to have a low BMI and an education of short duration (table 1). Daily current smoking was more common among those with an early menarche. Nulliparity showed a weak inverse relationship with age at menarche (table 1).

Among the 27 697 women in the cross-sectional study of the association between age at menarche and prevalence of chronic LBP, 7300 women (26%) reported chronic LBP in

HUNT2 (figure 1). In the prospective study with 11 659 women available for analysis of risk, 2353 women (20%) reported chronic LBP at end of follow-up in HUNT3.

Table 1 Baseline mean values and category percentages for potential confounders, by age at menarche and menopause

	Age at menarche (year)*				Age at menopause (year)†				
	≤ 11	12-13	14-15	≥ 16	≤ 46	47-49	50-52	≥ 53	Pre-menopausal
Number of women included	2288	12 176	9388	1099	1044	972	1579	826	5633
Age in HUNT2‡ (year)	41.1	41.8	45.9	47.6	55.9	56.3	58.4	60.2	45.8
BMI‡ (kg/m^2)	27.1	26.0	25.5	24.9	26.6	26.8	26.9	27.5	25.9
Physical activity per week§ (%)									
< 1 hour hard	73	74	78	78	85	84	86	85	76
1-2 hours hard	19	19	16	15	11	12	11	11	18
≥ 3 hours hard	8	7	6	7	4	4	4	4	6
Cigarette smoking§ (%)									
never	39	43	42	43	31	38	45	51	35
daily former	25	25	27	28	28	28	30	32	30
daily current	37	33	32	29	41	35	26	17	34
Education§ (year) (%)									
≤ 9	24	27	35	40	56	54	58	58	27
10-12	48	47	43	38	29	33	27	27	46
≥ 13	28	25	22	22	14	13	15	15	27
Nulliparity§ (%)	15	15	12	11	7	6	6	3	5
Age at first childbirth‡,¶ (year)	22.6	22.8	23.1	24.0	23.1	23.2	23.3	23.2	22.9

*Among women with information about chronic LBP, BMI, physical activity, education, smoking, nulliparity, age at first delivery and age at menarche.

†Among women at least 40 years old in HUNT2 with information about chronic LBP, BMI, physical activity, education, smoking, nulliparity, age at first delivery and age at menarche and menopause.

‡Mean value within category of age at menarche or menopause.

§Percentages of categories for potential confounder within category of age at menarche or menopause.

¶Among women with at least 1 child.

BMI, body mass index; HUNT, Trøndelag Health Study; LBP, low back pain.

Table 2 Associations between age at menarche and prevalence of chronic LBP in HUNT2 in cross-sectional analysis

	Total number of women in category of age at menarche*	Number of women with chronic LBP	Crude AR of chronic LBP (%)	RR (95% CI) with adjustment for age only	RR (95 % CI) with additional adjustment†
Number of women included			27 697	27 697	24 951
Age at menarche (year)					
≤ 11	2487	806	32.4	1.39 (1.30 to 1.49)	1.33 (1.24 to 1.43)
12	5536	1499	27.1	1.17 (1.11 to 1.24)	1.13 (1.06 to 1.21)
13	7789	1953	25.1	1.08 (1.02 to 1.14)	1.07 (1.01 to 1.14)
14	6861	1713	25.0	1.00 (reference)	1.00 (reference)
15	3759	994	26.4	1.03 (0.96 to 1.10)	1.04 (0.97 to 1.12)
16	975	252	25.8	0.99 (0.89 to 1.11)	1.02 (0.91 to 1.15)
≥ 17	290	83	28.6	1.12 (0.93 to 1.35)	1.31 (1.08 to 1.59)
P for categorical effect				< 0.001	< 0.001
P for linear trend				< 0.001	< 0.001
P for quadratic effect‡				< 0.001	< 0.001

*In analysis adjusted for age only.

†Adjustment for age, BMI, physical activity, education, smoking, nulliparity and age at first delivery.

‡In model also including linear effect.

AR, absolute risk; BMI, body mass index; HUNT, Trøndelag Health Study; LBP, low back pain; RR, relative risk.

A U-shaped relationship between age at menarche and prevalence of chronic LBP was suggested in the cross-sectional study (table 2). Women with an early menarche at age ≤11 years had a noticeably larger absolute risk (AR=32%) than those with an age at menarche of 14 years (AR=25%).The U-shaped relationship was retained after adjustment for age, BMI, physical activity, education, smoking, nulliparity and age at first delivery (table 2). The prospective analysis revealed a similar U-shaped relationship between age at menarche and risk of chronic LBP, with an estimated 32% and 43% increased risk after adjustment among women with menarche at age ≤11 years and ≥17 years, respectively, compared to those with age at menarche 14 years (table 3).

An interaction was observed between age at menarche and baseline age in the cross-sectional analysis (p=0.026). Definite U-shaped relationships between age at menarche and prevalence of chronic LBP were found among women in the two age intervals 20-39 years and 40-49 years in HUNT2 (supplemental table 1). Although a U-shaped relationship was still suggested among the oldest women aged 50-69 years (supplemental table 1), the association was much weaker. No interaction with baseline age was found in the prospective analyses of risk of chronic LBP in HUNT3 (p=0.35; supplemental table 2).

In the cross-sectional analysis an interaction was also found between age at menarche and duration of education (p=0.031). The U-shaped relationship with age at menarche was most evident in women with 10-12 years of education, but estimates were also compatible with a relationship of this kind in the categories representing shorter or longer duration of education (supplemental table 3). In the prospective analysis no significant interaction between age at menarche and duration of education was observed (p=0.84; supplemental table 4).

Sensitivity analyses with additional adjustment for HADS revealed only minor changes in the association with age at menarche, both in the cross-sectional (supplemental table 5) and the prospective (supplemental table 6) situations.

Participation rates in HUNT3 depended only weakly on age at menarche, with slightly higher rates among women with a late menarche. Within broad categories of age at menarche, however, participation rates were quite similar among those reporting LBP in HUNT2 and those not reporting LBP. Among women with age at menarche ≤11 years, the two participation rates were 55% and 58%, respectively, among those with age at menarche 12-13 years 56% and 57%, among women with menarche 14-15 years 58% and 58%, and among women with age at menarche ≥16 years 59% and 61%.

Table 3 Associations between age at menarche and risk of chronic LBP in HUNT3 in prospective analysis

	Total number of women in category of age at menarche*	Number of women with chronic LBP	Crude AR of chronic LBP (%)	RR (95% CI) with adjustment for age only	RR (95 % CI) with additional adjustment†
Number of women included			11 659	11 659	10 854
Age at menarche (year)					
≤ 11	930	236	25.4	1.34 (1.17 to 1.53)	1.32 (1.15 to 1.52)
12	2228	468	21.0	1.11 (1.00 to 1.24)	1.12 (1.00 to 1.25)
13	3340	641	19.2	1.01 (0.91 to 1.12)	1.01 (0.91 to 1.13)
14	3014	582	19.3	1.00 (reference)	1.00 (reference)
15	1600	314	19.6	1.01 (0.89 to 1.14)	1.02 (0.90 to 1.16)
16	421	82	19.5	1.00 (0.81 to 1.23)	1.01 (0.81 to 1.25)
≥ 17	126	30	23.8	1.24 (0.90 to 1.70)	1.43 (1.04 to 1.98)
P for categorical effect				0.001	0.002
P for linear trend				0.001	0.008
P for quadratic effect‡				0.001	< 0.001

*In analysis adjusted for age only.

†Adjustment for age, BMI, physical activity, education, smoking, nulliparity and age at first delivery.

‡In model also including linear effect.

AR, absolute risk; BMI, body mass index; HUNT, Trøndelag Health Study; LBP, low back pain; RR, relative risk.

Age at menopause

Early menopause was primarily associated with daily current smoking and with nulliparity (table 1). Premenopausal women tended to have a relatively long duration of education and were engaged in more physical activity than postmenopausal women.

In the cross-sectional study of association between age at menopause and chronic LBP in HUNT2, 11 332 women were included, and a total of 3439 women (30%) reported chronic LBP (figure 2). In the prospective study among the remaining 5394 women who did not report chronic LBP in HUNT2, a total of 1100 women (20%) reported chronic LBP at end of follow-up in HUNT3.

No association between age at menopause and prevalence or risk of chronic LBP was observed, neither in the cross-sectional (table 4) nor in the prospective (table 5) data. Being premenopausal had no particular influence on prevalence or risk of chronic LBP. Additional adjustment for HADS in sensitivity analyses produced very similar estimates.

Participation rates in HUNT3 were somewhat higher for women with an older age at menopause. Yet within broad categories of age at menopause, participation rates were very similar for those reporting LBP in HUNT2 and those not reporting LBP. Premenopausal women represented an exception, with a participation rate equal to 65% among those reporting LBP, compared to 71% among those without LBP.

Table 4 Associations between age at menopause and prevalence of chronic LBP in cross-sectional analysis, among women at least 40 years old in HUNT2

	Total number of women in category of age at menopause	Number of women with chronic LBP	Crude AR of chronic LBP (%)	RR (95% CI) with adjustment for age only	RR (95 % CI) with additional adjustment*
Number of women included			11 332	11 332	10 054
Age at menopause (year)					
≤ 40	263	90	34.2	1.10 (0.92 to 1.32)	1.08 (0.88 to 1.32)
41-43	269	88	32.7	1.06 (0.88 to 1.28)	1.05 (0.86 to 1.27)
44-46	743	260	35.0	1.12 (0.98 to 1.27)	1.06 (0.92 to 1.21)
47-49	1170	394	33.7	1.07 (0.96 to 1.20)	1.05 (0.93 to 1.18)
50-52	1859	601	32.3	1.01 (0.90 to 1.13)	1.03 (0.92 to 1.15)
53-55	818	290	35.5	1.09 (0.95 to 1.25)	1.06 (0.91 to 1.23)
≥ 56	182	46	25.3	0.78 (0.59 to 1.02)	0.79 (0.59 to 1.06)
Premenopausal	6028	1670	27.7	1.00 (reference)	1.00 (reference)
P for categorical effect				0.09	0.56
P for linear trend†				0.15	0.49

*Adjustment for age, BMI, physical activity, education, smoking, nulliparity, age at first delivery and age at menarche.

†Among postmenopausal women.

AR, absolute risk; BMI, body mass index; HUNT, Trøndelag Health Study; LBP, low back pain; RR, relative risk.

Table 5 Associations between age at menopause and risk of chronic LBP in HUNT3 in prospective analysis, among women at least 40 years old in HUNT2

	Total number of women in category of age at menopause	Number of women with chronic LBP	Crude AR of chronic LBP (%)	RR (95% CI) with adjustment for age only	RR (95 % CI) with additional adjustment*
Number of women included			5394	5394	4941
Age at menopause (year)					
≤ 40	108	24	22.2	1.06 (0.73 to 1.55)	1.05 (0.70 to 1.57)
41-43	102	26	25.5	1.21 (0.85 to 1.73)	1.10 (0.74 to 1.62)
44-46	308	67	21.8	1.03 (0.80 to 1.34)	1.03 (0.79 to 1.34)
47-49	500	96	19.2	0.91 (0.73 to 1.15)	0.94 (0.74 to 1.19)
50-52	841	155	18.4	0.87 (0.70 to 1.09)	0.86 (0.68 to 1.09)
53-55	368	83	22.6	1.07 (0.82 to 1.40)	1.05 (0.79 to 1.40)
≥ 56	86	12	14.0	0.66 (0.38 to 1.16)	0.68 (0.37 to 1.26)
Premenopausal	3081	637	20.7	1.00 (reference)	1.00 (reference)
P categorical effect				0.33	0.59
P for linear trend†				0.11	0.31

*Adjustment for age, BMI, physical activity, education, smoking, nulliparity, age at first delivery and age at menarche.

†Among postmenopausal women.

AR, absolute risk; BMI, body mass index; HUNT, Trøndelag Health Study; LBP, low back pain; RR, relative risk.

DISCUSSION

In this study an association was found between age at menarche and both prevalence and risk of LBP. The main feature was a decline in risk with increasing age at menarche, with relatively high risk estimates for ages ≤12 years, but little variation in risk for ages at menarche in the interval 13-16 years. However, the small group of women with a very late menarche, at an age ≥17 years, also showed a higher risk, and an overall relationship emerged that was approximately U-shaped. No association could be established between age at menopause and risk of LBP. Risk estimates were largely similar among pre- and postmenopausal women.

Strengths and limitations

Results in this study were based on cross-sectional and cohort data derived from surveys of the entire population in a Norwegian county. The similar results found with the two study designs provide additional support to the main findings. In principle, more weight should be attached to the cohort data, but the cross-sectional data set was considerably larger. The information on age at menarche referred anyhow to an event that mostly occurred a number of years before. In this situation the difference between the two study designs is probably less important.

Recall of age at menarche may be subject to error, but studies of validity[18] and reliability[19] indicate that the error is generally rather small. Minor random errors in reported age at menarche would in any case mainly be expected to attenuate the relationships observed. For menopause, the relevant event mostly occurred a relatively short time before data collection, improving the accuracy of the information. Recall of age at menopause is also regarded as fairly reliable.[20] However, reporting may be slightly biased, with women with an early menopause tending to overestimate their age at menopause and women with a late menopause reporting underestimates.[20] Also, the age specified when menstruation stopped may not represent the exact age at the final menstrual period, which requires a 12-month interval of amenorrhea before a strict assessment can be made.[21] In any case, neither potential source of bias is likely to create an apparent lack of association with age at menopause, as observed in this study.

In the cohort data, no information was available on changes in potential risk factors or LBP status in the period between HUNT2 and HUNT3. Thus, women who were recorded as being premenopausal in HUNT2 may have been postmenopausal during part of the subsequent follow-up period. The self-reported information used to assess LBP was also incomplete in the sense that pain intensity was not recorded. Moreover, participation rates were rather low in the cohort study. However, a bias in relative risk estimates will only arise if participation rates differ between women with and without LBP in HUNT3 within categories of age at menarche or menopause. These rates are unknown, but LBP in HUNT3 was strongly associated with LBP in HUNT2, which was used to compare corresponding participation rates in HUNT3 for women with and without LBP in HUNT2. The fact that these rates were quite similar suggests that no major response bias has been introduced, except possibly for premenopausal women in the analyses involving menopausal status.

Age at menarche can be affected by various influences in childhood or puberty.[22] Information on body size or physical activity at those stages was not available in the present study, but adjustment was made in the statistical analysis for similar factors recorded much later in life. The population studied had a nearly uniform ethnic background and socioeconomic differences were generally small.[16] Socioeconomic status was taken into account by adjustment for duration of education. It is not possible to rule out potential confounding by other variables in the association between age at menarche and risk of LBP, but it seems unlikely that unknown factors should account entirely for the relationship observed.

Previous studies

To the best of our knowledge, the only other large study of relationships between age at menarche and occurrence of chronic LBP is the Dutch cross-sectional study of Wijnhoven et al.,[4] including 11 428 women in the age interval 20-59 years. Women with an age at menarche ≤11 years showed a greater prevalence of combined chronic LBP and upper extremity pain. Yet no definite relationship was demonstrated for prevalence of chronic LBP without upper extremity pain, although risk estimates displayed a declining trend with increasing age at menarche. The top category represented ages at menarche ≥15 years. Overall, the results of Wijnhoven et al. may still be compatible with those obtained here. The

much smaller Swedish study of Bergenudd et al.,[7] including 252 women, did not find any association between age at menarche and occurrence of back pain.

Pelvic girdle pain in connection with pregnancy has often been combined with LBP in epidemiological work. A large Norwegian study[23] found a pronounced inverse association between age at menarche and pelvic girdle syndrome in pregnancy. A small Swedish study of combined LBP and pelvic pain during pregnancy[24] found no association. It is not entirely clear, however, whether LBP experienced during pregnancy represents the same medical disorder as LBP during other periods in a woman's life.[25, 26]

Age at menarche has also been considered as a potential risk factor in studies focusing on musculoskeletal disorders in a more general sense. One Norwegian study dealing with data from the same Nord-Trøndelag population[27] found an increased prevalence of widespread musculoskeletal complaints among women with age at menarche ≤12 years, while another study from a neighbouring county[28] found no association. Yet another study from Nord-Trøndelag[29] found an increased prevalence of headache for age at menarche ≤12 years.

Associations between age at menopause and LBP were examined in the relatively large cross-sectional study of Adera et al. in the United States, including 5325 women.[8] Compared to premenopausal women, considerably higher prevalence estimates of LBP were found among women with an age at menopause <30 and 30-39 years. However, it was not possible to distinguish between women with a natural menopause and those with medical procedures underlying the menopause. Thus these results cannot be expected to be similar to those in the present study. For ages at menopause 40-49 and ≥50 years the risk estimates were lower[8] and may be more consistent with our results. The Swedish study of Bergenudd et al.[7] did not show any association between age at menopause and back pain.

Several studies have compared prevalence of back pain more generally among pre- and postmenopausal women, not considering specific values of age at menopause. Some cross-sectional studies[30-32] found little evidence of any difference in prevalence. Other cross-sectional studies,[33, 34] distinguishing between several stages of the menopausal transition, indicated a higher prevalence of LBP in postmenopausal phases. However, in some studies[33, 35] the prevalence decreased at the final postmenopausal stage, although prevalence estimates were higher in late perimenopausal or early postmenopausal periods.

Still other studies recorded pain scores for general back pain[36] or LBP[37, 38] and found either an increasing trend in scores moving to later postmenopausal stages[36, 37] or essentially no difference between periods.[38]

If there is a short-term increase in risk of back pain during particular periods following menopause, the effect will not necessarily become apparent in analyses of associations with age at menopause such as those carried out in the present study. Most studies of back pain related to menopausal stages were based on information from less than 1000 women,[7, 30-33, 36-38] and the definitions of the medical condition considered varied widely. Chronic LBP as defined in our study[14] may represent a more serious disorder, involving a smaller proportion of the general female population. Some studies[33, 34, 37, 38] introduced no adjustment for the age when information was collected or only a crude adjustment. In analyses of risk related to menopause, the study design often creates a strong association between age at menopause and attained age in the data available for analysis, and it may be particularly important to carry out accurate age adjustment.

A meta-analysis of studies of musculoskeletal pain[39] found an increased prevalence among peri- and postmenopausal women compared to premenopausal women. Restricting attention to moderate or severe pain, the prevalence also increased moving from the perimenopausal to the postmenopausal category.

Interpretation

It is well-known that the risks of breast cancer[40] and endometrial cancer[41] are inversely related to age at menarche. These relationships have mainly been explained in terms of a longer lifetime exposure to oestrogens among women with early menarche. This may also be a potential explanation of the increased risk of LBP seen in the present study in these women. The explanation is consistent with the increase in risk of LBP observed among women using hormone therapy or oral contraceptives,[4] and with the association found between risk of LBP and a woman's first childbirth.[9] This kind of hormonal influence may affect soft tissues supporting the spine,[42] followed by laxity in joints and ligaments, leading to pain.[6] A hormonal effect may easily be attenuated in older age categories, in accordance with the interaction partly seen in the present study with baseline age.

Oestrogen loss may contribute to low bone mineral density (BMD) and development of osteoporosis.[5] This is consistent with indications that early menarche is associated with higher BMD[43] and a lower risk of vertebral fractures.[44] However, it is not clear what the relationship is between BMD and the overall risk of LBP.[45] If LBP is associated with high BMD,[46] this could explain the part of the association seen here in the lower half of the range for age at menarche, but this is not the case if LBP is associated with low BMD,[45] or if LBP is to some extent the cause of the high BMD.[46] Alternative explanations could involve hormonal effects on body size or growth during puberty, as suggested for relationships between age at menarche and cardiovascular disease.[47] Oestrogens may also play a role in modulation of pain[48] but it is difficult to state how this affects the experience of LBP.[49]

U-shaped relationships with age at menarche have previously been found for risk of cardiovascular disease[50] and diabetes.[51] A greater risk of disease among the relatively small group of women with age at menarche ≥16 years may possibly reflect underlying metabolic disorders associated with delayed onset of puberty.[51] It is not obvious how this would influence the risk of LBP, although the risk may in general depend on lipid levels.[11]

If the association between risk of LBP and age at menarche reflects effects of hormonal factors, the lack of association in this study with age at menopause or menopausal status may seem surprising. Perhaps changes in hormonal status when women are older must be present during a longer period of time before the risk of LBP is affected. This would accord with increased prevalence of LBP found by Adera et al.[8] among women with an age at menopause <40 years, when the menopause mostly must have been induced. In the present study, the great majority of the postmenopausal women must have experienced natural menopause. It is also possible that the association found with age at menarche represents essential developmental factors which are not relevant to menopause. With a lack of association with age at menopause, a risk factor analyses of the total number of reproductive years, defined as the difference between ages at menopause and menarche, will mainly reflect associations with age at menarche only. For this reason the number of reproductive years was not considered as potential risk factor in our analysis.

The association found in this study with age at menarche may at least partly be consistent with a hormonal explanation of the general difference between men and women in risk of

LBP. This difference has otherwise been explained in terms of childbearing, child care, heavier workloads, different distribution of muscle and bone mass and psychological factors.[3] However, the present study does not lend support to a hypothesis involving a major additional increase in the risk difference after the menopausal phase.[52] Further studies are needed to investigate the nature of the risk difference and the influence of hormones on risk of LBP in both females and males.

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Ethics approval The work was approved by the Regional Committee for Medical and Health Research Ethics in Central Norway (approval number 2014/968/REK midt), and HUNT was also approved by the Norwegian Data Inspectorate. Each participant in the surveys signed a written informed consent regarding the collection and use of data for research purposes. The participants have given written informed consent.

Data sharing statement The data set analysed belongs to a third party, the HUNT study (the Trøndelag Health Study). The authors of the current manuscript are not affiliated with the project as such, but have been given permission to analyse the data after obtaining the necessary Norwegian permits. Because of the confidentiality requirements according to Norwegian law, a data set of this kind with information from a complete county at the individual level cannot be made public. However, research groups wishing to analyse data from the HUNT study may apply to the HUNT organisation (https://www.ntnu.edu/hunt) to get access to the data, after having obtained the permits needed according to Norwegian law.

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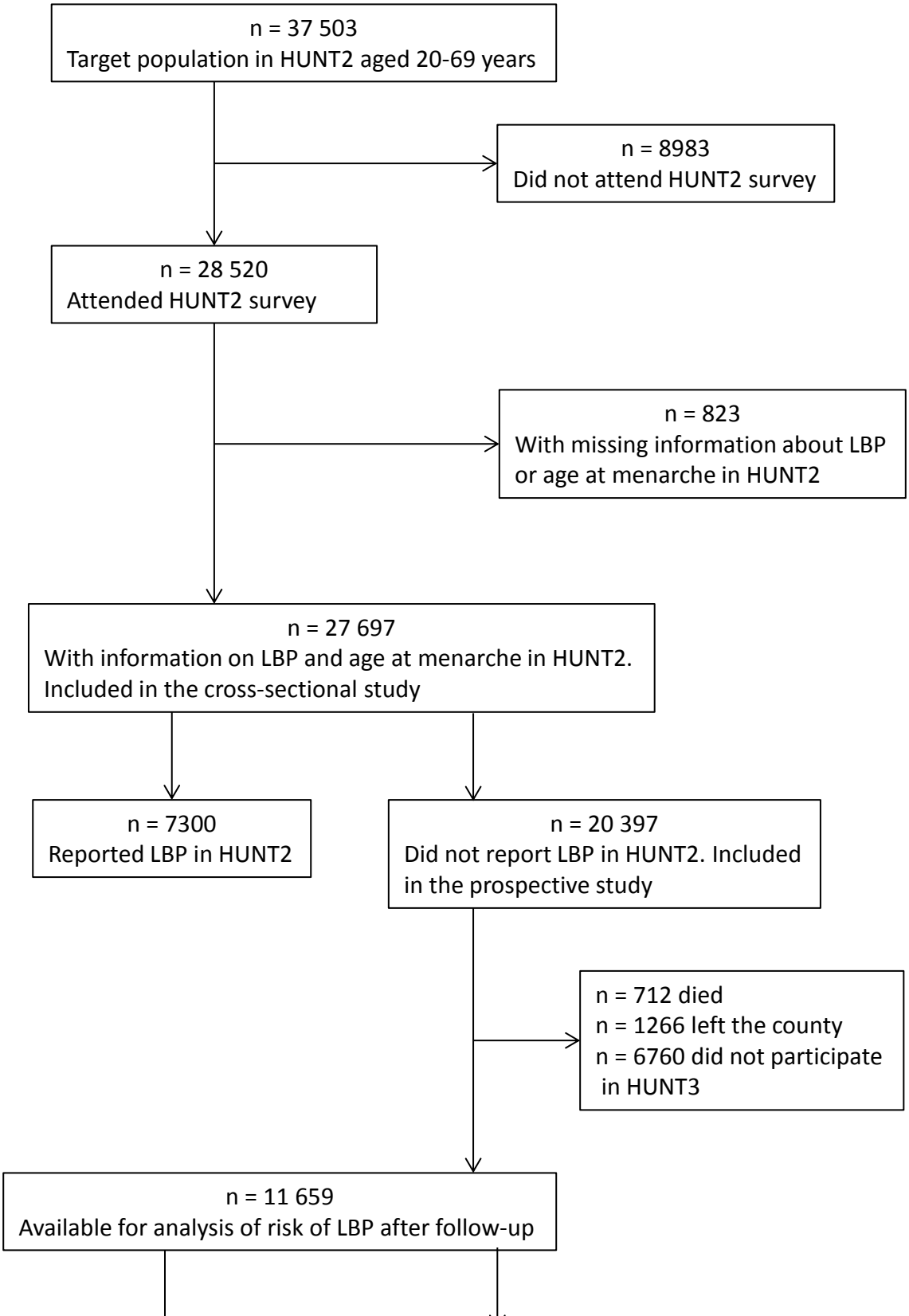
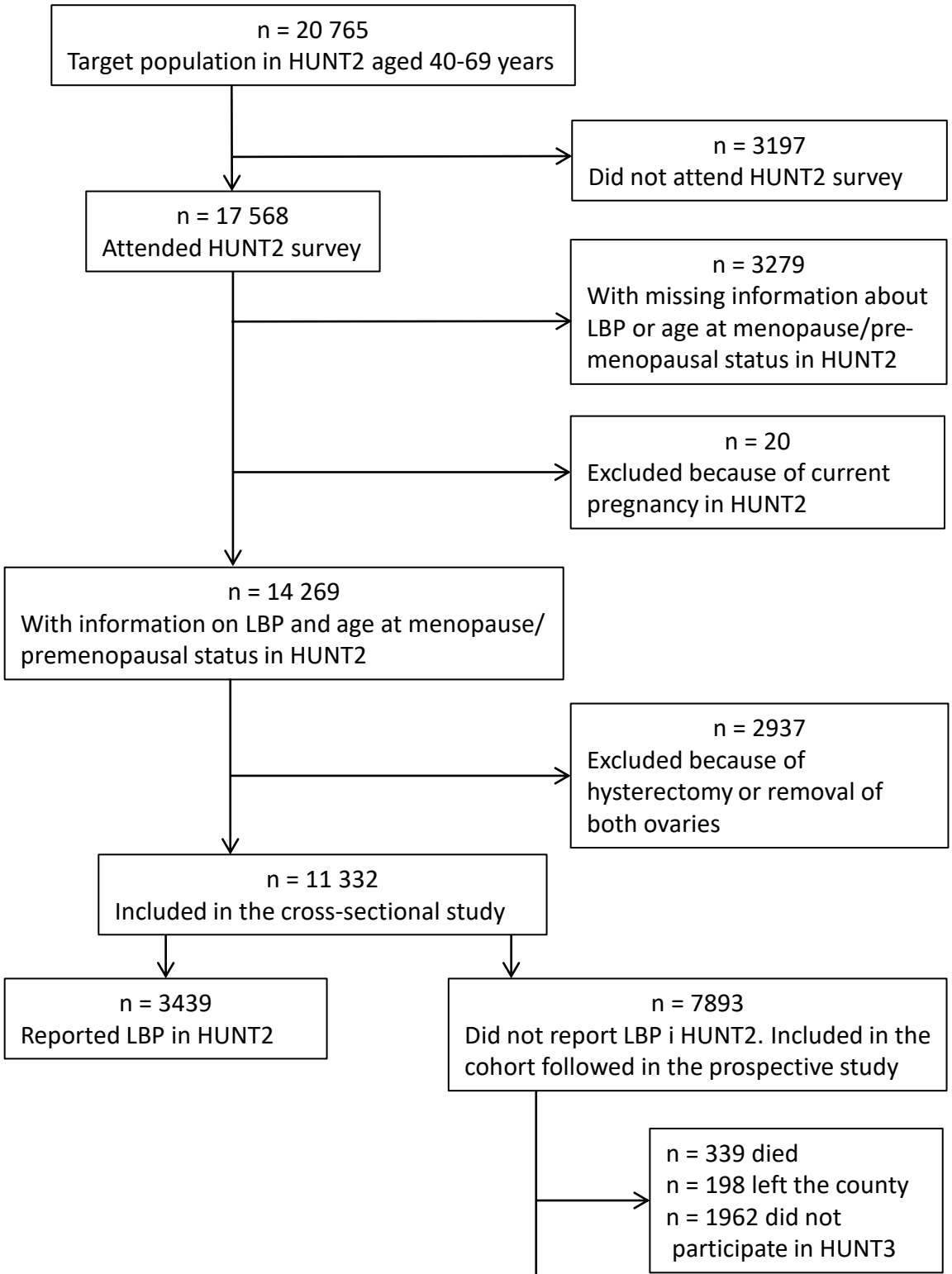
Legend for figures

Figure 1. Flow chart for the cross-sectional and prospective studies of age at menarche as a potential risk factor. HUNT, Trøndelag Health Study; LBP, low back pain.

Figure 2. Flow chart for the cross-sectional and prospective studies of age at menopause as a potential risk factor. HUNT, Trøndelag Health Study; LBP, low back pain.





Supplemental table 1 Associations between age at menarche and prevalence of chronic LBP in HUNT2 in cross-sectional analysis, in broad intervals of age

	Age 20-39 years RR (95% CI)*	Age 40-49 years RR (95% CI)*	Age 50-69 years RR (95% CI)*
Number of women included	10 298	6508	8145
Age at menarche (year)			
≤ 11	1.54 (1.34 to 1.77)	1.36 (1.19 to 1.56)	1.18 (1.05 to 1.33)
12	1.16 (1.03 to 1.32)	1.14 (1.02 to 1.29)	1.12 (1.02 to 1.23)
13	1.09 (0.96 to 1.22)	1.11 (0.99 to 1.24)	1.06 (0.97 to 1.15)
14	1.00 (reference)	1.00 (reference)	1.00 (reference)
15	1.09 (0.93 to 1.29)	1.12 (0.98 to 1.28)	0.98 (0.89 to 1.08)
16	1.36 (1.07 to 1.74)	1.02 (0.80 to 1.30)	0.93 (0.78 to 1.09)
≥ 17	1.48 (0.97 to 2.26)	1.75 (1.22 to 2.51)	1.11 (0.85 to 1.45)
P for categorical effect	< 0.001	< 0.001	0.013
P for linear trend	< 0.001	0.009	< 0.001
P for quadratic effect†	< 0.001	0.001	0.21

*****Adjustment for age, BMI, physical activity, education, smoking, nulliparity and age at first delivery.

†In model also including linear effect.

BMI, body mass index; HUNT, Trøndelag Health Study; LBP, low back pain; RR, relative risk.

Supplemental table 2 Associations between age at menarche and risk of chronic LBP in prospective analysis in HUNT3, in broad intervals of age in HUNT2

	Age 20-39 years	**Age 40-49 years**	**Age 50-69 years**
	RR (95% CI)*	**RR (95% CI)***	**RR (95 % CI)***
Number of women included	4254	3144	3456
Age at menarche (year)			
≤ 11	1.34 (1.06 to 1.68)	1.33 (1.05 to 1.68)	1.30 (1.00 to 1.69)
12	1.15 (0.95 to 1.38)	0.99 (0.80 to 1.21)	1.24 (1.02 to 1.51)
13	1.01 (0.85 to 1.21)	1.01 (0.84 to 1.22)	1.03 (0.86 to 1.24)
14	1.00 (reference)	1.00 (reference)	1.00 (reference)
15	1.20 (0.96 to 1.51)	0.96 (0.76 to 1.21)	0.95 (0.77 to 1.18)
16	1.13 (0.75 to 1.71)	0.79 (0.51 to 1.21)	1.08 (0.78 to 1.49)
≥ 17	1.60 (0.94 to 2.75)	1.16 (0.53 to 2.53)	1.54 (0.97 to 2.46)
P for categorical effect	0.10	0.19	0.08
P for linear trend	0.46	0.048	0.06
P for quadratic effect†	0.002	0.32	0.019

*Adjustment for age, BMI, physical activity, education, smoking, nulliparity and age at first delivery.

†In model also including linear effect.

BMI, body mass index; HUNT, Trøndelag Health Study; LBP, low back pain; RR, relative risk.

Supplemental table 3 Associations between age at menarche and prevalence of chronic LBP in HUNT2 in cross-sectional analysis, by duration of education

	Education ≤ 9 years	**Education 10-12 years**	**Education ≥ 13 years**
	RR (95% CI)*	**RR (95% CI)***	**RR (95 % CI)***
Number of women included	7597	11 361	5993
Age at menarche (year)			
≤ 11	1.16 (1.03 to 1.31)	1.56 (1.40 to 1.73)	1.22 (1.02 to 1.45)
12	1.13 (1.03 to 1.24)	1.16 (1.05 to 1.28)	1.10 (0.94 to 1.29)
13	1.06 (0.97 to 1.16)	1.10 (1.01 to 1.21)	1.04 (0.90 to 1.21)
14	1.00 (reference)	1.00 (reference)	1.00 (reference)
15	0.99 (0.89 to 1.10)	1.12 (1.00 to 1.26)	1.01 (0.84 to 1.22)
16	0.95 (0.80 to 1.13)	1.00 (0.80 to 1.24)	1.32 (1.01 to 1.73)
≥ 17	1.42 (1.10 to 1.84)	1.30 (0.95 to 1.77)	0.99 (0.56 to 1.75)
P for categorical effect	0.008	< 0.001	0.21
P for linear trend	0.006	< 0.001	0.19
P for quadratic effect†	0.06	< 0.001	0.048

*Adjustment for age, BMI, physical activity, education, smoking, nulliparity and age at first delivery.

†In model also including linear effect.

BMI, body mass index; HUNT, Trøndelag Health Study; LBP, low back pain; RR, relative risk.

Supplemental table 4 Associations between age at menarche and risk of chronic LBP in prospective analysis in HUNT3, by duration of education recorded in HUNT2

	Education ≤ 9 years	**Education 10-12 years**	**Education ≥ 13 years**
	RR (95% CI)*	**RR (95% CI)***	**RR (95 % CI)***
Number of women included	2957	4997	2900
Age at menarche (year)			
≤ 11	1.31 (0.98 to 1.74)	1.28 (1.05 to 1.56)	1.36 (1.04 to 1.79)
12	1.08 (0.88 to 1.33)	1.15 (0.98 to 1.34)	1.05 (0.81 to 1.35)
13	1.10 (0.91 to 1.32)	1.01 (0.87 to 1.17)	0.92 (0.72 to 1.16)
14	1.00 (reference)	1.00 (reference)	1.00 (reference)
15	1.13 (0.91 to 1.39)	1.05 (0.86 to 1.27)	0.77 (0.56 to 1.06)
16	0.95 (0.65 to 1.37)	1.14 (0.83 to 1.57)	0.87 (0.50 to 1.50)
≥ 17	1.75 (1.07 to 2.85)	0.95 (0.50 to 1.79)	1.87 (1.06 to 3.29)
P for categorical effect	0.29	0.21	0.012
P for linear trend	0.61	0.06	0.031
P for quadratic effect[b]	0.08	0.06	0.015

*Adjustment for age, BMI, physical activity, education, smoking, nulliparity and age at first delivery.

†In model also including linear effect.

BMI, body mass index; HUNT, Trøndelag Health Study; LBP, low back pain; RR, relative risk.

Supplemental table 5 Associations between age at menarche and prevalence of chronic LBP in cross-sectional analysis in HUNT2, with and without adjustment for HADS

	With standard adjustment*	With standard adjustment* among individuals with known HADS score	With standard adjustment*and adjustment for HADS score
	RR (95% CI)	RR (95% CI)	RR (95 % CI)
Number of women included	24 951	21 773	21 773
Age at menarche (year)			
≤ 11	1.33 (1.24 to 1.43)	1.31 (1.21 to 1.42)	1.27 (1.18 to 1.37)
12	1.13 (1.06 to 1.21)	1.13 (1.05 to 1.21)	1.12 (1.05 to 1.19)
13	1.07 (0.01 to 1.14)	1.07 (1.00 to 1.14)	1.07 (1.00 to 1.14)
14	1.00 (reference)	1.00 (reference)	1.00 (reference)
15	1.04 (0.97 to 1.12)	1.05 (0.97 to 1.13)	1.02 (0.95 to 1.10)
16	1.02 (0.91 to 1.15)	1.07 (0.94 to 1.21)	1.05 (0.92 to 1.19)
≥ 17	1.31 (1.08 to 1.59)	1.34 (1.08 to 1.65)	1.28 (1.04 to 1.57)
P for categorical effect	< 0.001	< 0.001	< 0.001
P for linear trend	< 0.001	< 0.001	< 0.001
P for quadratic effect†	< 0.001	< 0.001	< 0.001

*****Adjustment for age, BMI, physical activity, education, smoking, nulliparity and age at first delivery.

†In model also including linear effect.

BMI, body mass index; HADS, Hospital Anxiety and Depression Scale; HUNT, Trøndelag Health Study; LBP, low back pain; RR, relative risk.

Supplemental table 6 Associations between age at menarche and risk of chronic LBP in prospective analysis in HUNT3, with and without adjustment for HADS

	With standard adjustment*	With standard adjustment* among individuals with known HADS score	With standard adjustment* and adjustment for HADS score
	RR (95% CI)	RR (95% CI)	RR (95 % CI)
Number of women included	10 854	9666	9666
Age at menarche (year)			
≤ 11	1.32 (1.15 to 1.52)	1.37 (1.18 to 1.59)	1.36 (1.17 to 1.57)
12	1.12 (1.00 to 1.25)	1.16 (1.03 to 1.31)	1.15 (1.02 to 1.30)
13	1.01 (0.91 to 1.13)	1.04 (0.92 to 1.16)	1.04 (0.93 to 1.16)
14	1.00 (reference)	1.00 (reference)	1.00 (reference)
15	1.02 (0.90 to 1.16)	1.05 (0.92 to 1.21)	1.04 (0.91 to 1.20)
16	1.01 (0.81 to 1.25)	1.07 (0.85 to 1.36)	1.07 (0.84 to 1.35)
≥ 17	1.43 (1.04 to 1.98)	1.31 (0.89 to 1.92)	1.25 (0.85 to 1.83)
P for categorical effect	0.002	0.002	0.003
P for linear trend	0.008	0.004	0.003
P for quadratic effect†	< 0.001	0.001	0.001

*Adjustment for age, BMI, physical activity, education, smoking, nulliparity and age at first delivery.

†In model also including linear effect.

BMI, body mass index; HADS, Hospital Anxiety and Depression Scale; HUNT, Trøndelag Health Study; LBP, low back pain; RR, relative risk.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5, 6
Objectives	3	State specific objectives, including any prespecified hypotheses	3, 5
Methods			
Study design	4	Present key elements of study design early in the paper	3, 6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	6, 7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8, 9
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	8
Bias	9	Describe any efforts to address potential sources of bias	17
Study size	10	Explain how the study size was arrived at	6, 7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	8,9
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 (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	7 9-16
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	17, 18
Outcome data	15*	Report numbers of outcome events or summary measures over time	11,13,15,16 Table 2-5

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 (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9, 12 Table 2-4 Supplemental table 1-6
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12
Discussion			
Key results	18	Summarise key results with reference to study objectives	12, 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, 18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18-20
Generalisability	21	Discuss the generalisability (external validity) of the study results	20-22
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	17

*Give information separately for exposed and unexposed groups.

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 http://www.strobe-statement.org.