



Original Research

Is there still a social gradient in respiratory symptoms? A population-based Nordic EpiLung-study

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ABSTRACT

Background: Respiratory symptoms are a common public health issue that can partly be attributed to preventable risk factors, such as tobacco smoking and occupational exposure, which are more common in individuals with lower socioeconomic status.

Objective: Our aim was to evaluate the social gradient in respiratory symptoms in Nordic countries.

Methods: This study included participants aged 30–65 years from five cross-sectional population-based questionnaire surveys in 2016 in Finland and Sweden (N = 25,423) and in 2017–2019 in Norway (N = 27,107). Occupational skill levels 1 and 2 (occupations requiring compulsory education) were combined and compared to skill levels 3 and 4 (occupations requiring upper secondary and tertiary education). Meta-analysis was conducted to obtain pooled age- and sex adjusted odds ratios (aORs) of associations between occupational skill and the respiratory symptoms including recurrent wheeze, dyspnoea, and productive cough.

Results: In the meta-analysis, recurrent wheeze, dyspnoea, and productive cough showed a social gradient. The participants with occupational skill 1 and 2 had higher risk for recurrent wheeze (aOR 1.78, 95% CI 1.34–2.22) and dyspnoea (aOR 1.59, 95% CI 1.29–1.90) compared to occupational skill 3 and 4 in Sweden and Finland. Similarly increased risk was observed for combined assessment of dyspnoea and wheeze (aOR 1.05, 95% CI 1.03–1.07) in Norway. In a meta-analysis including all three countries, the aOR for productive cough was 1.31 95% CI 1.07–1.56.

Conclusions: Occupations with lower, compared to higher, skill levels were associated with an increased risk of recurrent wheeze, dyspnoea, and productive cough.

1. Introduction

Respiratory symptoms are a public health concern that increases the

frequency of healthcare use and limits the daily life of many patients [1]. Respiratory symptoms and their causes are not equally distributed between low-, middle-, and high-income countries, with the lowest

Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; FinEsS, Finnish Estonian Sweden Study; HUNT, Trøndelag Health Study; ISCO-08, International Standard Classification of Occupations; OLIN, Obstructive Lung Disease in Northern Sweden Study; SES, socioeconomic status; WSAS, West Sweden Asthma Study.

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prevalence of respiratory symptoms in middle-income countries [2]. High-income Nordic countries have a high level of public education and healthcare to provide health equity.

Nevertheless, several Nordic studies have suggested a social gradient in respiratory health. For example, over 20 years ago, Pallasaho et al. [3] reported an increased risk for respiratory symptoms among those with low socioeconomic status (SES) based on occupation. Moreover, several studies in the Nordic countries have reported an association between low SES and chronic obstructive pulmonary disease (COPD) [4,5]. Additionally, health inequality owing to SES has been found in individuals with asthma [6–8]. For example, low SES has been associated with asthma and wheezing in Sweden, especially in women [9]. In Denmark, Håkansson et al. [10] have reported social biases in access to specialist asthma care. Furthermore, Ilmarinen et al. [11] have reported that low educational level was associated with worse asthma control in Nordic countries.

On the other hand, the educational and income-related inequality in Sweden between 1996 and 2016 showed mixed trends [7], as the educational inequality associated with asthma and asthmatic wheezing decreased while it increased for productive cough, mainly among men. Furthermore, as stated above, respiratory diseases might be underdiagnosed or treated with lower intensity among individuals with low SES. Therefore, self-reported respiratory symptoms may be a less biased indicator of the social gradient than the diagnosis of chronic respiratory disease.

Different measures of SES have an impact on health. For instance, (1) health literacy increases with educational level, (2) living conditions improve with income level, and (3) working conditions differ by type of occupation. In the current study, we used a classification combining occupation and education needed for each trade, International Standard Classification of Occupations (ISCO-08), as exposure to estimate the risk for different respiratory symptoms in five randomly selected, large-scale, population-based samples in Finland, Sweden, and Norway. Additionally, we compared the risk for respiratory symptoms between the five centres. The study aimed to estimate whether there is a social gradient in respiratory symptoms in Nordic countries.

2. Methods

2.1. Data collection and sources

The present Nordic EpiLung study was a cross-sectional multi-centre study combining survey data from 2016. There were two centres in Finland: the Finland, Estonia, Sweden (FinEsS) Helsinki [12] and Vaasa-Seinäjoki [13] studies; two centres in Sweden: the Obstructive Lung Disease in Northern Sweden (OLIN) [14]; and West Sweden Asthma Study (WSAS) study [15]. Additionally, the results were estimated in the Trøndelag Health Study (HUNT) 2017–2019 cohort [16]. The Finnish and Swedish studies shared an identical core questionnaire about respiratory symptoms, and these self-reported data were pooled in meta-analyses. The Norwegian sample was not combined into the pooled analysis as the question about respiratory symptoms was not identical to the Finnish and Swedish questionnaires.

2.2. Study population

The study population included those aged 30–65 years on the day of cohort entry, having complete data on smoking habits and occupation. The study flow charts are shown in the supplement (Supplement Figures 1–5). The response rate was similar and moderate in all centres, 50.3% in FinEsS Helsinki, 52.5% in FinEsS Seinäjoki-Vaasa, 58.3% in OLIN, 50.1% in WSAS, and 54.0% in HUNT.

2.3. Occupational level

Self-reported occupations were classified according to ISCO-08 in

each centre. Then these occupations were further classified into ISCO-skill levels coherently following the classification [17]. ISCO-skill level is a composite variable of SES based on an occupation that considers the education needed for each trade. For example, workers in skill level 1 need primary education, whereas, workers in skill level 4 occupations need a high educational level. Thus, skill levels 1 and 2 were classified as low occupation levels as the total number of years in school is often less than 12 years.

2.4. Smoking status

Smoking status included current smokers, former smokers who had stopped smoking more than 12 months before, and never-smokers. We included an estimation of number of cigarettes smoked daily.

2.5. Respiratory symptoms

All centres had a question on **Productive cough** “Do you usually have phlegm when coughing, or do you have phlegm in your chest, which is difficult to bring up?” in Finland and Sweden, whereas the wording “Do you cough daily in periods of the year? and if yes, do you bring up phlegm?” was used in Norway. The Swedish and Finnish centres had questions on **Dyspnoea mMRC score ≥ 2** “Do you get short of breath when you walk with other people of your own age on level ground at normal pace?” and **Recurrent wheeze** “Do you usually have wheezing, whistling or a noisy sound in your chest when breathing?”. The Norwegian centre had a combined question on **Wheeze or dyspnoea** “Have you had any kind of attack of wheezing or breathlessness during the last 12 months?”

2.6. Statistical analysis

Each centre performed statistical analyses using IBM SPSS Statistics software version 27 (IBM SPSS, Armonk, NY, USA). Pearson chi-square test was used to compare categorical variables; and the z-test was used for post hoc analyses. A p-value of <0.05 was considered statistically significant. Binary logistic regression analyses were performed to calculate Odds Ratios (ORs) with 95% confidence intervals (CIs) by using dyspnoea, recurrent wheeze, dyspnoea/wheeze last 12 months, and productive cough, physician diagnosed asthma and COPD as dependent variables. Model 1 includes crude values. Associations with skill levels were adjusted for age and sex by including these as covariates in the model 2. Whereas Model 3 was adjusted for age, sex, BMI, and smoking. ISCO-08 skill levels 1 and 2 comprised low occupational levels, and skill levels 3 and 4 comprised high occupational levels. The reference group consisted of patients without respective symptoms. Meta-analyses for adjusted Odds Ratios (aOR) were conducted using Stata Statistical Software version 16.1, StataCorp LLC, College Station, TX, USA. Sensitivity analysis for never smokers, males, females, and age groups with cut of age 50 years were performed using binary logistic regression.

3. Results

A total of 49,017 participants aged 30–65 years were included in the study. The location of the cohorts with their primary demographics is shown in Fig. 1. Detailed demographics are shown in Table 1. The HUNT cohort in Norway had the highest proportion of ever smokers but the lowest level of current smokers, and the participants still smoking were heavy smokers. HUNT cohort had a high proportion of fishermen and farmers and very little industry and work-related exposure. HUNT cohort included five small cities with 15–22,000 inhabitants. In Sweden, the WSAS cohort had the least occupational exposure to vapour, gas, dust, and fumes (VGDF) despite average skill levels and big factories in the area. In comparison, the rural OLIN cohort had a higher skill level than WSAS, more occupational exposure to VGDF, and a higher

Demographics of population aged 30 to 65 years in Nordic EpiLung Study

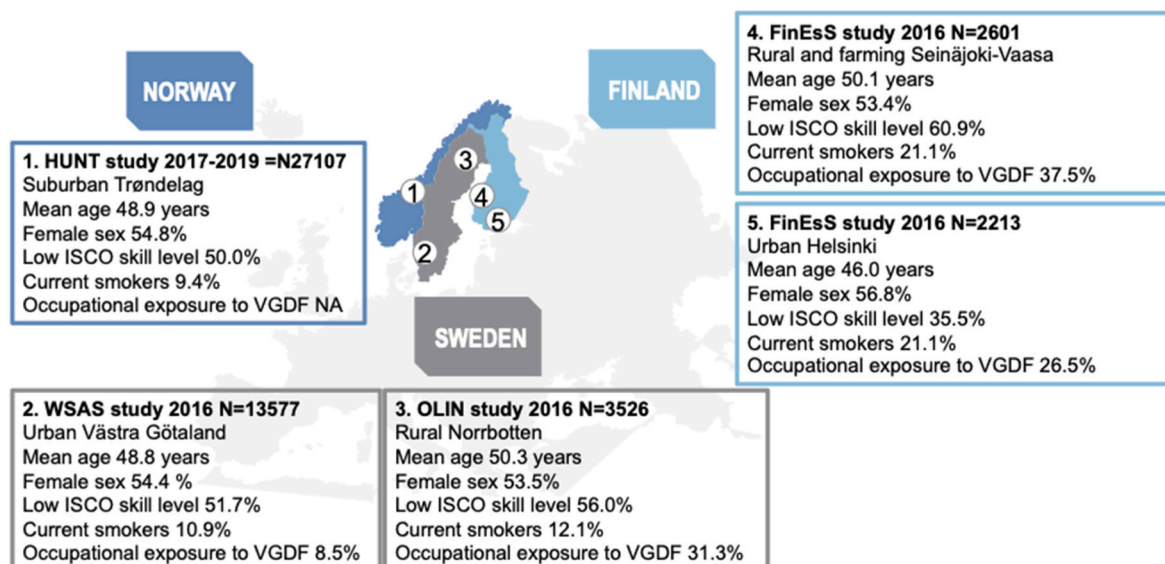


Fig. 1. Overview of the study cohorts. Low skill level is defined as ISCO-08 skill level 1 or 2. **Abbreviations** Finnish Estonian Sweden Study (FinEsS), Trøndelag Health Study (HUNT), International Standard Classification of Occupations (ISCO-08) Obstructive Lung Disease in Northern Sweden Study (OLIN), socioeconomic status (SES), and West Sweden Asthma Study (WSAS).

Table 1

Demographics of population aged 30–65 years in five cross-sectional studies in Finland, Norway, and Sweden.

	1 NORWAY	2 SWEDEN	3 SWEDEN	4 FINLAND	5 FINLAND
Study name	HUNT 4	WSAS 2	OLIN	FinEsS Seinäjoki-Vaasa	FinEsS Helsinki
Participants included	27107	13570	3526	2601	2213
Female sex	14843 (54.8%)	7398 (54.5%)	1888 (53.5%)	1390 (53.4%)	1256 (56.8%)
Age years, mean, (SD)	48.9 (9.6)	48.7 (10.1)	50.3 (9.8)	50.1 (10.4)	46.0 (10.1)
BMI kg/m ² , mean (SD)	27.4 (4.6) (M = 66)	25.7 (4.2) (M = 147)	26.6 (SD 4.6)	26.6 (SD 4.8)	25.5 (SD 4.6)
Allergic rhinitis	5962 (29.8%) (M = 7,082)	4298 (31.7%)	1022 (29.0%)	473 (18.2%)	659 (29.8%)
Exercise 1 time/week or less	NA	4819 (42.6%) (M = 2,260)	1684 (48.9%) (M = 80)	748 (28.9%) (M = 18)	637 (29.1%) (M = 38)
Current smokers	2556 (9.4%)	1467 (10.9%)	427 (12.1%)	548 (21.1%)	467 (21.1%)
Heavy current smokers*	1236 (58.3%) (M = 437)	350 (23.9%)	74 (17.8%) (M = 11)	182 (34.1%) (M = 14)	81 (17.5%)
Ex-smokers	11751 (43.4%)	3162 (23.5%)	727 (20.6%)	735 (28.3%)	524 (23.7%)
Never smokers	12800 (47.2%)	8849 (65.7%)	2372 (67.3%)	1318 (50.7%)	1222 (55.2%)
Second-hand smoke at home	NA	2414 (18.0%) (M = 140)	564 (16.5%) (M = 98)	231 (9.0%) (M = 38)	201 (9.2%) (M = 19)
Second-hand smoke at work	NA	1290 (8.7%) (M = 238)	345 (10.0%) (M = 90)	219 (8.5%) (M = 32)	185 (8.4%) (M = 34)
Childhood exposure to farming environment	NA	1388 (10.4%) (M = 179)	508 (14.7%) (M = 63)	994 (39.5%) (M = 85)	262 (11.9%) (M = 12)
ISCO-08 skill level 1	1190 (4.4%)	483 (3.6%)	156 (4.4%)	142 (5.5%)	118 (5.3%)
ISCO-08 skill level 2	12355 (45.6%)	6543 (48.2%)	1820 (51.6%)	1442 (55.4%)	669 (30.2%)
ISCO-08 skill level 3	7294 (26.9%)	2453 (18.1%)	472 (13.4%)	547 (21.0%)	524 (23.7%)
ISCO-08 skill level 4	6268 (23.1%)	4091 (30.1%)	1078 (30.6%)	470 (18.1%)	902 (40.8%)

BMI = body mass index, M = missing, NA = not available, SD = standard deviation. Data is shown n/%, mean (SD) median. * Heavy current smoker, daily ≥ 15 cigarettes, proportion calculated from all current smokers.

proportion of never-smokers. The urban FinEsS Helsinki had the youngest population, the highest skill levels and a high level of currently smoking participants. Rural and farming FinEsS Seinäjoki-Vaasa had the lowest skill level, most occupational exposures to VGDF, the highest level of current smoking, and the lowest prevalence of allergic rhinitis.

3.1. Social inequalities in respiratory symptoms

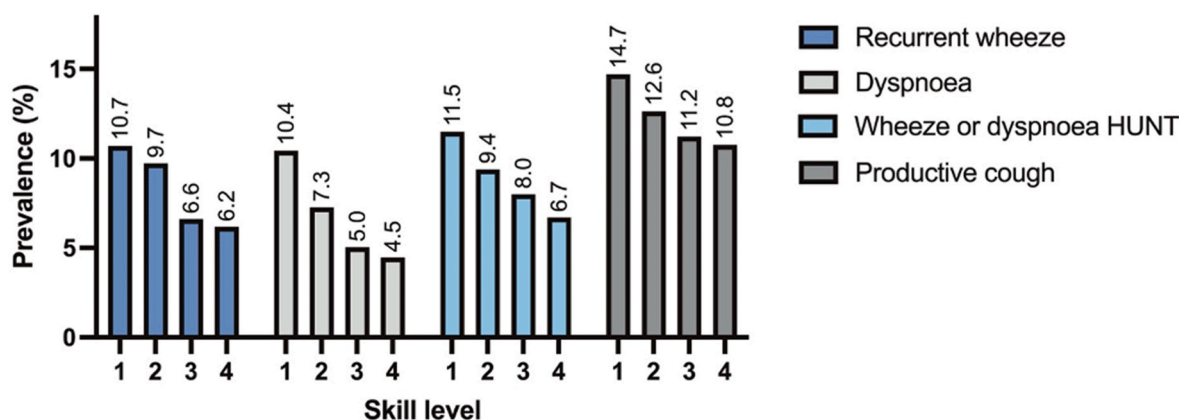
3.1.1. Recurrent wheeze

The prevalence of recurrent wheeze decreased from 10.7% in skill level 1–6.2% in skill level 4 in the pooled data from Finland and Sweden (Fig. 2). When comparing cohorts, the prevalence of wheeze was the

highest in OLIN, Sweden (Fig. 3). A social gradient in recurrent wheeze was seen in all centres (Fig. 4 and Supplement Table 1). In the meta-analysis, odds for recurrent wheeze were higher in skill levels 1 and 2 than in skill levels 3 and 4 (aOR 1.78, 95% CI 1.34–2.22).

3.1.2. Dyspnoea

The prevalence of dyspnoea decreased from 10.4% in skill level 1–4.5% in skill level 4 in the pooled data from Finland and Sweden (Fig. 2). A social gradient in dyspnoea was seen in all centres when considering the prevalence of dyspnoea in each skill level (Fig. 3) and when comparing skill levels 1 and 2 to 3 and 4 in the adjusted regression analyses (Fig. 4 and Supplement Table 1). In the meta-analysis, odds for



NOTE: pooled prevalence estimates populations

	Recurrent wheeze/Dyspnoea	Wheeze or dyspnoea HUNT	Productive cough
Skill level 1	N=899	N=1190	N=2089
Skill level 2	N=10474	N=12355	N=22829
Skill level 3	N=3996	N=7294	N=11290
Skill level 4	N=6541	N=6268	N=12809

Fig. 2. The pooled prevalence of recurrent wheeze, dyspnoea, wheeze or dyspnoea, productive cough in Nordic cross-sectional cohorts, population aged 30–65 years. Recurrent wheeze and Dyspnoea includes Finnish and Swedish cohorts, Wheeze or dyspnoea includes HUNT (Trøndelag Health Study) Norwegian cohort and Productive cough includes all five cohorts from Finland, Sweden, and Norway. Numbers in each skill level refer to total population studied.

dyspnoea were higher in skill levels 1 and 2 than in skill levels 3 and 4 (aOR 1.59, 95% CI 1.29–1.90).

3.1.3. Wheeze or dyspnoea during the last 12 months in the Norwegian cohort

The prevalence of wheeze or dyspnoea decreased from 11.5% in skill level 1–6.7% in skill level 4 in Norway (Fig. 2). A social gradient in wheeze or dyspnoea was seen in the adjusted analyses (aOR 1.05, 95% CI 1.03–1.07) (Supplement Table 1).

3.1.4. Productive cough

The prevalence of productive cough decreased from 14.7% in skill level 1–10.8% in skill level 4 in pooled data from Finland, Norway, and Sweden (Fig. 2). When comparing cohorts, the prevalence of productive cough was the highest (20.8%–24.6%) in Helsinki, Finland, and the lowest (4.7–8.6%) in WSAS, Sweden (Fig. 3). The social gradient in productive cough was seen in all centres. In the meta-analysis, odds for productive cough were higher in skill levels 1 and 2 than in skill levels 3 and 4 (aOR 1.31, 95% CI 1.07–1.56) (Fig. 4 and Supplement Table 1).

The sensitivity analysis highlights the significant association between ISCO-08 skill levels and respiratory symptoms revealing notable variations in risk across different demographic segments (Supplement Table 2–6). There was a social gradient trend in asthma and statistically significant association in COPD (Supplement Table 7).

4. Discussion

In this large-scale, population-based multicentre study in Finland, Sweden, and Norway, we found social gradients in respiratory symptoms. In the meta-analysis, the pooled ORs for recurrent wheeze, dyspnoea, and productive cough were all higher in lower occupational skill levels (1 or 2) than in higher skill levels (3 or 4). The prevalence of respiratory symptoms varied between cohorts with distinct socioeconomic profiles and marked differences in allergic rhinitis, occupational exposure to VGDF, smoking, and exercise levels.

Recurrent wheeze, dyspnoea, and productive cough showed a social gradient also after adjustment for age and sex, in line with other studies performed in the Nordic countries [3–5,18,19]. In Sweden, Schyllert et al. have reported a longitudinal trend of an increase in educational inequality in productive cough, a decrease in asthmatic wheeze and a

decrease in income inequality in both symptoms [7]. The Swedish study also reported increased differences between educational groups in occupational exposures to VGDF, smoking, and reduction of childhood exposure to farming environments.

An explanation could be a well-known association between SES and living and working conditions, diet, exercise, and smoking habits. These factors are in turn, associated with worse health outcomes. For instance, it has been shown that tobacco smoking, the use of electronic cigarettes, secondhand smoking, exposure to moulds, air pollution, a Western diet and obesity are associated with respiratory symptoms [20–26]. Also, respiratory symptoms may differ by sex. For example, women report respiratory symptoms more often without being diagnosed with the respiratory disease than men [27] and women exposed to cigarette smoking report more respiratory symptoms than men [28]. However, men have manual occupations in industry with occupational exposures to VGDF more often and, thus, higher odds for respiratory symptoms than women [18].

Increased educational and health literacy levels, legislation and public health efforts have contributed to decreased prevalence of current smoking in the Nordic countries, with the lowest proportion of current smokers in Norway and the highest proportion in Finland. Current smoking and occupational exposures to VGDF were almost twice as common in Finland compared to the other cohorts. Furthermore, ever being a smoker was most common in Norway and least common in Sweden. The prevalence of ever smoking was still lower in the Nordic countries compared to other European countries [29,30]. Smoking is strongly associated with respiratory symptoms [12,21,25,28,31–33] and harmful exposure might accumulate for those with low SES because both exposure to tobacco smoke, personal smoking and exposure to VGDF are more common in this group; and may thus contribute to the health inequality seen in our study.

4.1. Clinical impact

It is important knowledge that such a phenomenon, health inequality, can be still found in the very high-income, high-education, and public health care surroundings, such as Nordic countries. Even greater social gradients in respiratory symptoms are expected in low-income countries where, for example, biofuel exposure is more common for lower social classes [34–37]. Taken together, cross-sectional

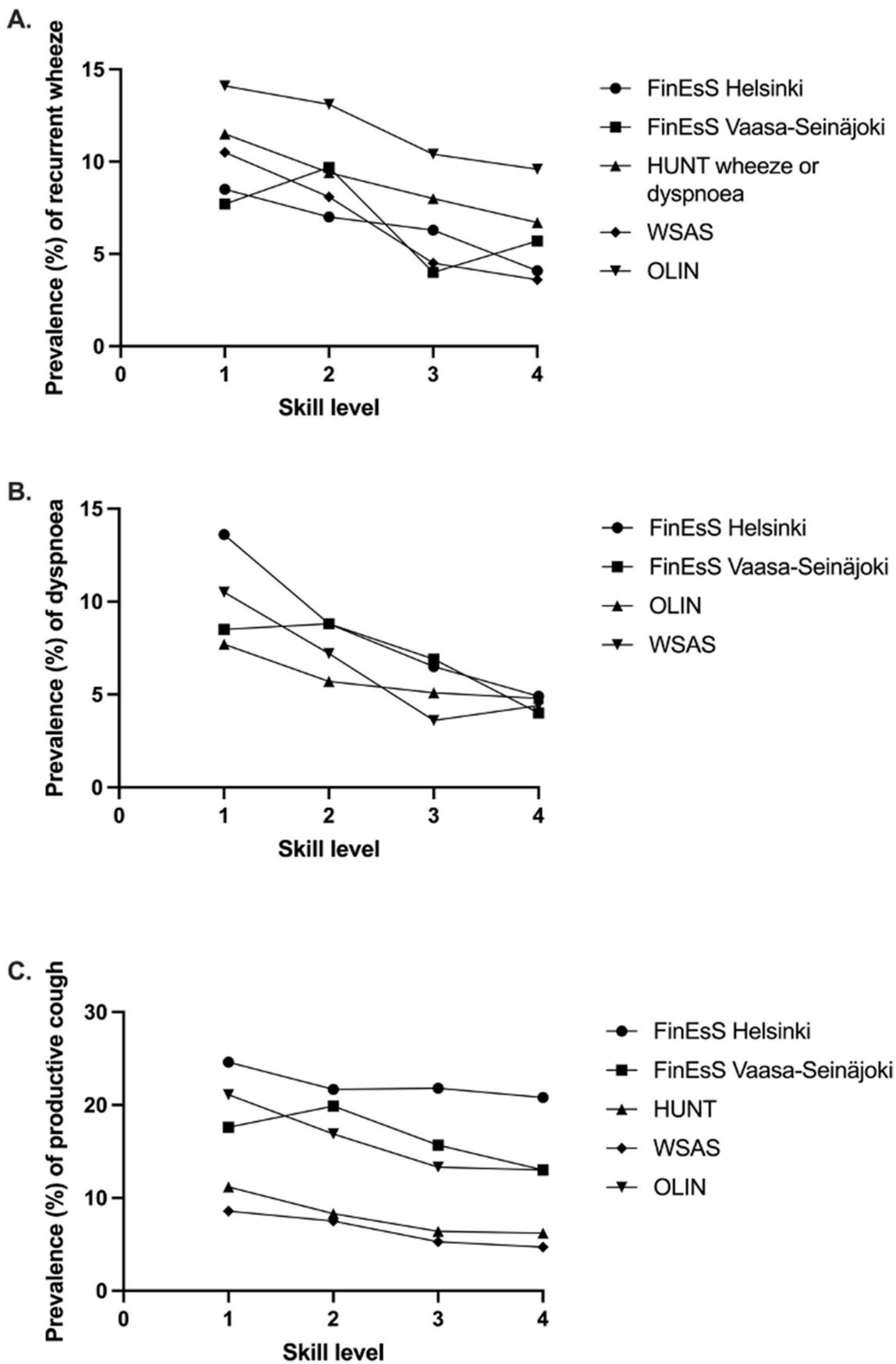


Fig. 3. Prevalence of A. recurrent wheeze, B. dyspnoea mMRC ≥ 2 and C. productive cough in individual studies according to ISCO-08 skill level. **Abbreviations** Finnish Estonian Sweden Study (FinEsS), Trøndelag Health Study (HUNT), International Standard Classification of Occupations (ISCO-08) Obstructive Lung Disease in Northern Sweden Study (OLIN), socioeconomic status (SES), and West Sweden Asthma Study (WSAS).

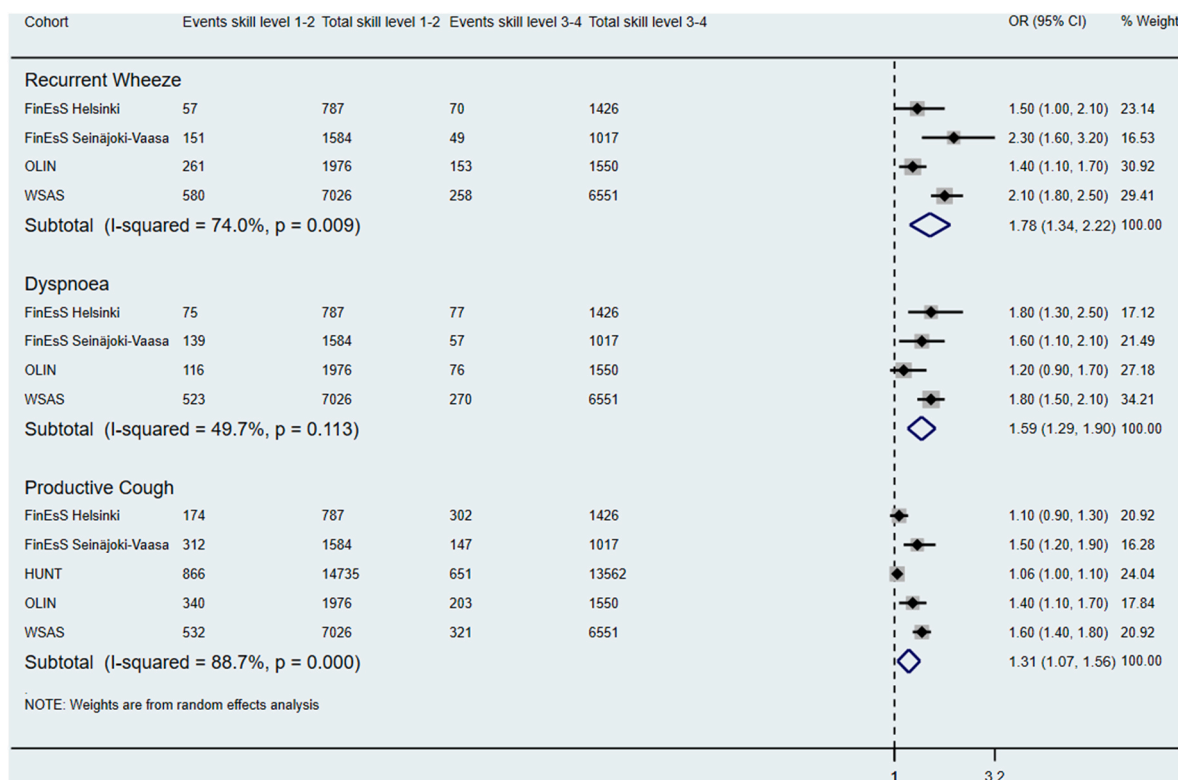


Fig. 4. Meta-analysis of the association between ISCO-08 skill level (1–2 vs 3–4) and respiratory symptoms, analysed by binary logistic regression adjusted for age and sex. **Abbreviations** Finnish Estonian Sweden Study (FinEsS), Trøndelag Health Study (HUNT), International Standard Classification of Occupations (ISCO-08) Obstructive Lung Disease in Northern Sweden Study (OLIN), socioeconomic status (SES), and West Sweden Asthma Study (WSAS).

studies can detect health inequalities in the communities by asking about respiratory symptoms. Further community-based research with focus on smoking cessation and improved work and living environment is needed to decrease social disparities in respiratory health. The challenge for traditional research is to find those needing support. Communities should first be aware of inequalities to be able to achieve better and equal respiratory health in a population. Community-based interventions could be offered for patients with poor respiratory disease control in the form of hospitalisations, unplanned visits, or the use of only short-acting medicines because of costs.

4.2. Strengths and limitations

The strengths of this study included the large-scale, multicentre study design with the possibility to pool data from five centres that have used almost identical study methods. The questionnaires that were used were based on internationally acclaimed protocols. The large general population-based samples had moderate response rates with an underrepresentation of younger age groups and males. However, Räisänen et al. [14] have reported from OLIN studies that the non-response bias seems not to affect prevalence estimates of respiratory symptoms. Langhammer et al. [38] have reported that nonparticipants had lower socioeconomic status, more symptoms, and higher morbidity and mortality. Therefore, the social gradient might be underestimated due to moderate response rates.

Main occupations were self-reported and were coded according to the ISCO-08 classification in all the centres to avoid coding differences between the centres [17]. ISCO-08 skill level is a multidimensional SES indicator that was chosen considering consent and data availability. As a limitation, this study did not include registry data on SES indicators such as education or income, or medicine or health care use. Social gradient can be caused by access to medication and health care.

The used self-reported respiratory symptoms were selected

considering cross-cultural validation in translations. Dyspnoea was assessed with dyspnoea mMRC score of ≥ 2 which is a respiratory symptom associated with mortality [39,40]. Questionnaire wording and layout were highly similar in Finland and Sweden but different in Norway. This might be a source of bias as the questionnaire layout and language might influence prevalence and risk estimates [41]. The combined question for wheeze and dyspnoea used in HUNT study might underestimate social gradient in comparison to dyspnoea mMRC score of ≥ 2 . A Norwegian study by Bakke et al. [42] reported that educational level is an associated with respiratory symptoms even after adjusting to sex, age, smoking and occupational exposure. We did not adjust the analysis used in meta-analysis for modifying factors, such as BMI and smoking habits because they are influenced by SES. These sensitivity analyses are shown in Supplementary Tables 1–6.

5. Conclusion

Social gradient in respiratory symptoms such as recurrent wheeze, dyspnoea, and productive cough, existed in the high-income Nordic countries. The observed socioeconomic inequality requires awareness and community-based intervention programs.

Ethics approval and consent to participate

All individual participants provided written consent. The Ethics Committee of the Department of Medicine of Helsinki University Central Hospital approved FinEsS Helsinki and Seinäjoki-Vaasa studies (approval number 200/13/03/00/15). The Regional Ethical Review Board in Umeå, Sweden approved the OLIN studies (approval number 2015/404–31). The Regional Committee for Medical and Health Research Ethics Mid-Norway approved HUNT (approval number 2017/2364). The Regional Ethical Review Board in Gothenburg approved WSAS (approval number 052–16).

Availability of data and materials

According to the ethical permissions and GDPR data protection act, individual data cannot be shared or pooled.

Contribution

Heidi Andersén: Conceptualization, Formal analysis, Visualization, Writing - review & editing, **Laxmi Bhatta:** Formal analysis, Writing - review & editing, **Muwada Bashir:** Formal analysis, Writing - review & editing, **Bright Nwaru:** Formal analysis, Writing - review & editing, **Arnulf Langhammer:** Writing - review & editing, **Steinar Krokstad:** Writing - review & editing, **Päivi Piirilä:** Writing - review & editing, **Hanna Hisinger-Mölkänen:** Writing - review & editing, **Helena Backman:** Conceptualization, Formal analysis, Writing - review & editing, **Hannu Kankaanranta:** Conceptualization, Supervision, Writing - review & editing, **Linnea Hedman:** Conceptualization, Formal analysis, Supervision, Writing - review & editing.

All authors revised the work critically and approved the final version of the manuscript. All authors take responsibility for the accuracy and integrity of the work.

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CRedit authorship contribution statement

Heidi Andersén: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. **Laxmi Bhatta:** Conceptualization, Data curation, Formal analysis, Writing – review & editing. **Muwada Bashir:** Conceptualization, Formal analysis, Writing – review & editing. **Bright**

Nwaru: Conceptualization, Formal analysis, Methodology, Visualization, Writing – review & editing. **Arnulf Langhammer:** Conceptualization, Methodology, Writing – review & editing. **Steinar Krokstad:** Conceptualization, Methodology, Writing – review & editing. **Päivi Piirilä:** Conceptualization, Methodology, Writing – review & editing. **Hanna Hisinger-Mölkänen:** Conceptualization, Writing – review & editing, Formal analysis. **Helena Backman:** Conceptualization, Methodology, Writing – review & editing. **Hannu Kankaanranta:** Conceptualization, Methodology, Project administration, Resources, Software, Supervision, Validation, Writing – review & editing. **Linnea Hedman:** Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Resources, Software, Supervision, Writing – review & editing.

Declaration of competing interest

AL reports that the HUNT Lung Study in HUNT 2 and 3 was partly funded by non-demanding funds from AstraZeneca. AL has received fee from AstraZeneca, Boehringer-Ingelheim, GSK, and Diagnostica for lectures and participation in advisory boards.

HB reports personal fees from Astra Zeneca, personal fees from Boehringer Ingelheim and personal fees from GlaxoSmithKline, outside the submitted work.

HHM was previously an employer of Orion Pharma but does not have any conflict of interests related to this epidemiological study.

HK reports personal fees from Astra Zeneca, personal fees from Orion Pharma, personal fees from Mundipharma, personal fees from Boehringer Ingelheim, personal fees from Chiesi Pharma AB, personal fees from GlaxoSmithKline, personal fees from MSD, personal fees from Novartis, personal fees from Sanofi Genzyme, outside the submitted work.

Other authors have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.rmed.2024.107561>.

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