Low socioeconomic position and neighborhood deprivation are associated with uncontrolled asthma in elderly

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TITLE: LOW SOCIOECONOMIC POSITION AND NEIGHBORHOOD DEPRIVATION ARE ASSOCIATED WITH UNCONTROLLED ASTHMA IN ELDERLY

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ABSTRACT

Background While uncontrolled asthma in adults is frequent in Europe, the impact of socioeconomic position (SEP) was little investigated. We aimed to investigate the respective association of individual- and area-level SEP with uncontrolled asthma among French elderly women.

Methods Analyses were conducted in the Asthma-E3N study, among participants with current asthma (i.e., asthma attacks, treatment, or symptoms in previous year). Asthma control was evaluated using Asthma Control Test (uncontrolled: score ≤19); SEP was defined at both individual- and area-level, using educational level (low, medium, high), the French Deprivation index (tertiles defined at national level), and by merging them in a combined-SEP index. Associations between SEP and asthma control were estimated for 2,258 women by logistic regression adjusted for age. Analyses were stratified by asthma controller medication use estimated through a drug reimbursement database.

Results Women were 70 years on average and 24% had uncontrolled asthma. A low educational level (11%) was associated with an increased risk of uncontrolled asthma [odds ratio (95% confidence interval) =1.9(1.4,2.6)], especially among women not using controller medication [3.1(1.9,5.1)]. Using the combined-SEP index, the highest risk of uncontrolled asthma was observed among women with the most disadvantaged socioeconomic profile (low educational level and low-SEP neighborhood) [2.5(1.5,4.2)].

Conclusions Women with low SEP had more often uncontrolled asthma, which might be partly explained by inadequate asthma treatment. To achieve the best management of asthma for elderly patients, a specific attention should be given not only to disadvantaged population and neighborhoods, but also to disadvantaged populations in affluent neighborhoods.

Keywords: asthma control, elderly, neighborhood deprivation, socioeconomic position.

List of abbreviations: ACT, Asthma control test; GINA, Global initiative for asthma; ICS, Inhaled corticosteroids; SABA, Short-acting b2 agonists; SEP, Socioeconomic position.

INTRODUCTION

Asthma is a common chronic respiratory disease affecting more than 350 million people worldwide [1]. Asthma cannot be cured, but can be managed with controller medications for the major part of patients [2]. However, uncontrolled asthma in adults is still frequent in Europe. Several general population studies consistently reported that asthma control is not achieved for 45 to 60% of patients [3]. Poor asthma control is associated with substantial individual morbidity as well as direct and indirect economic costs [4,5].

To date, determinants of asthma control in adults, especially social determinants, have been little studied, in contrast to those investigated for asthma prevalence or incidence [6,7]. In addition, studies on the association between socioeconomic position (SEP) and asthma control in European adults reported mixed results. Some studies using only individual-SEP variables reported an association between low SEP and uncontrolled asthma defined either by GINA guidelines [8], Asthma Control Questionnaires [9], or a heavy use of short-acting beta2 agonists (SABA) [10] whereas others did not found any statistically significant association [11,12]. Mixed results could be partly explained by a heterogeneous evaluation of asthma control. In this context, the use in a same study of complementary methods to define asthma control, either from a multidimensional construct through a self-reported standardized questionnaire or a unidimensional construct based on the number of canisters of SABA as previously suggested [13], may allow clarifying associations between SEP and asthma control. In addition, it is suggested that lower SEP is associated with lower adherence to medical treatment in patients suffering from chronic diseases [14]. A lack of adherence to a controller treatment, the cornerstone of asthma maintenance therapy and a major determinant of asthma control [14], could contribute to social disparities in asthma control. For example, a Danish study showed an association between higher individual SEP, defined by income and educational level, and a higher use of inhaled corticosteroids (ICS) [15].

Regarding the association between area-level SEP and asthma control in adults, the literature is scarce as compared to the literature among children. To our knowledge, only one study, performed in United States, investigated the link between area-level SEP and asthma outcomes (including asthma severity

and quality of life). They found that area-level SEP predicted asthma quality of life but not severity after taking into account individual-SEP [16]. In the European literature, positive correlations between neighborhood deprivation and emergency calls/ visits or hospitalization for asthma attacks were reported in ecological studies suggesting that neighborhood socioeconomic characteristics could play a role in asthma control [17,18]. Both individual- and area-level SEP should therefore be considered together when studying social disparities in asthma control [19,20]. To our knowledge, there is no study evaluating associations between both individual- and area-level SEP with asthma control in adult populations.

The aim of the present study was to investigate the respective association of individual- and area-level SEP with asthma control in a French elderly population. Our study population offered the unique opportunity to test three hypotheses: i) a low individual-SEP is associated with uncontrolled asthma; ii) a regular use of ICS modifies the association; iii) living in low-SEP neighborhood is a risk factor for uncontrolled asthma.

MATERIALS AND METHODS

Population

The E3N study (*étude épidémiologique auprès des femmes de la Mutuelle Générale de l'Education Nationale [MGEN]*), is a prospective cohort (1990-) on chronic diseases, among 98,995 women members of a French health insurance plan covering employees (and spouses) of the French national education, i.e. teachers of all grades from kindergarten to university, school employees and manual workers, aged 40-65 years at baseline and followed every two years [21]. In order to improve the respiratory characterization of women from E3N, a nested case-control study on asthma (Asthma-E3N) was performed in 2011 [22].

Asthma-E3N study included 7,100 women who reported ever asthma (defined by a positive answer to the single question "Have you ever had an asthma attack?") at least once between 1992 and 2008 and 14,200 aged-matched "women without asthma" randomly selected (among the remaining). The

Asthma-E3N questionnaire was self-completed and returned by mail (92% response rate) [22]. In addition, for all participants, dispensed non-hospital medications were comprehensively collected from the MGEN drug reimbursement database.

Current asthma

Current asthma was defined among women with ever asthma by the presence of asthma attack, asthma treatment, or asthma-like symptoms (wheezing, woken up with a feeling of chest tightness, attack of shortness of breath at rest, attack of shortness of breath after exercise, or woken up by a shortness of breath attack) in the previous 12 months [22,23].

Asthma control

Asthma control was defined by the Asthma Control Test (ACT), a questionnaire designed and validated to measure the multidimensional nature of asthma control [24]. The questionnaire is composed of five questions on the last 4-week period: activity limitation ("Did asthma keep you from getting as much done at work or home?"), symptom frequency ("How often have you had shortness of breath?"), sleep interference ("Did asthma symptoms wake you up at night or earlier than usual?"), use of rescue treatment ("Did you use your rescue inhaler or nebulizer medication?"), and a self-rating of control level ("How would you rate your asthma control?"), resulting in a score ranging from 5 to 25 (fully controlled). We used a binary variable with a 19-threshold to identify patients with uncontrolled asthma (≤19) [25].

In addition, we used a complementary evaluation of asthma control based on the number of SABA canisters reimbursed in the last 12 months, derived from the MGEN drug reimbursement database. We created a dichotomous variable, with a cut-off at 6 SABA canisters dispensed in a 12-month period to identify patients with uncontrolled asthma, as proposed by Schatz et al. [13].

Asthma controller medication

The number of canisters of inhaled corticosteroids (ICS, alone or combined) reimbursed in the last 12 months, also derived from the MGEN drug reimbursement database, was considered as a categorical

variable to define non-ICS users (0 canister reimbursed), irregular-ICS users (1 to 3 canister(s)) and regular-ICS users (4 or more canisters) as previously suggested [26,27].

Individual- and area-level SEP

Individual-level SEP was evaluated using women's educational level collected in 1990, using 3 categories: low (<high school diploma), medium (high school to 2-level university), and high (≥3 level-university). Area-level SEP was evaluated using the French Deprivation index (FDep), an ecological deprivation index generated by principal component analysis from a set of 4 census-derived variables (2009 French national census): the median household income, the percentage of high school graduates in the population aged 15 years and older, the percentage of blue-collar workers in the active population and the unemployment rate [28]. We showed in a previous study that FDep was reliable to capture socioeconomic residential conditions of the E3N women [29]. FDep was calculated at IRIS level, geographical units of 2,000 inhabitants on average (hereafter referred to as neighborhood). FDep was categorized in tertiles (first tertile=lowest deprivation, e.g., high SEP; third tertile=highest deprivation, e.g., low SEP) for whole France, and then applied to Asthma-E3N women's previously geocoded residential addresses [30]. We created, as performed in other contexts [20,31–33] a "combined-SEP index" in nine categories from least disadvantaged socioeconomic profile (high educational level + high SEP neighborhood) to most disadvantaged socioeconomic profile (low educational level + low SEP neighborhood; Figure A1 in supplementary materials).

Covariates

Age, smoking status (never vs. ever), overweight (body mass index ≥25kg/m²), health-related quality of life assessed by the Asthma Quality of Life questionnaire (AQLQ) [34], and medical visit for asthma (at least one visit to a general practitioner or a chest specialist in the last 12 months) were recorded in 2011.

Statistical analysis

Cross-sectional associations between SEP and asthma control were evaluated by binary logistic regressions (Reference category: controlled asthma [ACT >19 or ≤6 SABA canisters]).

To test for a potential effect modification by a regular use of an asthma controller treatment, analyses were stratified by ICS use, using only ACT-defined asthma control due to low sample size for uncontrolled asthma estimated with the SABA. To test for a potential neighborhood-SEP effect, we used two approaches [20]: 1) we evaluated if the association between educational level and asthma control differed within the same neighborhood deprivation level by stratifying the association by FDep tertiles; 2) We evaluated the association between the combined-SEP index and asthma control with the least disadvantaged socioeconomic profile as the reference category. The Wald test was used as a formal test for interaction. Tests for linear trend were also computed by considering the categorical variables (i.e. individual education, area-deprivation, and ICS-use level) as continuous variables in the models. Neighborhood dependence between observations was considered using generalized estimated equations (SAS GENMOD procedure) in models including FDep. Since our main objective was to investigate the effect of individual and area-level SEP on asthma control, analyses were adjusted only for age. Indeed, smoking and BMI might be mediators rather than confounders of the investigated association and were not entered in the main model. Sensitivity analyses were performed to test the robustness of the results. The association between individual-SEP and asthma control was stratified by age (<65 vs. ≥65 years), smoking status, and overweight. Analyses were also performed among never smokers to exclude women with potential chronic obstructive pulmonary disease [35]. We run also a model adjusted for age plus smoking and BMI. In addition, we performed a multiple imputation to estimate ACT missing values and to run a sensitivity analysis on the whole population (see detailed method and Table A1 in supplementary materials) [36]. All analyses were performed using the SAS 9.4 statistical software (SAS Institute, Cary, NC).

RESULTS

Population description

Among the 6,274 women who completed the Asthma-E3N questionnaire (response rate: 88%), 3,023 women reported current asthma, among whom those with missing values on educational level or ACT,

were excluded for the main analyses (Figure 1). Women with missing data on educational level or ACT items (n=765), excluded from the main analysis, were slightly older (p=0.07) and less often overweight (p=0.003) than those included, but did not differ regarding the smoking status, educational level, or FDep (not shown).

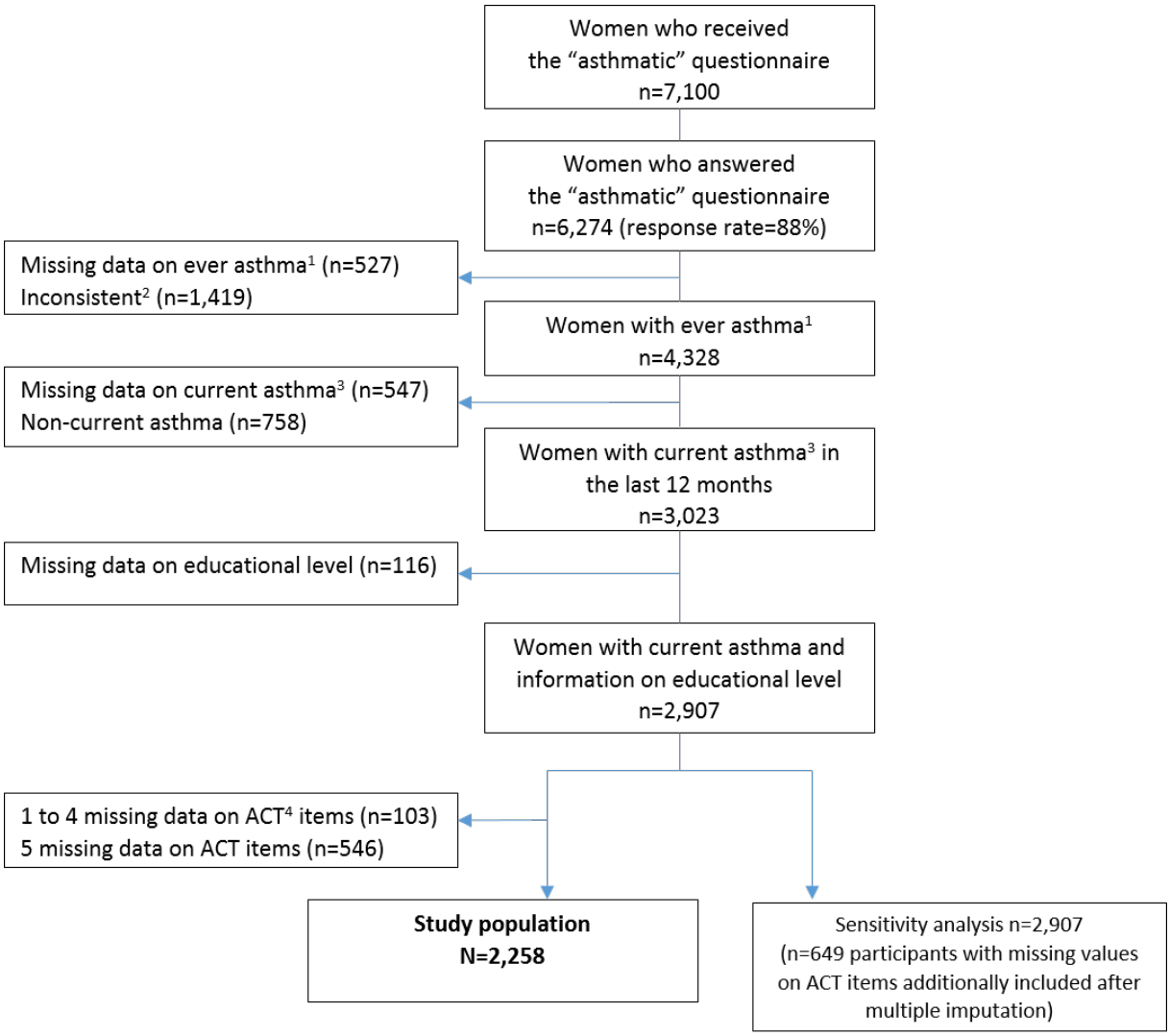

Figure 1 Flow-chart of the study population (n=2,258)
[1] Ever asthma: positive answer to "Have you ever had attacks of breathlessness with wheezing?" OR "have you ever had asthma attacks";
[2] Inconsistent: women who received an "asthmatic questionnaire" but answered no at the question "ever asthma";
[3] Current asthma: women with ever asthma and at least one of 5 symptoms in the last 12 months (wheezing, woken up with a feeling of chest tightness, attack of shortness of breath at rest, attack of shortness of breath after exercise, or woken up by a shortness of breath attack) or asthma treatment or asthma attack in the last 12 months;
[4] ACT=Asthma Control Test.

According to SEP characteristics (Table A2), women with low educational level were significantly older, less often ever smoker, and more often overweight than women with higher educational level. In addition, women with low educational level had more medical visits for asthma (i.e. at least one visit to a general practitioner or a chest specialist in the last 12 months) compared to women with higher educational level.

In the study population (main analyses, n=2,258), 24% had uncontrolled asthma defined by ACT and 2% had heavy use of SABA (>6 canisters) (Table 1).

	All	Controlled asthma (ACT >19)	Uncontrolled asthma (ACT ≤19)	p
n (%)	2,258 (100)	1,710 (75.7)	548 (24.3)	
Age (years), m (SD)	69.7 ±6.0	69.2 ±5.9	71.5 ±6.3	<0.0001
Smoker ever	50.6	51.5	47.7	0.12
Overweight (BMI ≥25kg/m²)	42.0	40.9	45.3	0.07
Educational level,				
High	38.4	40.5	31.9	<0.0001
Medium	50.5	50.0	52.2	
Low	11.1	9.5	15.9	
FDep				
High-SEP neighborhood	46.5	47.4	43.7	0.02
Medium-SEP	30.3	30.8	28.7	
Low-SEP	23.2	21.8	27.6	
SABA*				
0	64.0	68.8	49.3	<0.0001
1-6	33.6	68.3	31.7	
>6	2.4	0.9	6.9	
ICS*				
0	46.5	52.5	28.1	<0.0001
1-3	20.8	19.9	23.5	
≥4	32.7	27.7	48.4	
AQLQ, m (SD)	5.8 ±1.0	6.1 ±0.7	4.7 ±1.0	<0.0001
Medical visit for asthma †	57.0	48.7	83.4	<0.0001

Table 1 Characteristics of the study population, by level of asthma control (ACT-based definition) (n=2,258)

Results are in percent unless otherwise stated, m (SD): mean (standard deviation): p-value from Chi2 test for categorical variable and from student test for continuous variable;

BMI=body mass index, FDep=French Deprivation Index, ACT=Asthma Control Test, ICS=Inhaled corticosteroids, SABA=short acting beta2-agonists, AQLQ=Asthma Quality of Life Questionnaire;

* Number of canisters dispensed in the last 12 months;

† At least one medical visit for asthma (i.e. visit to a general practitioner or a chest specialist) in the last 12 months;

Missing data: smoking status n=14; BMI n=37; FDep n=21; Medical visit for asthma n=51; AQLQ n=338.

Women with uncontrolled asthma were significantly older, had a lower educational level and lived more frequently in low-SEP neighborhoods than women with controlled asthma. Regarding asthma

medications, women with uncontrolled asthma had more asthma treatment reimbursements, but about half of them had no regular-ICS treatment. They also had more frequent medical visits and a lower AQLQ score than women with controlled asthma.

Association between educational level and asthma control

A lower educational level was associated with an increased risk of uncontrolled asthma using both ACT and SABA-based definition (Table 2).

	n uncontrolled/ controlled asthma[1]	ACT score ≤19 vs. >19[1]	SABA >6 vs. ≤6[2]
		OR (95%CI)	OR (95%CI)
Educational level			
High (ref.)	175/692	1.00	1.00
Medium	286/855	1.2 (1.0, 1.5)	1.6 (0.9, 3.0)
Low	87/163	1.9 (1.4, 2.6)	2.8 (1.3, 6.4)
p for trend		0.0001	0.01

Table 2 Age-adjusted association between educational level and asthma control (n=2,258)
Presented results are Odds ratio (95% Confidence Interval) for uncontrolled vs. controlled asthma; test for linear trend was computed by considering educational level as a continuous variable;
ACT= Asthma control test; SABA=short acting beta2-agonists;
[1] ACT-based definition: uncontrolled asthma corresponds to ACT score ≤19;
[2] SABA-based definition: uncontrolled asthma corresponds to more than 6 SABA canisters dispensed in a 12-month period.

The strength of the association between educational level and asthma control using the ACT-based definition differed according to ICS use (*p* for interaction=0.008), more specifically it decreased with the increasing use of ICS (Figure 2).

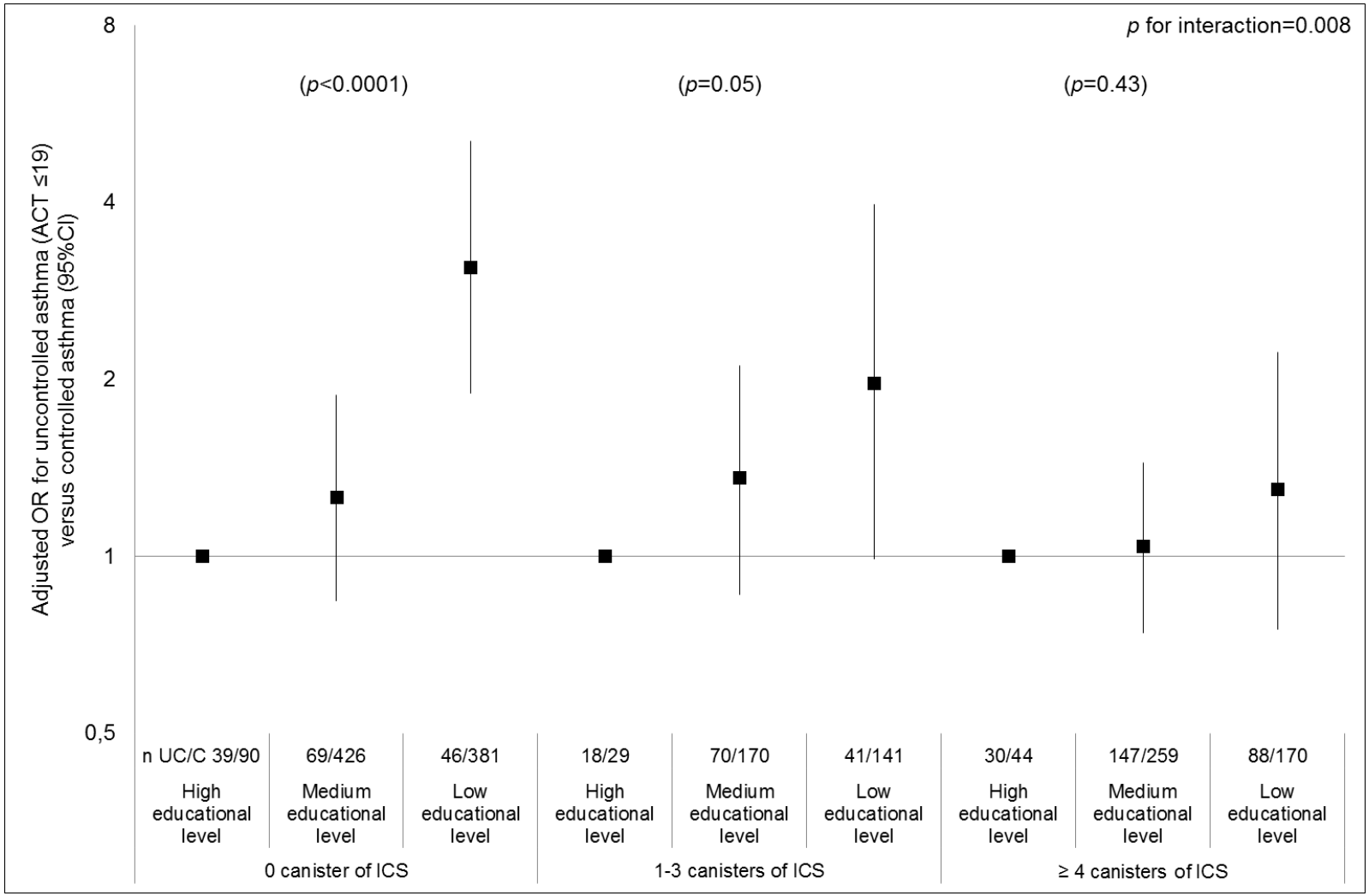

Figure 2 Age-adjusted association between educational level and asthma control, stratified by ICS use (n=2,258)

Presented results are Odds Ratio (95%Confidence Interval) for uncontrolled (Asthma Control Test ≤19) vs. controlled asthma (ACT>19); p for trend in brackets;
The Wald test was used as a formal test for interaction and test for linear trend was computed by considering educational level as a continuous variable;
ICS=Inhaled Corticosteroids

The strongest association was observed among non-ICS users [3.1 (1.9, 5.1), for low vs. high educational level]. Among women with a regular ICS treatment (≥4 canisters/year), the odds ratio was almost 2.5-fold lower than for women with no ICS treatment [1.3 (0.8, 2.2)] and the association was no longer significant.

Association between educational level, neighborhood deprivation, and asthma control

The association between educational level and asthma control (ACT) stratified by FDep showed similar trends within each level of neighborhood SEP with an increased risk of uncontrolled asthma for women with the lowest educational level, compared to those with high educational level (Figure A2). The interaction term was not statistically significant (p=0.78). Nevertheless, we observed a significant association between a low educational level and asthma control for women living in high-SEP neighborhoods (*p* for trend=0.003) whereas it was no longer statistically significant among women living in low-SEP neighborhoods (*p* for trend=0.15).

Lastly, using the combined-SEP index, we observed that women with a more disadvantaged socioeconomic profile were more likely to have uncontrolled asthma than women with a less disadvantaged socioeconomic profile (Figure 3).

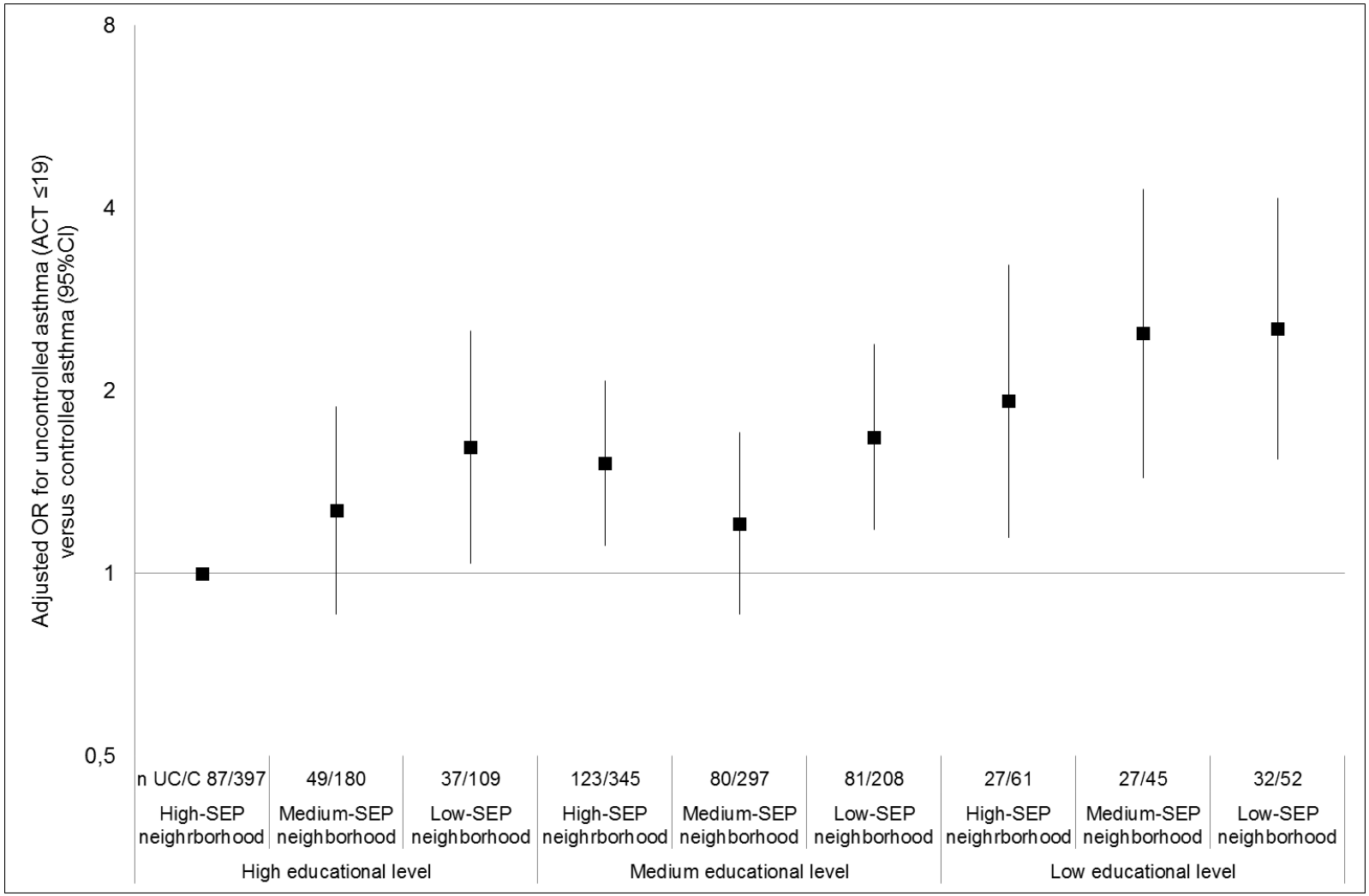

Figure 3 Age-adjusted association between combined-SEP index[1] and asthma control (n=2,258)

Presented results are Odds Ratio (95% Confidence Interval) for uncontrolled (Asthma Control Test ≤19) vs. controlled asthma (C: ACT>19); p for trend=0.008 (test for linear trend was computed by considering the combined-SEP index as a continuous variable);

[1] Combined-SEP index = educational level + French Deprivation index, reference category= least disadvantaged women (high educational level + high-SEP neighborhood; see also Figure A1).

The trend was less clear among women in the intermediate socioeconomic profile. The highest odds ratio [2.5 (1.5, 4.2)] was observed for women with the most disadvantaged socioeconomic profile (low educational level and low-SEP neighborhood).

Sensitivity analyses

Analyses stratified by age, smoking status, and overweight (Figure A3) or restricted to non-smokers (Table A3) showed a consistent increased risk of uncontrolled asthma with low educational level in each subgroup. The model adjusted for age plus smoking and BMI showed similar results than those from the main analysis (not shown). After multiple imputation, 649 additional women with 1 to 5 missing ACT-items (Figure 1) were included in the analyses. They reported significantly less asthma symptoms and had less asthma treatment reimbursement (Table A4). Using the imputed data (n=2,907), we observed similar results to those presented above, either using educational level [1.2 (1.1, 1.3) and 1.8 (1.6, 2.0) for medium and low educational level respectively, vs. high] or the combined-SEP index (Figure A4). Associations between educational level and SABA, performed on the whole population (Table A5), showed similar results as those described in Table 2.

DISCUSSION

To the best of our knowledge, this is the first study to investigate associations between SEP, defined at individual- and area-level, and asthma control among an elderly population with current asthma. Uncontrolled asthma, evaluated either by questionnaire or by reliever medication use, was more frequent among women with medium and low educational level compared with women with high educational level. A social gradient was observed for both estimates. The stratified analysis by ICS use showed that the association persisted only among women with no regular ICS treatment. Furthermore, individual and neighborhood SEP seemed to have independent impacts on asthma control. A higher risk of uncontrolled asthma was observed among women living in low-SEP neighborhoods compared to those living in high-SEP neighborhoods whatever their educational level, but also among women with low educational level living in high-SEP neighborhoods.

Our findings of social disparities in asthma control in this elderly women population were consistent with two previous studies using also individual educational level in younger populations with asthma [8,9]. However, in these two studies, they found a significant association only among participants with the lowest educational level. Interestingly, analysis stratified by ICS use showed that the association between low-SEP and uncontrolled asthma persisted only among women with no regular ICS treatment. Similarly, previous studies did not found any significant association between educational level and asthma control or symptoms frequency among patients with regular asthma maintenance treatment [12,37]. Such results suggest that the association between educational level and asthma control could partly be explained by an inappropriate asthma treatment or a suboptimal asthma management [26]. In our population, half women had no ICS reimbursement in the past 12 months but most of them had a controlled asthma according to the ACT, suggesting that they had rather a mild asthma that can be controlled with "as-needed SABA with no controller" according to GINA severity criteria [38]. However, almost one third of the women with uncontrolled asthma had no ICS reimbursement at all, a proportion relatively consistent with the literature [39] and we observed the highest social disparities for asthma control for these women. It is recognized that asthma is underdiagnosed and undertreated in elderly patients [40]. Older people with asthma tend to underestimate the seriousness of their disease [40] and do not spontaneously report their symptoms to the general practitioners [41]. The underreporting of asthma symptoms could be more frequent in elderly women with low education level, potentially because of lower expectations about their health [42], which could lead to inappropriate asthma treatment. Furthermore, it has been underlined that adherence to long term treatment in chronic illness is unequally distributed across SEP with poorer adherence among low-SEP patients [43].

Individual- and area-level SEP seem to have independent impacts on asthma control. First, when stratifying analyses by FDep, we observed a significant association between a low educational level and asthma control among women living in the higher SEP neighborhoods. Although interaction test was not statistically significant, negative health outcomes for low-SEP persons living in high-SEP neighborhoods were similarly observed in other study settings [32]. This result could reflect that resources and benefices generally associated with high-SEP neighborhoods could not be used or mobilized by the entire population [44]. For example, in France, in high-SEP urban neighborhoods,

doctors' fees are often higher than average and not fully reimbursed by social security system, putting the poorest people living in these neighborhoods out of the way. Cultural and social barriers may also contribute to fostering a lower access to care. According to the relative deprivation hypothesis [20,44], a large gap between some individuals' situations and the other people living nearby could affect health through psychosocial stress [45], which is a risk factor for poor asthma outcomes [46,47]. Second, when using the combined-SEP index, we found that women with the most disadvantaged socioeconomic profile had a two-fold higher risk of uncontrolled asthma compared with women with the least disadvantaged socioeconomic profile. Besides inappropriate asthma treatment, the cumulative impact of environmental hazards and social stressors (i.e. poor housing conditions, limited access to health-food, etc.) encountered by people who live in low-SEP neighborhoods might partly explain this result [48].

Our study, which is the first to investigate the role of both individual- and area-level SEP on asthma control among elderly women, has some potential limitations and several strengths. Due to low sample size in some strata of the combined-SEP index (9 categories), specific hypotheses were tested only for individual-SEP. The individual-SEP was assessed solely with educational level; however, we believe that it is the most appropriate SEP indicator in our population compared to income information for example (not available) [49]. Asthma treatments in France are fully covered by public health insurance when a doctor has prescribed the treatment, thus material disadvantage in access to asthma treatment are unlikely to explain social disparities in asthma control observed among non-regular ICS users [44]. The E3N population is not representative of the general French elderly population and has higher educational level and probably healthier conditions. However, even in this specific population, we found social disparities in asthma control with a marked social gradient. Regarding the asthma control definition, a substantial proportion of women did not complete the ACT at all (22%) but the sensitivity analysis using imputed data showed consistent results compared with those obtained with the complete-case analysis, although strength of the associations was slightly lower. One possible explanation is that women who did not respond to the ACT had no current asthma and therefore did not feel concerned by evaluating asthma control over the past 4 weeks. A misclassification between asthma and COPD may occur in our elderly population [40]. However, Sanchez et al. showed that the anticholinergic use was

low among E3N women suggesting that number of COPD cases is low in this population [27]. Also results from the sensitivity analysis restricted to women who never smoked were very similar to the findings in the entire population. The robustness of the results in a large population of women with current asthma is an important strength of our study. We used two different methods to assess asthma control with consistent results. SABA dispensed in a 1-year period reflect asthma control over the long term, whereas ACT, a multidimensional concept that encompasses at least three domains of the disease (symptoms, exacerbations, and activity limitations), reflects asthma control over a short period of time (few weeks) [50]. To evaluate asthma treatment (SABA and ICS), we used objective data from a comprehensive drug database which reduced potential reporting or recall biases and is particularly relevant in such an elderly population [51]. The relative homogeneity of E3N women in term of sociodemographic characteristics is also an asset to study contextual effects. Furthermore, there was a low percentage of movers in the population [30] and women had resided on average at least 20 years at their last known address (not shown), which limited a potential healthy mover effect [29].

In conclusion, our study suggested negative effects of both low individual- and area-level SEP on asthma control that could partly be explained by an inappropriate asthma treatment, care, or access to health services. To achieve the best management of asthma for elderly patients, a specific attention should be given not only to disadvantaged population and neighborhoods, but also to disadvantaged populations in affluent neighborhoods.

COMPETING INTERESTS

The authors declare that they have no conflicts of interest.

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APPENDIX A: SUPPLEMENTARY MATERIALS

METHODS

Multiple imputation:

We used the multiple imputation method to estimate asthma control among women with missing values on the Asthma Control Test. The multiple imputation aims to allow for the uncertainty about the missing data by creating several different plausible imputed data sets and combining results obtained from each of them (1).

Given the rather low proportion of missing data (10.3%) in the dataset (2) and the rejection of the missing completely at random assumption, we assumed a missing at random pattern of missing data and performed 20 imputations using PROC MI SAS procedure (3,4). The set of variables included in the imputation model is shown in Table A1 (5).

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283 TABLES

- Age
- Frequency of wheezing in the past 12 months
- Woken up with a feeling of chest tightness in the past 12 months
- Attack of shortness of breath (SOB) at rest in the past 12 months
- Attack of SOB after exercise in the past 12 months
- Woken by attack of SOB in the past 12 months
- Woken by attack of coughing in the last 12 months
- Symptoms exacerbations
- Difficulty in breathing
- Breathlessness (4 classes)
- Exacerbations in the last 12 months (deterioration in asthma requiring: treatment with an oral corticosteroid, or an emergency department visit or hospitalization or a change of asthma treatment)
- Asthma exacerbations >2 days in the past 12 months
- Seasonal asthma exacerbations in the past 12 months
- Asthma attacks in the past 3 months
- Woken up because of asthma in the past 3 months
- Breath difficulty frequency in the past 3 months
- Chronic obstructive pulmonary disease ever
- Rhinitis ever
- Eczema ever
- Smoking (never, ex and current smokers)
- Body Mass Index (<20,[20-25[,[25-30[,≥30kg/m²)
- Hospitalizations for asthma attacks in the past 12 months
- Emergency visit because of asthma in the past 12 months
- Medical visit for asthma in the past 12 months
- Asthma Quality of Life Questionnaire score, past 2 weeks
- Number of canisters of Short acting beta agonist dispensed in the past 12 months (claims database)

284 **Table A1 Set of variables included in the imputation model**

	High	Medium	Low	p
n (%)	867 (38.4)	1,141 (50.5)	250 (11.1)	
Age (years), m (SD)	69.0 ±5.8	70.1 ±6.1	70.9 ±6.5	<0.0001
Smoker ever	59.8	44.9	44.3	<0.0001
Overweight (BMI ≥25kg/m²)	35.9	43.7	55.1	<0.0001
FDep	56.3	41.3	36.1	<0.0001
High-SEP neighborhood				
Medium-SEP	26.6	33.2	29.5	
Low-SEP	17.1	25.5	34.4	
ACT ≤19	20.2	25.1	34.8	<0.0001
SABA*				
0 canister	67.0	61.0	68.0	0.001
1-6	31.6	36.5	27.2	
>6 canisters	1.5	2.5	4.8	
ICS*				
0 canister	49.2	43.4	51.6	0.02
1-3	21.0	21.0	18.8	
≥4 canisters	29.8	35.6	29.6	
AQLQ, m (SD)	5.9 ±1.0	5.8 ±1.0	5.5 ±1.1	<0.0001
Medical visit for asthma †	51.7	58.3	69.5	<0.0001

Table A2 Characteristics of the study population, by educational level (n=2,258)

Results are in percent unless otherwise stated, m (SD): mean (standard deviation);

BMI=body mass index, FDep=French Deprivation Index, SEP= socioeconomic position, ACT=Asthma Control Test, ICS=Inhaled corticosteroids, SABA=short acting beta2-agonists, AQLQ=Asthma Quality of Life Questionnaire;

* Number of canisters dispensed in the last 12 months;

† At least one medical visit for asthma in the last 12 months;

Missing data: smoking status n=14; BMI n=37; FDep n=21; Medical visit for asthma n=51; Asthma Quality of Life Questionnaire n=338.

		Educational level			
	n uncontrolled /controlled asthma	High (ref.)	Medium	Low	*p* for trend
All	283/826	1.00	1.23 (0.89; 1.70)	2.11 (1.36; 3.29)	0.002
Stratified by ICS reimbursed in the last 12 months (*p* interaction= 0.15)					
0 canister of ICS	81/401	1.00	0.93 (0.52; 1.65)	3.36 (1.69; 6.68)	0.003
1-3 canister(s)	63/171	1.00	1.29 (0.65; 2.55)	1.53 (0.56; 4.15)	0.36
≥4 canisters	139/254	1.00	1.23 (0.74; 2.03)	1.53 (0.73; 3.21)	0.25
Stratified by FDep (*p* interaction= 0.29)					
High-SEP neighborhood	126/377	1.00	1.63 (1.02; 2.64)	2.54 (1.26; 5.14)	0.005
Medium-SEP	85/257	1.00	1.00 (0.56; 1.79)	2.10 (0.93; 4.79)	0.15
Low-SEP	70/184	1.00	0.76 (0.38; 1.53)	1.35 (0.60; 3.04)	0.52

Table A3 Age-adjusted association between educational level and asthma control among never smokers (n=1,109)
OR (95%CI) for uncontrolled (Asthma Control Test ≤19) vs. controlled asthma (ACT>19);
ICS=inhaled corticosteroids, FDep = French Deprivation index (missing n=10), SEP: socioeconomic position.

	Women with no current asthma (n=758)	Women with current asthma (n=3,023)						
		Full data on ACT		Missing data on ACT				
		Controlled asthma	Uncontrolled asthma	1-4 missing ACT items		5 missing ACT-items		
n (%)	758 (100.0)	1,774 (58.7)	576 (19.1)	107 (3.5)	*p* value†	566 (18.7)	*p* value†	*p* value††
Age, m ±s	68.3 ±5.6	69.2 ±5.9	71.5 ±6.3	73.3 ±6.7	***	69.7 ±5.9	NS	***
BMI, ≥25kg/m²	27.3	41.0	45.8	35.9	NS	35.4	*	***
Smoking ever	48.3	51.2	46.9	43.0	NS	52.0	NS	NS
Asthma-like symptoms								
Wheezing and SOB	0.0	33.1	67.5	42.5	*	18.1	***	-
SOB at rest	0.0	19.3	50.0	29.7	*	16.7	NS	-
SOB after exercise	0.0	70.8	84.7	75.5	NS	81.2	***	-
Woken chest tight	0.0	33.8	67.5	42.3	NS	28.0	**	-
Woken SOB attack	0.0	14.2	44.0	20.0	NS	11.3	NS	-
ICS reimbursements*								
0 canister	84.0	52.4	27.8	44.9	**	76.7	***	***
1-3 canister(s)	9.8	19.8	23.4	10.3		11.6		
≥4 canisters	6.2	27.8	31.6	44.9		11.8		
SABA reimbursements*, m ±s	0.12 ±0.6	0.62 ±1.4	1.67 ±7	0.69 ±1.6	NS	0.29 ±1.1		
Low educational level	8.7	9.5	15.9	9.7	NS	10.8	NS	NS
Low-SEP neighborhood (FDep)	22.4	21.9	27.9	20.6	NS	19.1	NS	NS

Table A4 Women characteristics according to asthma status and response to ACT

Results are in percent unless otherwise stated, m ±sd: mean ±standard deviation;

ACT=Asthma Control Test, BMI=body mass index, SOB= shortness of breath, ICS=Inhaled corticosteroids, SABA=short acting beta2-agonists, FDep=French Deprivation Index, SEP: socioeconomic position;

* Number of canisters dispensed in the last 12 months;

† *p* value (t-test or chi2) comparing to women with controlled asthma;

†† *p* value (t-test or chi2) comparing to women with no current asthma;

Statistical significance: non-significant (NS) >0.05, * ≤0.05, ** ≤0.01, *** <0.0001.

	Canisters of SABA dispensed in the last 12 months (>6 canisters (ref.) vs. ≤6)
Educational level	
High (ref.)	1.00
Medium	1.6 (0.8; 3.0)
Low	2.9 (1.3; 6.3)
p for trend	0.009

Table A5 Age-adjusted association between educational level and number of canisters of SABA dispensed, imputed data (n=2,907)

OR (95%CI), SABA= short acting beta2-agonists.

FIGURES

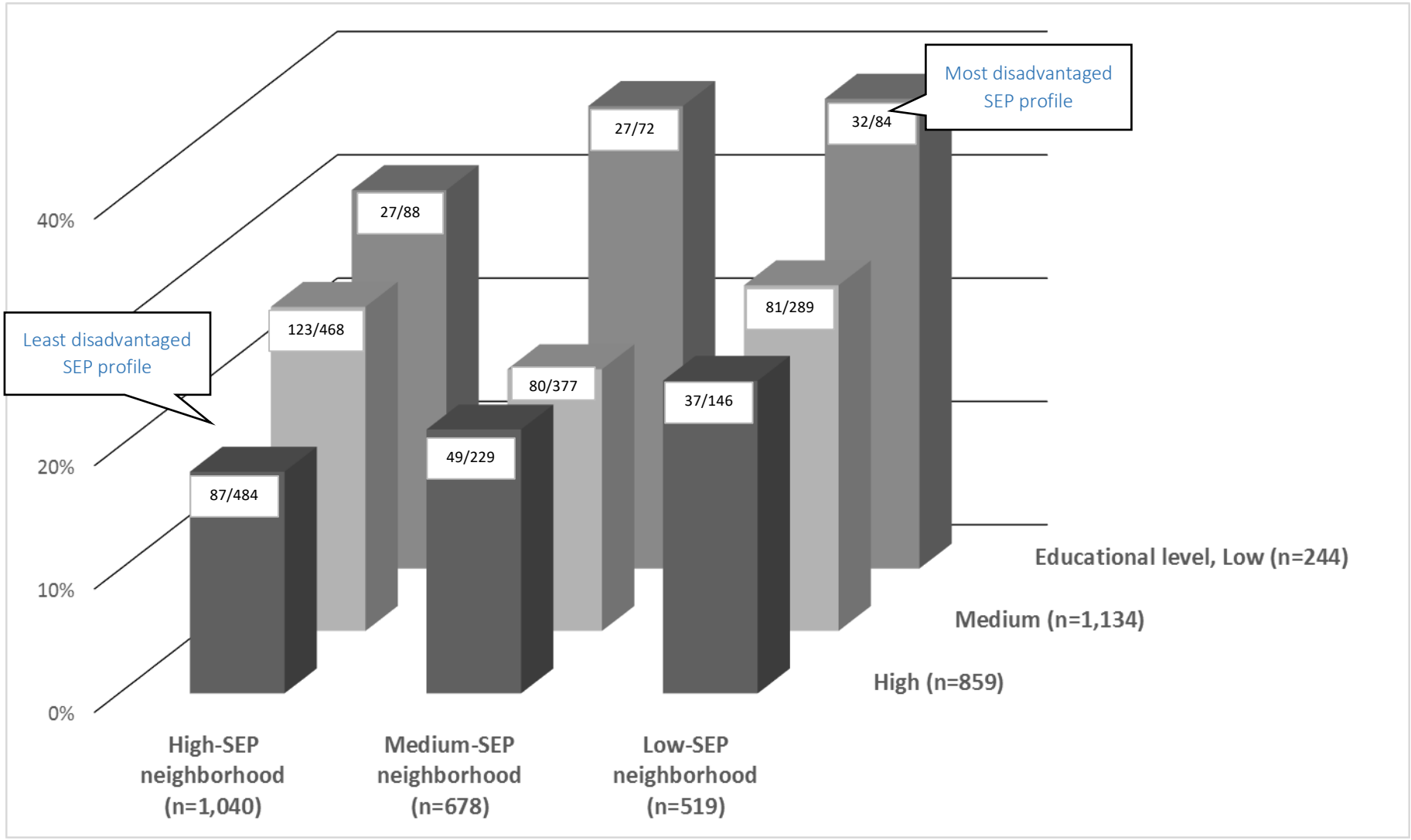

Figure A1 Percentage of women from the Asthma-E3N study with uncontrolled asthma (Asthma Control Test ≤19) by educational level and area-level SEP
Columns: French Deprivation Index; Lines: Educational level; Numbers on the bars correspond to: n uncontrolled asthma/n total.

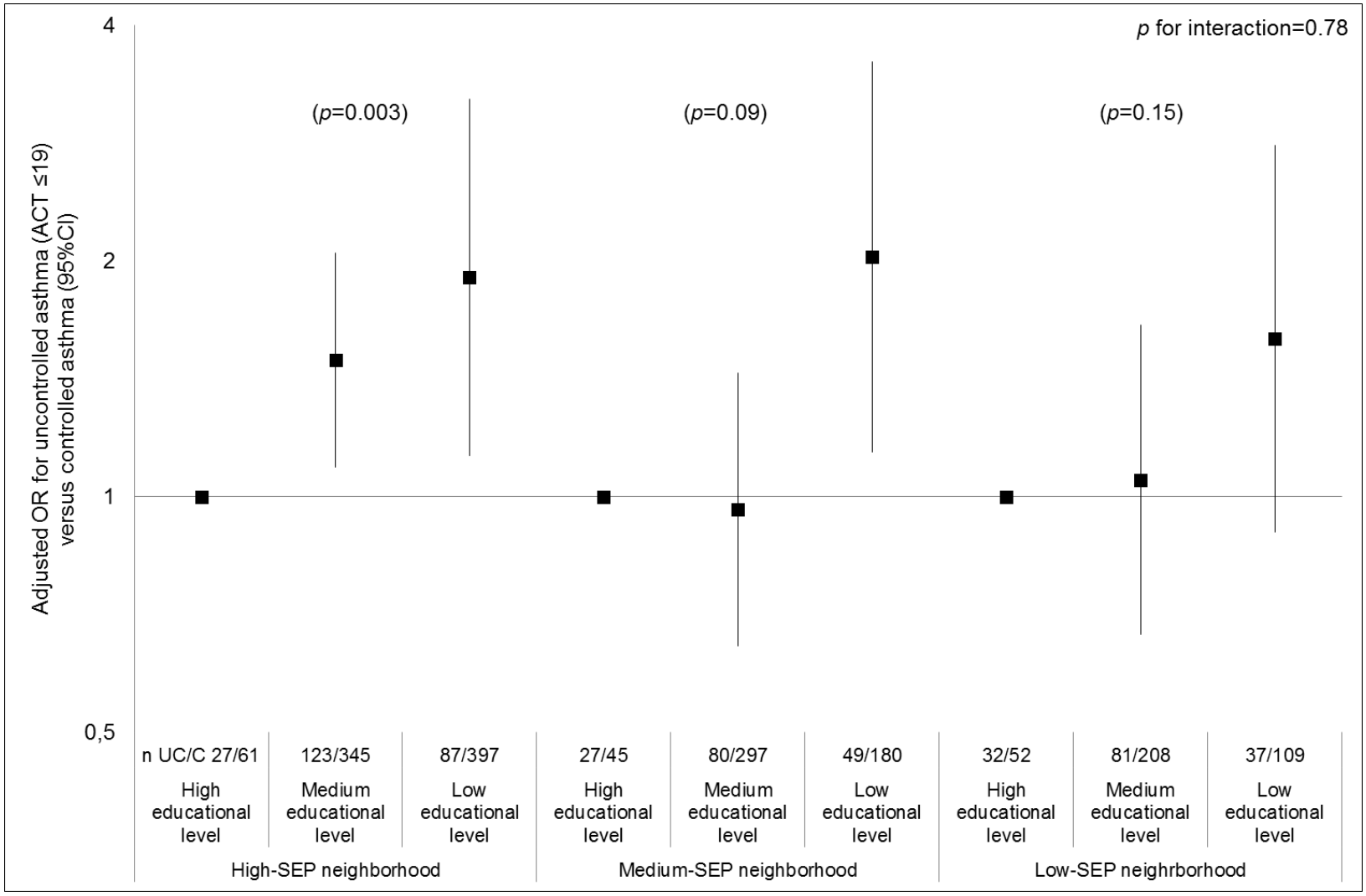

Figure A2 Age-adjusted association between educational level and asthma control, stratified by FDep (n=2,258)

OR (95%CI) for uncontrolled (Asthma Control Test ≤19) vs. controlled asthma (ACT>19); p for trend in brackets;

The Wald test was used as a formal test for interaction and test for linear trend was computed by considering educational level as a continuous variable;

FDep=French Deprivation index

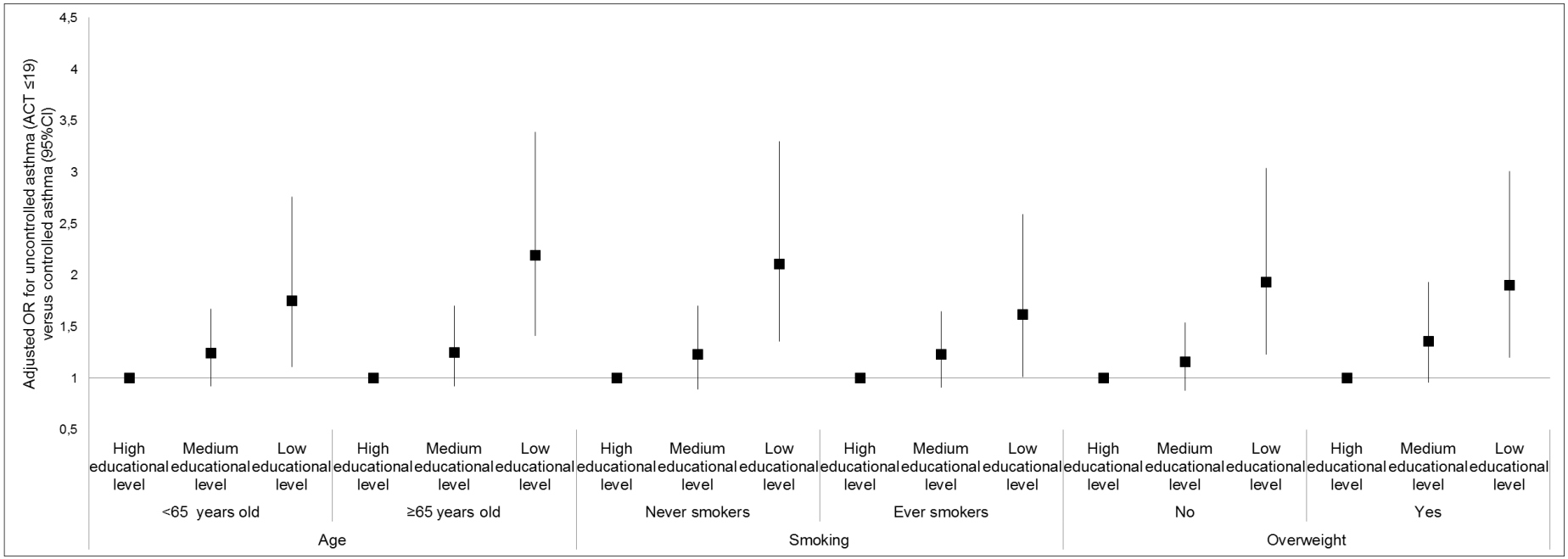

Figure A3 Age-adjusted association between educational level and asthma control (ACT), stratified by age, smoking and overweight

OR (95%CI) for uncontrolled (Asthma Control Test ≤19) vs. controlled asthma (ACT>19); Overweight (body mass index ≥25kg/m²);
P-value for interaction: age (<65 / >=65 years old) p=0.72; smoking (never/ever smokers) p=0.69; overweight (yes/no) p=0.38. The Wald test was used as a formal test for interaction.

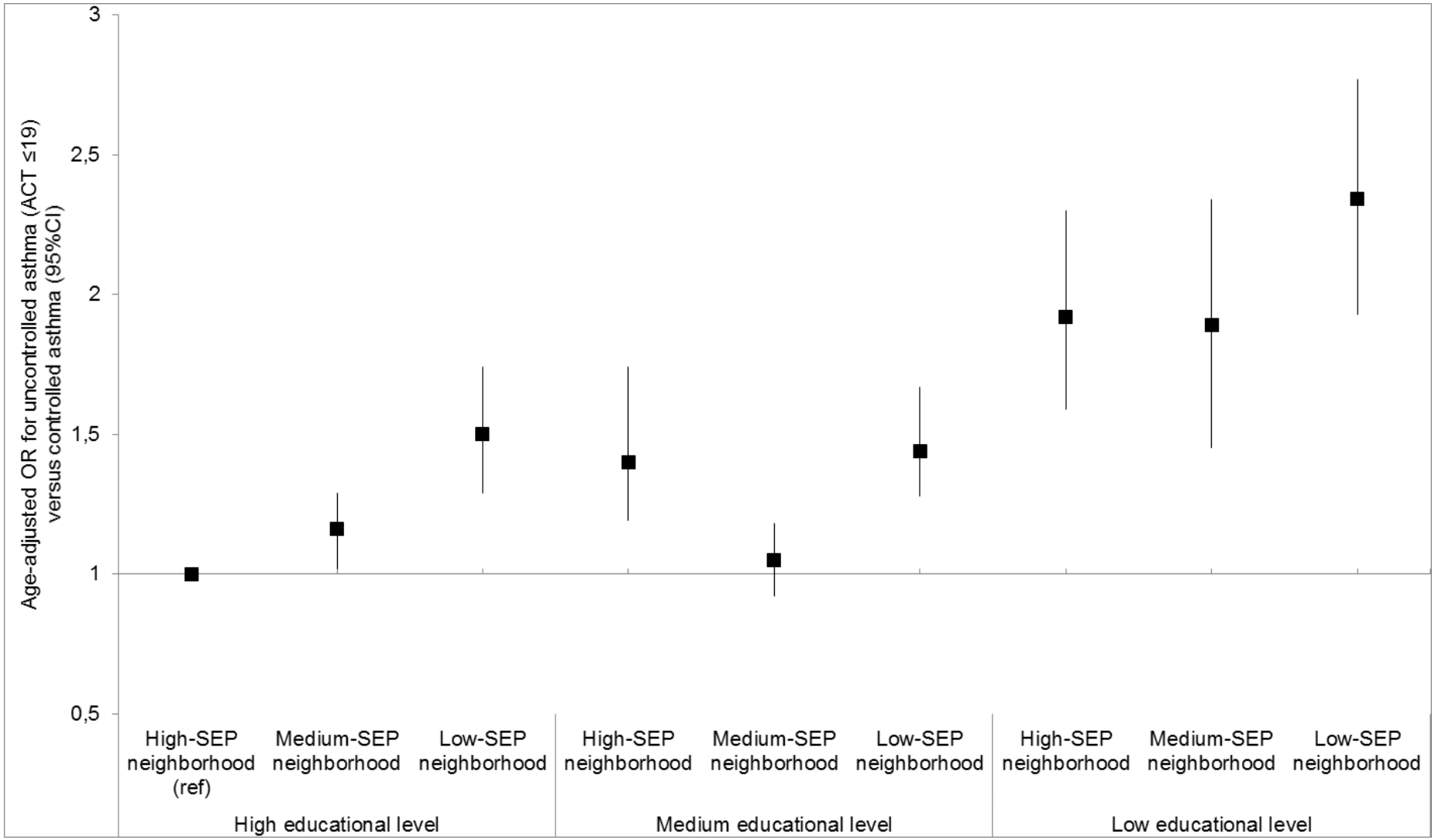

Figure A4 Age-adjusted association between combined-SEP[1] and asthma control (ACT), <u>imputed data (n=2,907)</u>

OR (95%CI) for uncontrolled (Asthma Control Test ≤19) vs. controlled asthma (ACT>19);

[1] Combined-SEP = educational level + French Deprivation index, reference category= least disadvantaged women (high educational level + high-SEP neighborhoods; see also Figure A1)