Healthy diet associated with better asthma outcomes in elderly women of the French Asthma-E3N study

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Abstract

Purpose: The impact of a healthy diet on asthma prevention and management, particularly among elderly women, remains poorly understood. We investigated whether a healthy diet would be associated with fewer asthma symptoms, and, among women with asthma, with reduced uncontrolled asthma and metabolic-related multimorbidity.

Methods: We included 12,991 elderly women (mean age=63years) from the Asthma-E3N study, a nested case-control study within the French E3N cohort. Negative binomial regressions were used to analyse associations between a healthy diet (evaluated by the Alternate Healthy Eating Index-2010 (AHEI-2010)) and a validated asthma symptom score, and logistic regressions to analyse associations between the AHEI-2010 with the asthma control test and multimorbidity profiles previously identified by clustering methods on medications used.

Results: After adjustment for potential confounders, a linear inverse association was found between the AHEI-2010 score and the asthma symptom score (mean score ratio (95% CI)=0.82 (0.75-0.90) for the highest versus lowest quintile; p for trend<0.0001). In addition, women in the highest versus lowest AHEI-2010 tertile were at a lower risk to belong to the "Predominantly metabolic multimorbidity-related medications profile" compared to the "Few multimorbidity-related medications" profile (OR=0.80 (0.63-1.00) for tertile 3; p for trend=0.05;n=3,474).

Conclusion: Our results show that a healthy dietary intake could play an important role in the prevention and management of asthma over the life course.

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Availability of data and material: Requests for access to data, statistical code, questionnaires, and technical processes may be made by contacting the corresponding author at marie-christine.boutron@gustaveroussy.fr

Code availability: Statistical Analysis Software (SAS) were used.

Authors' contributions: WAH, MCB and RV designed and conducted the research; WAH, AB, SC, OD, NL, NLM, BL, CM, VS, MCB and RV provided essential reagents or provided essential materials; WAH and RV analysed data or performed statistical analysis; WAH, MCB and RV wrote the manuscript and had primary responsibility for final content; WAH, AB, OD, VS, MCB and RV were involved in interpreting the results and editing the manuscript for important intellectual content; All authors read, edited and approved the final manuscript.

Ethics approval: The E3N study was authorized by the French National Commission for Data Protection and Privacy (CNIL n°106.246). E3N data enrichment with the MGEN database was granted ethical approval (CCTIRS n°13.794) and was authorized by the CNIL (n°327346V14).

80   **Consent to participate:** All participants signed informed consent in compliance with the rules of the

81   French National Commission for Computed Data and Individual Freedom (Commission Nationale

82   Informatique et Libertés).

83

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86   Informatique et Libertés).

Introduction

88 As recently underlined in the Lancet[1], given the immense societal and individual burden of asthma,

89 there is an urgent need to further develop novel strategies to limit the disease and its consequences.

90 Asthma control, the main objective of asthma management, remains suboptimal in roughly one

91 asthma patient out of two, with even higher rates among women[2, 3]. In this context, investigating

92 the role of modifiable lifestyle factors such as diet is key for the primary and secondary prevention of

93 this highly prevalent disease. While there are promising findings for possible dietary intervention to

94 reduce asthma in children[4], the impact of diet on asthma in adults, and even more so among the

95 elderly, remains largely unknown.

96 Among adults over 65 years, the prevalence of asthma varied from 4 to 13% [5], a rate likely

97 underestimated as it is frequently underdiagnosed in this age group[6]. The burden of asthma is

98 more significant in the elderly than in their younger counterparts[7, 8] with more hospitalisations[6,

99 8], and worse health-related quality of life[5, 6, 8] and asthma control[6]. Asthma in the elderly is a

100 phenotype of interest, especially in women because asthma tends to be more prevalent (9.9% vs

101 6.2%) and more severe in women than in men [9]. Obesity is now an established risk factor for

102 asthma[10, 11], with recent studies supporting the hypothesis that obesity is causally related to

103 asthma[12], and with a higher risk in elderly women as compared to men [13]. Furthermore,

104 multimorbidity is common in asthma patients, especially in the elderly[13]. Besides obesity, allergic

105 rhinitis, chronic obstructive pulmonary disease (COPD), gastroesophageal reflux, and sleep apnoea

106 syndrome that are the most common asthma-related multimorbidities, recent studies have

107 suggested that other chronic conditions such as cardiovascular diseases (CVD), metabolic syndrome,

108 or type 2 diabetes mellitus are also involved[14].

109 Although published studies on the diet–asthma association have traditionally focused on specific

110 nutrients or foods, it is important in terms of dietary recommendations to emphasize overall dietary

111 patterns rather than specific foods and nutrients to account for synergistic effects on health of foods

112 and nutrients within the overall diet[15]. Several dietary scores have been proposed to globally

113 assess diet quality and among them, the Alternate Healthy Eating Index-2010 (AHEI-2010) score, that

114 reflects a healthy diet, has been associated with a lower risk of chronic diseases[16]. Among middle-

115 aged women and men, a better adherence to a healthy diet evaluated by the AHEI-2010 was

116 associated with a lower asthma symptom score[17, 18] and better asthma control[18]. Being a

117 continuous measure of asthma, the asthma symptom score that has been associated with new onset

118 of asthma, provides more power to detect risk factors for asthma as compared to a dichotomous

119 definition[19]. Up to now, the role of a healthy diet on asthma symptoms, asthma control, and

120   asthma-related metabolic and cardiovascular morbidities, which are commonly associated with both

121   asthma[20] and an unhealthy diet[21], remains unknown among elderly women.

122   In a large study among elderly women, we aimed to investigate 1) the association between a healthy

123   diet assessed with the AHEI-2010, and the asthma symptom score and, 2) among patients with

124   asthma, the association of this dietary score with uncontrolled asthma and with specific metabolic

125   and cardiovascular multimorbidity-related medications profile.

Methods

Study population

The E3N study (Etude Epidémiologique auprès des femmes de la Mutuelle Générale de l'Education Nationale [MGEN]) is a prospective cohort which was initiated in 1990 to investigate risk factors of major non-communicable diseases in among 98,997 women affiliated to the a French national health insurance plan covering mostly teachers [22]. Since 1990, information on lifestyle and medical history has been collected approximately every 2 years by means of self-administered questionnaires.

Current analyses were conducted on women participating in the Asthma-E3N study, a nested case–control study on asthma within the E3N study, conducted in 2011. Briefly, 7,100 cases, e.g., women who gave a positive answer to the single question "Have you ever had an asthma attack?" in the main questionnaires at least once between 1992 and 2008, and 14,200 age-matched women without asthma, i.e., women who never reported any asthma attack between 1992 and 2008. Out of the 21,300 women invited to participate to the Asthma-E3N study, 19,404 women responded to the respiratory health questionnaire (91% response rate) (**Figure 1**). We excluded women who did not complete the food questionnaire in 1993 or in 2005, or had an implausibly high (top 1% of the ratio between energy intake and energy requirement (EIER)) or low (bottom 1% of the EIER ratio) total energy intake in 1993 or in 2005 (n=3,708). For the asthma symptom score, we further excluded women who did not answer to the asthma symptom questions (n=2,705). For "multimedication" profiles, we first selected women who reported "ever asthma" (n=3,474), and for asthma control, we further excluded women without current asthma (n=1,140). The analytic population included 12,991 women for the asthma symptom score, 2,587 women for the asthma control, and 3,474 women for the "multimedication" profiles.

Comparison of excluded vs included participants is presented in **eTable 1**. Excluded participants because of missing dietary data (n=3,708) were older than included participants(n=12,991). After adjustment for age, excluded participants had a lower educational level, were less often married, and had more missing data for asthma outcomes, as compared to included women. When additionally excluding participants because of missing data for the asthma symptom score (n=2,705), excluded women were significantly older than included participants. After adjustment for age, excluded participants consumed slightly more energy intake, were less physically active, were more often current smokers, had a lower educational level, and were more often overweight or obese, as compared to included women.

The study protocol was approved by the French Institutional Ethics Committee, and all participants provided their written informed consents.

Diet assessment

We calculated the AHEI-2010 from two validated semi-quantitative food history questionnaires administered in 1993 and 2005. The first part of the questionnaire was semi-quantitative and assessed consumption frequencies and portion sizes for the eight potential daily meals (breakfast, morning snack, aperitif before lunch, lunch, afternoon snack, pre-dinner aperitif, dinner, and after dinner snack) for 66 foods or food groups. Frequency was quantified in eleven potential categories: never or less than once a month; 1, 2, or 3 times a month, and 1 to 7 times a week. To facilitate the estimation of portion sizes, a photo booklet was also sent [23]. The second part of the questionnaire was qualitative and allowed detailing the consumption of specific foods within the food groups mentioned in the first part of the questionnaire.

The AHEI-2010 has been previously described [16]. It includes 11 items: 6 items considered as beneficial (vegetables, fruits, whole grains, nuts and legumes, long-chain Ω-3 fatty acids, and polyunsaturated fatty acids); 1 item for which moderate consumption is recommended (alcohol); and 4 items for which avoidance or low consumption is considered best (sugar-sweetened beverages and fruit juices, red/processed meat, *trans* fat, and sodium). In our study, we calculated a modified AHEI-2010 including all items except *trans* fat, which was not available. The total score ranged from 0 to 100, a higher score representing a healthier diet. When the sample size allowed it, we categorized the AHEI-2010 score in quintiles, otherwise in tertiles.

Asthma outcome assessment

The asthma symptom score has been previously proposed as a validated continuous measure of asthma in epidemiological studies[24, 25]. It is particularly relevant in epidemiological studies, as it can be used in participants both with and without asthma allowing integration of different asthma phenotypes and different levels of asthma prevention. It ranges from 0 to 5 according to the presence or absence of five respiratory symptoms during the past 12 months.

To assess asthma control, we used the asthma control test (ACT), a validated self-administered questionnaire based on five questions on activity limitations, frequency of symptoms, and frequency of use of quick-relief medication in the past 4 weeks[26]. The total ACT score ranges from 5 to 25 and we categorised asthma as controlled (ACT>19) versus uncontrolled (ACT≤19)[26]. Due to the large sample size, we further distinguished participants with a score of 25 and participants with a score of 20-24, as previously done [27]. Asthma control was therefore classified as: controlled asthma (ACT score =25), partly controlled asthma (ACT score between 20 and 24), and poorly controlled asthma (ACT score ≤19) [26].

192 Multimorbidity-related medication profiles in asthma were identified using latent class analysis (LCA)
193 based on data from the exhaustive MGEN drug database, and personal characteristics (body mass
194 index, sleep apnoea syndrome and smoking status), as previously described in detail[28]. Briefly,
195 non-hospital-delivered drug classes were identified over the 2 years before the Asthma-E3N
196 questionnaire from the exhaustive MGEN drug reimbursement database using the Anatomical
197 Therapeutic Chemical (ATC) code. Latent class analyses (LCA), *i.e.* a data-driven approach, were
198 performed to identify asthma groups characterised by specific multimorbidity-related medication
199 profiles. Three profiles were identified: 1) the "Few multimorbidity-related medications" profile, 2)
200 the "Predominantly allergic multimorbidity-related medications", and 3) "Predominantly metabolic
201 multimorbidity-related medications".

202

203 **Covariates**

204 Self-administered questionnaires were used to collect data on socio-demographic and lifestyle
205 characteristics. Energy intake was computed in 1993 and 2005 using a Food Composition Database
206 derived from the French Information Center on Food Quality (CIQUAL) and expressed in
207 kilocalories/day (kcal/day))[29]. Physical activity was assessed in 2005 using data from several
208 questions on different activities[30] and expressed in metabolic equivalent of tasks (METs) per week
209 (MET-hours/week). Smoking status, assessed in 2005, was categorized in 3 classes: never, former, or
210 current smoker. Educational level (< high school diploma, high school to 2-level university, 3- to 4-
211 level university, ≥ 5-level university) was collected in 1992. and marital status (married or not) was
212 collected in 1990. Having farmer parents was collected in 2007[31].

213 Body Mass Index (BMI), based on self-reported current weight and height and expressed in $kg/m2$,
214 was calculated in 2005 with the "last observation carried forward" method to take care of missing
215 data, and analyzed as a continuous variable or three categories: <20 (low weight, 20–25 (normal
216 weight) and ⩾25 kg/m^2 (overweight/obesity) using the WHO cut-off for overweight/obesity[32].

217

218 **Statistical analysis**

219 Since the asthma symptom score is a count outcome ranging from 0 to 5, with an excess of zero
220 counts, the strength of the association between the average of the AHEI-2010 score (quintiles) and
221 the asthma symptom score (count) was estimated by using negative binomial regression [33]
222 expressed as mean score ratios (MSRs) and 95% confidence intervals (95% CI). Change in the asthma
223 score is reported for an increase/decrease of 1 category (tertile or quintile) in the AHEI-2010 diet
224 score. Our main model was adjusted for age, energy intake, leisure-time physical activity, smoking

225 status, education level, marital status, and having farmer parents. To account for the study case-
226 control design, models were further adjusted for ever asthma; we also performed a stratified analysis
227 on asthma status, and tested the interaction between quintiles of AHEI-2010 and ever asthma.

228 Among participants with asthma, associations between tertiles of the AHEI-2010 with uncontrolled
229 asthma (binary outcome) and multimorbidity-related medications profiles (multicategorical
230 outcome) were evaluated by binary logistic and multinomial logistic regressions adjusted for age,
231 energy intake, leisure-time physical activity, smoking status, education level, marital status, and
232 having farmer parents. To handle missing data on ACT (n=729), multiple imputation was performed,
233 as previously reported[34]. The PROC MI SAS procedure was used to perform 20 imputations. We
234 conducted several sensitivity analyses for ACT: 1) using non-imputed data, 2) considering asthma
235 control in three categories (**eTable 2**), and 3) further adjusting for multimorbidity-related medication
236 profiles.

237 As obesity is a major risk factor for asthma[35] and healthy diet directly affects obesity[36], it can be
238 hypothesized that obesity acts as a mediator rather than a confounder in the diet-asthma
239 association[37]; therefore, models were not adjusted for BMI. To evaluate effect modification by BMI
240 in the diet-asthma association, we performed sensitivity analyses stratified on BMI and tested the
241 statistical significance of the interaction term. In addition, we used generalized structural equation
242 modeling (SEM), an exploratory approach that enables to test the existence of the hypothesized
243 relationships (i.e. "paths") between diet, BMI, and the asthma symptom score (**eFigure 1**) and
244 between diet, BMI, and asthma control (**eFigure 2**), while controlling for potential confounders[38],
245 using the gsem command in STATA. The association of the BMI with the AHEI-2010 was obtained by
246 linear regression model and measured by the difference in the expected BMI (β) according to
247 quintiles or tertiles of the AHEI-2010; associations between BMI and the AHEI-2010 with the asthma
248 symptom score were obtained by negative binomial regression models, and with asthma control
249 through logistic regression models. As obesity is one of the factors included in the LCA to derive the
250 multimorbidity-related medication profiles, we did not stratify on BMI nor apply SEM for this
251 outcome.

252 To account for potential residual confounding by smoking (never smokers, ex-smokers, current
253 smokers), we also conducted stratified analyses on the smoking status, and tested the statistical
254 significance of interaction term.

255 The test for trend across AHEI-2010 categories was calculated using quintile or tertile median values.

256 All tests were two-sided and p-values <0.05 were considered statistically significant. Analyses were
257 conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA) or STATA version 14.

258 **Results**

259 *Participant characteristics*

260 Participant characteristics are shown in **table 1** according to quintiles of the AHEI-2010. Women were
261 aged 63 years on average. Women in the highest quintile of the AHEI-2010 (i.e., healthier diet) were
262 older than those in the lowest quintile (i.e., unhealthier diet). After adjustment for age, women in the
263 highest quintile of the AHEI-2010 consumed fewer calories, were more physically active, less likely to
264 be current smokers, had more often farmer parents, and were less often overweight or obese, as
265 compared to women in the lowest quintile of the AHEI-2010.

266

267 *Association between the AHEI-2010 and the asthma symptom score*

268 Thirty-nine percent of women reported at least one asthma symptom. After adjustment for age
269 (table 2), women with higher AHEI-2010 scores had lower asthma symptom scores with MSRs (95%
270 CI) of 0.91 (0.83-0.99) for quintile 2 (Q2), 0.85 (0.78-0.93) for quintile 3 (Q3), 0.86 (0.79-0.94) for
271 quintile 4 (Q4), and 0.77 (0.71-0.85) for quintile 5 (Q5) as compared with the first quintile (p trend
272 <0.001). After adjustment for potential confounders (model 2), the association remained of similar
273 magnitude. Further adjustment for ever asthma led to a similar result (model 3).

274 In analyses stratified on BMI, MSRs remained below one in each category, and the interaction term
275 between the AHEI-2010 and BMI was not statistically significant (**figure 2**) (p for interaction=0.14).
276 Using SEM, we still reported a negative association between the AHEI-2010 and the asthma symptom
277 score, as well a significant negative dose-response relationship between the AHEI-2010 and BMI and
278 a significant positive association between BMI and the asthma symptom score (**eFigure 1**).

279 In analyses stratified on smoking status, associations remained statistically significant and of similar
280 magnitude in each category (**figure 2**) (p for interaction=0.98). Finally, when analyses were stratified
281 according to the asthma status, similar associations were reported between the AHEI-2010 and the
282 asthma symptom score among women with or without self-reported ever asthma (p for
283 interaction=0.22).

284 *Association between AHEI-2010 and uncontrolled asthma*

285 Among women with current asthma, 23% had uncontrolled asthma. After adjustment for age (**table**
286 **3**), only the second tertile of the AHEI-2010 was associated with a lower likelihood of uncontrolled
287 asthma: OR (95% CI) was 0.73 (0.56-0.94) for tertile 2, and 0.82 (0.64-1.06) for tertile 3, as compared
288 with tertile 1, p for trend=0.19. After adjustment for potential confounders (model 2), and further
289 adjustment for multimorbidity-related medication profiles (model 3), associations became weaker.
290 Similar findings were reported when using the non-imputed dataset (n=1,858; table 2) or the ACT
291 categorised into three categories (**etable 2**).

292 In analyses stratified on BMI, similar associations were reported, and the interaction term between
293 the AHEI-2010 and BMI was not statistically significant (**figure 3**) (p for interaction= 0.34). Using SEM,
294 we still reported no significant association between the AHEI-2010 and uncontrolled asthma, as well
295 a significant negative relationship between the AHEI-2010 and BMI, and a significant positive
296 association between BMI and uncontrolled asthma (**eFigure 2**).

297 After stratification for smoking, associations between the AHEI-2010 and uncontrolled asthma
298 remained of similar magnitude in each category with no statistical significance, except for AHEI-
299 tertile 2 in never smokers (**figure 3**) (p for interaction=0.64).

300

301 *Association between AHEI-2010 and multimorbidity-related medication profiles*

302 Among women with ever asthma, 44.7% belonged to the "Few multimorbidity-related medications ",
303 33% belonged to the "predominantly metabolic multimorbidity-related medications" profile, and
304 22.3% to the "predominantly allergic multimorbidity-related medications" profile. After adjustment
305 for age (**table 4**), women with higher AHEI-2010 score were at a lower risk to belong to the
306 "Predominantly metabolic multimorbidity-related medications" profile compared to the "Few
307 multimorbidity-related medications" profile: ORs (95% CI) were 0.94 (0.76-1.17) for tertile 2 and 0.75
308 (0.60-0.93) for tertile 3 vs. tertile 1 (p trend=0.01). Results remained similar after further adjustment
309 for potential confounders. By contrast, the AHEI-2010 was not associated with the "predominantly
310 allergic multimorbidity-related medications" profile.

311 After stratification for smoking (**figure 4**), similar associations were reported between the AHEI-2010
312 and multimorbidity-related medication profiles among never and ever smokers, with no interaction
313 between the AHEI-2010 and the smoking status (p=0.29 for the allergic profile, and 0.23 for the
314 metabolic profile).

Discussion

In this large study of more than 12,000 elderly women, a stronger adherence to a healthy diet evaluated by the AHEI-2010 was associated with a lower asthma symptom score, and among women with asthma, with disease characteristics associated with better asthma prognosis. These findings strengthen evidence supporting the promotion of a healthy diet to target reduction in asthma respiratory symptoms among elderly women, and confirm the importance of considering diet in the relation between asthma and comorbidities, especially cardiovascular diseases.

To our knowledge, five studies have investigated the association between the AHEI-2010 and asthma outcomes, among young[39] to middle-aged adults[17, 18, 40, 41], and using a dichotomous[39–41] or a continuous[17, 18] definition of asthma, and they reported mixed findings. The three studies that used a dichotomous definition of asthma, namely wheezing (yes/no), incident asthma (yes/no), or at least one out of three current asthma symptoms (yes/no), reported conflicting results. Using the asthma symptom score, two previous studies have investigated its association with the AHEI-2010 and reported that a healthy diet was associated with lower asthma symptoms[17, 18]. Regarding other dietary scores (a priori approach), the most studied are the Mediterranean diet score based on recommended foods or nutrients for disease prevention (such as the AHEI-2010) and the Dietary Inflammatory Index (DII) which relates to pathophysiological processes relevant to asthma (i.e. inflammation). To our knowledge, only one cross-sectional study reported a positive association between the Mediterranean diet and the asthma symptoms score in adults[18]. For the DII, one case-control[42] and two cross-sectional studies[41, 43] investigated associations with asthma in adults, and they all reported that a higher DII was associated with asthma [42] or current asthma[41, 43]. By contrast, using the *a posteriori* approach to derive data-driven dietary patterns (i.e., statistically derived independently of their relevance to any disease), at least 13 studies have looked at the association between dietary patterns, mostly derived using principal component analysis (PCA), and asthma symptoms or incidence in adults, and they have yielded mixed findings [44–47]. Our current findings are consistent with those based on younger populations and support the likely impact of a healthy diet in the prevention of asthma in elderly women. They extend results obtained from younger population and provide first evidence for the impact of a healthy diet in the prevention of asthma over the life course.

Regarding the impact of an overall healthy diet as a disease modifier, a healthier diet was associated in our study with a lower risk of uncontrolled asthma but the association did not reach statistical significance. Five studies have been published so far, all among middle-aged adults and overall, they reported mixed findings: three studies reported an association between an overall healthy diet and lower uncontrolled asthma[48–50], one reported no association[51] and one reported a borderline

349   significant association in women[18]. Published studies are very heterogeneous in term of tools used

350   to evaluate asthma control: two used the ACT[18, 50] and three used the asthma control

351   questionnaire (ACQ)[48, 49, 51]; in terms of tools used to collect dietary data: three used 24-h

352   dietary records[18, 48, 50], and two used a FFQ[49, 51]; and in terms of tools used to estimate the

353   overall diet: one used the Dietary Approaches to Stop Hypertension (DASH) score[48], one used the

354   DII[50], two used the Mediterranean diet score[49, 51], and one used the AHEI-2010[18]. All five

355   studies used dietary data collected at the same time as asthma control data or in the year before. In

356   our study, diet was evaluated by two validated semi-quantitative food history questionnaires

357   administrated in 1993 and 2005 whereas asthma control was evaluated in 2011. The assessment of

358   diet does not cover the ACT window of exposure and it is likely that participants may have modified

359   their diet between 1993 and 2011. Anyhow, it has been shown that diet remains globally stable in

360   this specific population, namely elderly women with a high level of education[52], and we used the

361   average diet between 1993 and 2005 which is likely more representative of the usual diet as

362   compared to one assessment only. Although diet might be a modifiable risk factor that could be

363   targeted to help reduce asthma exacerbations and reach a good level of asthma control, its potential

364   role on asthma control remains unclear, particularly among elderly women.

365   Besides allergic-related morbidities, that are common especially in childhood asthma, it has been

366   more recently reported that mechanisms involved in adult-onset asthma also include several

367   metabolic and inflammatory pathways also related to other chronic conditions such as obesity, the

368   metabolic syndrome, type 2 diabetes mellitus, or CVD[53]. Although the underlying mechanisms

369   remain unknown, it has been suggested that asthma and CVD share common risk factors such as

370   smoking, obesity, or more recently reported, air pollution exposure[54], consistent with common

371   etiological pathways. The AHEI-2010 is based on a comprehensive review to identify foods and

372   nutrients that have been consistently associated with lower risks of CVD, cancer, and type 2 diabetes

373   in clinical and epidemiological investigations[16]. The AHEI-2010 also captures additional information

374   on diet quality that may further decrease the risk of metabolic diseases[16]. Our findings provide

375   further evidence for a major role of an unhealthy diet as a common risk factor between asthma and

376   CVD. A better understanding of the role of a healthy diet could lead to risk management strategies

377   for patients with asthma to reduce their CVD risk.

378   Several hypotheses and mechanisms have been raised to explain the role of diet in asthma, including

379   oxidative stress and inflammation, and more recently, vitamin D, epigenetic regulation, and

380   imbalance in the gut microbiome [55]. Asthma is a chronic inflammatory disease of the airways, and

381   endogenous reactive oxygen species have been implicated in its pathogenesis[56]. It has been

382   extensively reported that a better quality diet (high in fruit, vegetables, whole grains, and legumes as

383 reflected by a high AHEI-2010) is associated with lower inflammatory biomarkers[57], and more

384 recently with a reduction in short-chain fatty acids[58] (produced by bacteria in the gut during

385 fermentation of fibre from dietary plant matter) known to reduce airway inflammation[59]. In this

386 manner, a dietary intervention based on a fibre-rich healthy diet might be relevant for both primary

387 and secondary prevention of asthma.

388 Diet, physical activity, and body composition are nutritional factors that are closely interrelated (at a

389 given time t) but also time-dependent, which makes it difficult to disentangle their separate effects

390 on asthma outcome[60]. Regarding interrelations (at a given time t), although obesity can result from

391 multiple factors (e.g., genetic predispositions, certain disease status, or medication use), it is most

392 often a result of unhealthy lifestyle, including excessive dietary energy intakes and insufficient

393 physical activity[61]. It has been shown that individuals with lower overall diet quality have higher

394 risk of obesity[36]. The established evidence that links diet to obesity and that links obesity to

395 asthma[10] and asthma control[62] can illustrate the role of obesity as a potential mediator in the

396 diet–asthma association[60]. In this context, several studies provided results with and, in addition,

397 without adjustment for BMI[63, 64] but it could lead to biased results[65]. Some novel analyzing

398 approaches, such as the counterfactual approach, provide a new tool to face the above issues in

399 mediation analysis[66]. To our knowledge, only two studies were conducted in the context of

400 nutritional factors and asthma, suggesting that BMI partly mediates the association between high

401 cured meat intake and worsening asthma symptoms over time[67], but does not mediate the

402 association between overall diet quality—assessed using the AHEI-2010—and improved asthma

403 symptoms[17]. From a longitudinal perspective, interrelations between nutritional factors and

404 asthma are also time-dependent. Indeed, in addition to the potential role of each nutritional factor at

405 a given time t on asthma at a time t+1, asthma at time t − 1 may have modified nutritional factors at

406 time t (e.g., asthma can lead to a decrease in physical activity), and each nutritional factor at time t −

407 1 may have modified another nutritional factor at time t (e.g., overweight/obesity can lead to

408 modifying dietary and/or physical activity behaviors). To our knowledge, only one study has been

409 conducted in the context of the time-dependent associations between physical activity, BMI and

410 asthma (also using data from the E3N study) and suggested an independent causal deleterious effect

411 of overweight and obesity on current asthma, but no independent causal effect of physical activity

412 on current asthma[30]. Although longitudinal data are warranted to fully address these issues, our

413 models stratified according to BMI yielded to similar associations between diet and asthma

414 outcomes, and estimates obtained from SEM and those obtained from standard models are very

415 close, showing that BMI is unlikely a major modifier or mediator in the association between diet with

416 asthma outcomes.

417   Our study has several strengths and limitations. First, our analysis was cross-sectional. However, our

418   findings are based on a large sample size, which allows accounting for several potential confounders

419   and performing stratified analyses to address the robustness of the findings. Secondly, diet was

420   evaluated in 1993 and 2005, and asthma in 2011. Although participants may have modified their diet

421   between 1993 and 2011, it has been shown that the diet remains globally stable in this specific

422   population of elderly women with a high level of education[52]. Although a substantial proportion of

423   women did not complete the ACT (28%), analyses with and without imputed data yielded similar

424   results. Besides, associations were consistent in several sub-populations and after adjustment for

425   many potential confounders. In addition, we used validated tools to estimate asthma symptoms[24,

426   25] and asthma control[26] as well as the diet[68]. Secondly, we acknowledge that the main source

427   of disease misclassification among this population of elderly women is probably misdiagnosis of

428   COPD, and that potential overlap between asthma and COPD may have contributed to the

429   association between the AHEI-2010 and asthma. However, we used the asthma symptom score that

430   measures specific symptoms of asthma (and not of COPD) rather than a dichotomous definition of

431   asthma which is more likely to include COPD patients. Moreover, similar associations were observed

432   whatever the smoking status, especially among never smokers who are less likely to suffer from

433   COPD. We also acknowledge that the association between a healthy diet and the "Predominantly

434   metabolic multimorbidity-related medications" profile might be due in part, to obesity. Indeed,

435   obesity (e.g., BMI ≥30 kg/m^2) was included in the LCA to identify asthma groups, and whereas the

436   "Few multimorbidity-related medications" profile and the "Predominantly allergic multimorbidity-

437   related medications" include respectively 3.4% and 1.5% of obese women, the "Predominantly

438   metabolic multimorbidity-related medications" profile includes 34% of obese women. Finally, the

439   relative homogeneity of the studied population (e.g., elderly women with mostly high educational

440   levels) actually helps with causal inferences about the relation between healthy diet and asthma

441   outcomes because the comparability of the high and low dietary score groups will be higher than in a

442   more heterogeneous populations (i.e., less potential for residual confounding).

443

444   In this elderly female population, we observed that a healthier dietary intake was associated with

445   lower asthma symptoms, and among women with asthma, lower risk to belong to a metabolic

446   multimorbidity-related medication profile. Overall, our findings show that a healthy diet may play an

447   important role in the prevention and management of asthma over the life course. There is a need for

448   longitudinal studies and RCTs to help understand better the role of the AHEI-2010 diet for the

449   primary and secondary prevention of asthma among elderly. More studies are also warranted to

450   better understand the role of a healthy diet as a common risk factor for patients with asthma to

451   better reduce their CVD risk, which could lead to risk management strategies among those patients.

452   Lastly, as the investigation of nutritional factors as a whole (diet, physical activity, obesity) is highly

453   relevant in the etiology of asthma and its control, both in terms of understanding the underlying

454   mechanisms and in terms of guiding efficient multidimensional public health interventions, there is a

455   crucial need for further prospective studies to address this issue.

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652

Table 1   Baseline characteristics of women according to quintiles of the AHEI-2010 diet score (n=12,991)

	AHEI-2010 diet score					P for trend	P for trend#
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5		
AHEI-2010 diet score, min-max	13.0-40.4	40.5-45.3	45.4-49.5	49.6-54.3	54.4-77.0		
AHEI-2010 diet score	35.9 (3.8)	43.1(1.4)	47.4 (1.2)	51.8 (1.3)	58.8 (3.7)		
Component score of AHEI-2010							
Vegetables, servings/d	5.4 (2.7)	6.2 (2.6)	6.6 (2.5)	6.9 (2.6)	7.4 (2.5)	**<0.0001**	**<0.0001**
Fruits, servings/d	1.4 (0.8)	1.7 (0.9)	1.9 (1.0)	2.1 (1.0)	2.5 (1.1)	**<0.0001**	**<0.0001**
Cereal fibers, g/d	2.2 (2.5)	2.7 (2.9)	3.2 (3.2)	3.8 (3.4)	4.7 (3.7)	**<0.0001**	**<0.0001**
Sugar-sweetened drinks and fruit juice, servings/d	0.8 (0.7)	0.6 (0.6)	0.5 (0.6)	0.4 (0.5)	0.3 (0.4)	**<0.0001**	**<0.0001**
Nuts and legumes, servings/d	0.5 (0.5)	0.7 (0.6)	0.7 (0.7)	0.8 (0.7)	1.0 (0.8)	**<0.0001**	**<0.0001**
Red and processed meat, servings/d	1.4 (0.6)	1.2 (0.6)	1.1 (0.5)	1.0 (0.5)	0.9 (0.5)	**<0.0001**	**<0.0001**
Long-chain n-3 fatty acids, mg/d	38.8 (24.3)	41.9 (27.0)	43.4 (28.9)	45.2 (30.0)	50.3 (36.3)	**<0.0001**	**<0.0001**
PUFA, % of energy	5.1 (1.3)	5.5 (1.3)	5.9 (1.4)	6.3 (1.5)	6.9 (1.7)	**<0.0001**	**<0.0001**
Sodium, mg/d	2,971 (841)	2,816 (795)	2,729 (763)	2,605 (719)	2,460 (679)	**<0.0001**	**<0.0001**
Alcohol, drinks/d	2.1 (2.2)	1.6 (1.7)	1.4 (1.4)	1.2 (1.1)	1.0 (0.8)	**<0.0001**	**<0.0001**
Age (years)	63.1 (6.2)	63.1 (6.1)	63.4 (6.2)	63.6 (6.2)	63.4 (5.9)	**0.01**	
Energy intake (kcal/d)	2,413 (565)	2,345 (549)	2,274 (525)	2,206 (494)	2,166 (480)	**<0.0001**	**<0.0001**
Leisure-time physical activity (METs/week)	58.8 (50.7)	61.1 (50.4)	61.9 (52.1)	60.5 (48.1)	63.3 (49.2)	**0.03**	**0.01**
Smoking status						**<0.0001**	**<0.0001**
Never smoker	1,205 (46.6)	1,291 (49.7)	1,237 (47.8)	1,269 (49.3)	1,324 (50.0)		
Occasional ex-smoker	276 (10.7)	299 (11.5)	311 (12.0)	307 (11.9)	284 (10.7)		
Regular ex-smoker	647 (25.0)	659 (25.4)	722 (27.9)	749 (29.1)	784 (29.6)		
Occasional current smoker	35 (1.4)	32 (1.2)	30 (1.2)	24 (1.0)	34 (1.3)		
Regular current smoker	172 (6.7)	147 (5.7)	123 (4.8)	83 (3.2)	105 (3.9)		
Missing	249 (9.6)	170 (6.5)	162 (6.3)	142 (5.5)	119 (4.5)		

Educational level						0.14	0.07
< high school diploma	256 (9.9)	251 (9.7)	239 (9.3)	445 (9.4)	498 (8.0)		
High school to 2-level university	1,257 (48.7)	1,286 (49.5)	1,301 (50.3)	1,343 (52.2)	1,340 (50.5)		
3- to 4-level university	504 (19.5)	471 (18.1)	480 (18.6)	477 (18.5)	517 (19.5)		
≥ 5-level university	481 (18.6)	522 (20.1)	483 (18.7)	445 (17.3)	498 (18.8)		
Missing	86 (3.3)	68 (2.6)	82 (3.1)	66 (2.6)	84 (3.2)		
Marital status						0.19	0.65
No	438 (17.0)	424 (16.3)	379 (14.7)	400 (15.5)	428 (16.2)		
Yes	2,044 (79)	2,098 (80.8)	2,112 (81.7)	2,098 (81.5)	2,123 (80.1)		
Missing	102 (4.0)	76 (2.9)	94 (3.6)	76 (3.0)	99 (3.7)		
Having farmer parents						**<0.0001**	**<0.0001**
No	2,304 (89.1)	2,253 (86.7)	2,202 (85.2)	2,228 (86.6)	2,249 (84.9)		
Yes	206 (8.0)	269 (10.4)	298 (11.5)	278 (10.8)	332 (12.5)		
Missing	74 (2.9)	76 (2.9)	85 (3.3)	68 (2.6)	69 (2.6)		
BMI (kg/m²)						**<0.0001**	**<0.0001**
< 20	288 (11.1)	309 (11.9)	312 (12.1)	314 (12.2)	362 (13.6)		
20-24.9	1,354 (52.4)	1,408 (54.2)	1,435 (55.5)	1,468 (57.0)	1,570 (59.3)		
25-29.9	716 (27.7)	673 (25.9)	658 (25.5)	628 (24.4)	594 (22.4)		
≥ 30	226 (8.8)	208 (8.0)	180 (6.9)	164 (6.4)	124 (4.7)		
BMI (kg/m²)	24.3 (4.1)	24.1 (4.0)	24.0 (4.0)	23.8 (3.7)	23.4 (3.5)	**<0.0001**	**<0.0001**
Asthma symptom score¶						**<0.0001**	**<0.0001**
0	1502 (58.1)	1540 (59.3)	1560 (60.3)	1581 (61.4)	1704 (64.3)		
1	680 (26.3)	733 (28.2)	693 (26.8)	661 (25.7)	678 (25.6)		
2	178 (6.9)	170 (6.5)	185 (7.2)	180 (7.0)	129 (4.9)		
≥3	224 (8.7)	155 (6.0)	147 (5.7)	152 (5.9)	139 (5.2)		
Asthma control test+						0.20	0.13
>19		490 (75.3)		501 (79.2)	440 (76.7)		
≤19		161 (24.7)		132 (20.8)	134 (23.3)		

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Multimorbidity-related medication profiles+				0.07	**0.03**
"Few multimorbidity-related medications"	510 (43.3)	508 (44.0)	532 (46.6)		
"Predominantly allergic multimorbidity-related medications"	391 (33.2)	380 (32.9)	376 (32.9)		
"Predominantly metabolic multimorbidity-related medications"	276 (23.5)	267 (23.1)	234 (20.5)		

Data are presented as n (%) or mean (SD) unless otherwise stated. P for trend were calculated using the quintile median values.

Age-adjusted models.

¶ Asthma symptom score: number of respiratory symptoms during the past 12 months: 1) breathless while wheezing; 2) woken up with chest tightness; 3) attack of shortness of breath at rest; 4) attack of shortness of breath after exercise; and 5) woken by attack of shortness of breath. Each item is scored from zero to one and the total asthma symptom score ranges from zero to five [21].

+ For ACT and multimorbidity-related medications profiles, distributions are given according to tertiles of the AHEI-2010 diet core (instead of quintiles). ACT: asthma control test, based on five questions in the last 4 weeks on: 1. activity limitations (does asthma keep you from getting as much done at work, school or at home, "some of the time" to "all of the time"); 2. shortness of breath ("three to six times per week" to "more than once daily"); 3. woken up by asthma symptoms at night ("once per week" to "every night"); 4. use of a β-agonist inhaler ("two times per week" to "three or more times daily"); and 5. self-rated asthma control ("somewhat controlled" to "not controlled at all"). Each item is scored from one to five and the total ACT score ranges from five to 25. Asthma control was classified into two categories based on ACT score (>19: controlled vs. ⩽19: uncontrolled) [22].

Multimorbidity-related medications profiles: using a clustering method, we previously identified three multimedication profiles among women with asthma: a "Few multimorbidity-related medications" profile, a "Predominantly allergic multimorbidity-related medications" profile, and a "Predominantly metabolic multimorbidity-related medications" profile [23].

Table 2   Association between the AHEI-2010 diet score (quintiles) and the asthma symptom score (n=12,991)

	N	AHEI-2010, mean (sd)	Age-adjusted model 1 MSR (95% CI)	Multivariable-adjusted model 2# MSR (95% CI)	Multivariable-adjusted model 3¶ MSR (95% CI)
AHEI-2010 diet score	12,991				
Quintile 1	2,584	35.9 (3.8)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Quintile 2	2,598	43.1 (1.4)	**0.91 (0.83-0.99)**	**0.92 (0.84-1.00)**	**0.92 (0.85-1.00)**
Quintile 3	2,585	47.4 (1.2)	**0.85 (0.78-0.93)**	**0.85 (0.78-0.93)**	**0.87 (0.80-0.95)**
Quintile 4	2,574	51.8 (1.3)	**0.86 (0.79-0.94)**	**0.87 (0.79-0.95)**	**0.90 (0.82-0.98)**
Quintile 5	2,650	58.8 (3.7)	**0.77 (0.71-0.84)**	**0.80 (0.73-0.88)**	**0.82 (0.75-0.90)**
P for trend			**< 0.0001**	**< 0.0001**	**< 0.0001**

MSR: mean score ratio.

P for trend were calculated using the quintile median values.

Multivariable-adjusted model 2 includes age, energy intake, physical activity, smoking, educational level, marital status and having farmer parents.

¶ Multivariable-adjusted model 3 includes model 2 variables (see above) plus ever asthma.

Table 3   Association between the AHEI-2010 diet score (tertiles) and uncontrolled asthma

	n	AHEI-2010, mean (sd)	Age-adjusted model 1 OR (95% CI)	Multivariable-adjusted model 2# OR (95% CI)	Multivariable-adjusted model 3* OR (95% CI)
Uncontrolled asthma (after imputation)¶	2,587				
AHEI-2010 tertile 1	895	38.3 (4.4)	1.00 (ref)	1.00 (ref)	1.00 (ref)
AHEI-2010 tertile 2	884	47.4 (2.0)	**0.73 (0.56-0.94)**	**0.72 (0.55-0.94)**	**0.73 (0.55-0.98)**
AHEI-2010 tertile 3	808	56.1 (4.3)	0.82 (0.64-1.06)	0.84 (0.65-1.10)	0.86 (0.65-1.12)
P for trend			0.11	0.19	0.24
Uncontrolled asthma (before imputation)	1,858				
AHEI-2010 tertile 1	651	38.2 (4.5)	1.00 (ref)	1.00 (ref)	1.00 (ref)
AHEI-2010 tertile 2	633	47.4 (2.0)	**0.76 (0.57-1.00)**	**0.75 (0.57-1.00)**	**0.76 (0.57-1.00)**
AHEI-2010 tertile 3	574	55.9 (4.2)	0.87 (0.66-1.14)	0.89 (0.67-1.18)	0.92 (0.69-1.2)
P for trend			0.32	0.39	0.51

P for trend were calculated using the tertile median values.

¶ Analysis after using multiple imputation to estimate ACT missing values, as in previous analyses in this population [40]. See online supplement for details.

Multivariable-adjusted model 2 includes age, energy intake, physical activity, smoking, educational level, marital status and having farmer parents.

* Multivariable-adjusted model 3 includes model 2 variables (see above) plus multimorbidity-related medication profiles.

Table 4   Association between the AHEI-2010 diet score (tertiles) and multimorbidity-related medication profiles (n = 3,474)

	Multimorbidity-related medication profiles								
	"Few multimorbidity-related medications" profile			"Predominantly allergic multimorbidity-related medications" profile			"Predominantly metabolic multimorbidity-related medications" profile		
	n	AHEI-2010, mean (sd)	OR (95% CI)	n	AHEI-2010, m (sd)	OR (95% CI)	n	AHEI-2010, m (sd)	OR (95% CI)
Age-adjusted model 1	1,550			1,147			777		
AHEI-2010 tertile 1	510	38.7 (4.1)	1.00 (ref)	391	38.1 (4.5)	1.00 (ref)	276	38.1 (4.3)	1.00 (ref)
AHEI-2010 tertile 2	508	47.3 (2.0)	1.00 (ref)	380	47.5 (2.1)	0.97 (0.80-1.17)	267	47.3 (2.0)	0.94 (0.76-1.17)
AHEI-2010 tertile 3	532	56.4 (4.4)	1.00 (ref)	376	56.2 (4.3)	0.91 (0.75-1.10)	234	55.5 (4.2)	**0.75 (0.60-0.93)**
P for trend						0.32			**0.01**
Multivariable-adjusted model 2#	1,550			1,147			777		
AHEI-2010 tertile 1	510	38.7 (4.1)	1.00 (ref)	391	38.1 (4.5)	1.00 (ref)	276	38.1 (4.3)	1.00 (ref)
AHEI-2010 tertile 2	508	47.3 (2.0)	1.00 (ref)	380	47.5 (2.1)	0.99 (0.81-1.20)	267	47.3 (2.0)	0.96 (0.77-1.21)
AHEI-2010 tertile 3	532	56.4 (4.4)	1.00 (ref)	376	56.2 (4.3)	0.96 (0.79-1.17)	234	55.5 (4.2)	**0.80 (0.63-1.00)**
P for trend						0.64			**0.05**

P for trend were calculated using the tertile median values.
#+ Multivariable-adjusted model 2 includes age, energy intake, physical activity, smoking, educational level, marital status and having farmer parents.

Figure legends

Figure 1   Study design and flow chart of participants
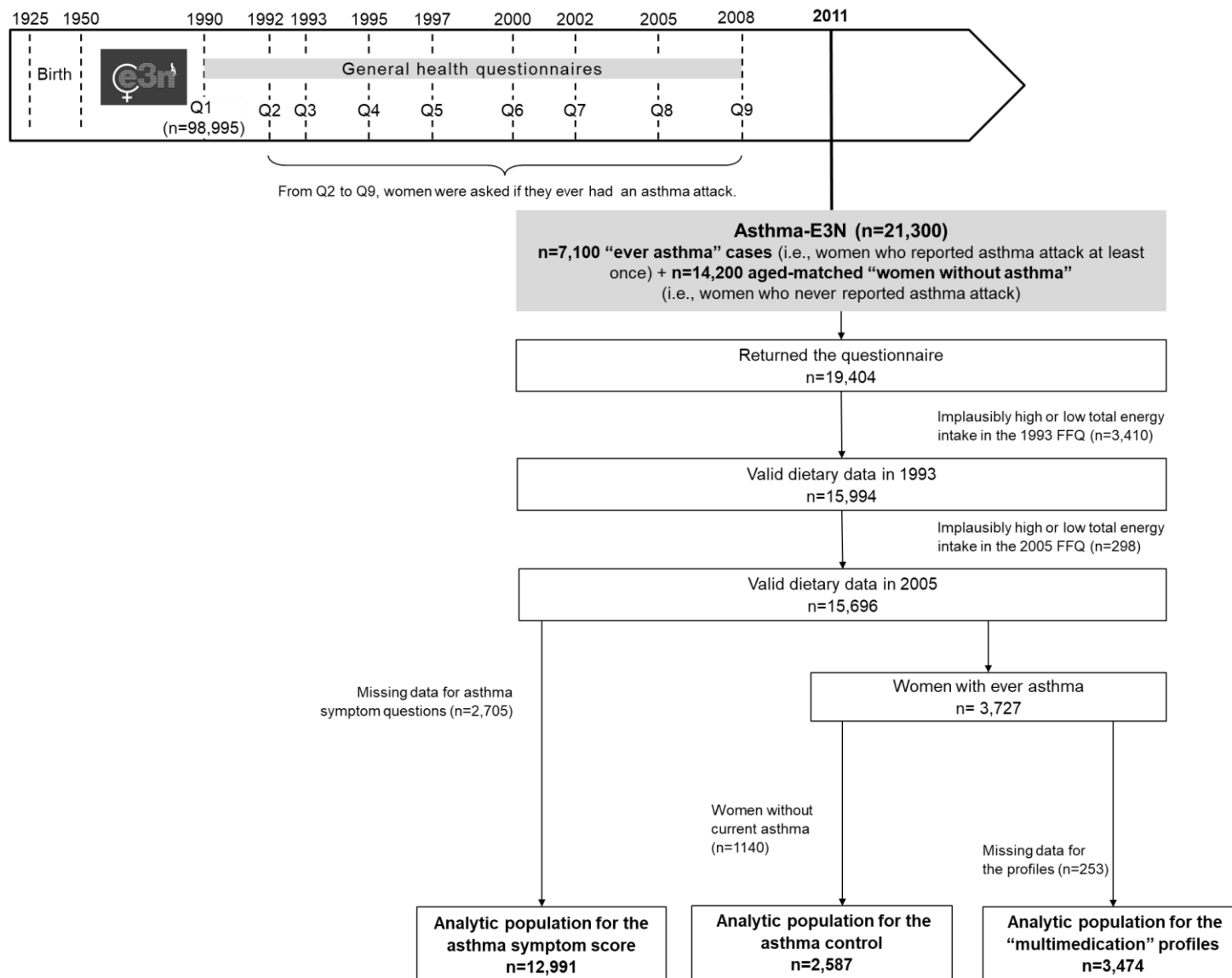

Figure 2   Associations between quintiles of the AHEI-2010 diet score and the asthma symptom score, stratified according to smoking status, body mass index (BMI) and ever asthma. Models were adjusted for age, energy intake, physical activity, smoking (excepted in models stratified by smoking status), educational level, marital status, and having farmer parents. The first quintile (Q1) serves as reference. Asthma symptom score ranges from 0 to 5.

Figure 3   Associations between tertiles of the AHEI-2010 diet score and uncontrolled asthma, stratified according to smoking status and BMI. Models were adjusted for age, energy intake, physical activity, educational level, marital status and having farmer parents. The first tertile (T1) serves as reference.

Figure 4   Associations between tertiles of the AHEI-2010 diet score and multimorbidity-related medication profiles, stratified according to smoking status. Models were adjusted for age, energy intake, physical activity, educational level, marital status and having farmer parents. The first tertile (T1) serves as reference.

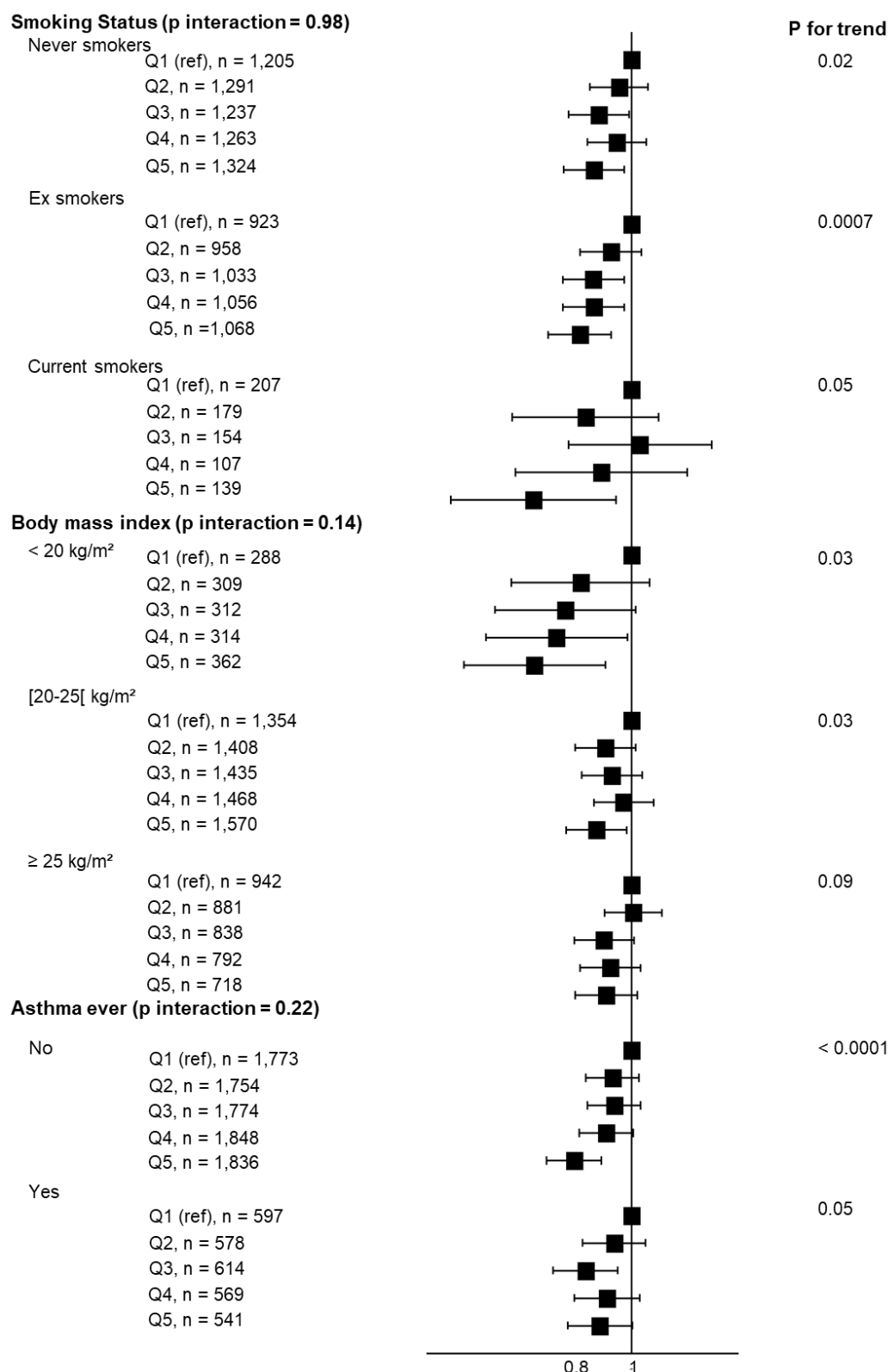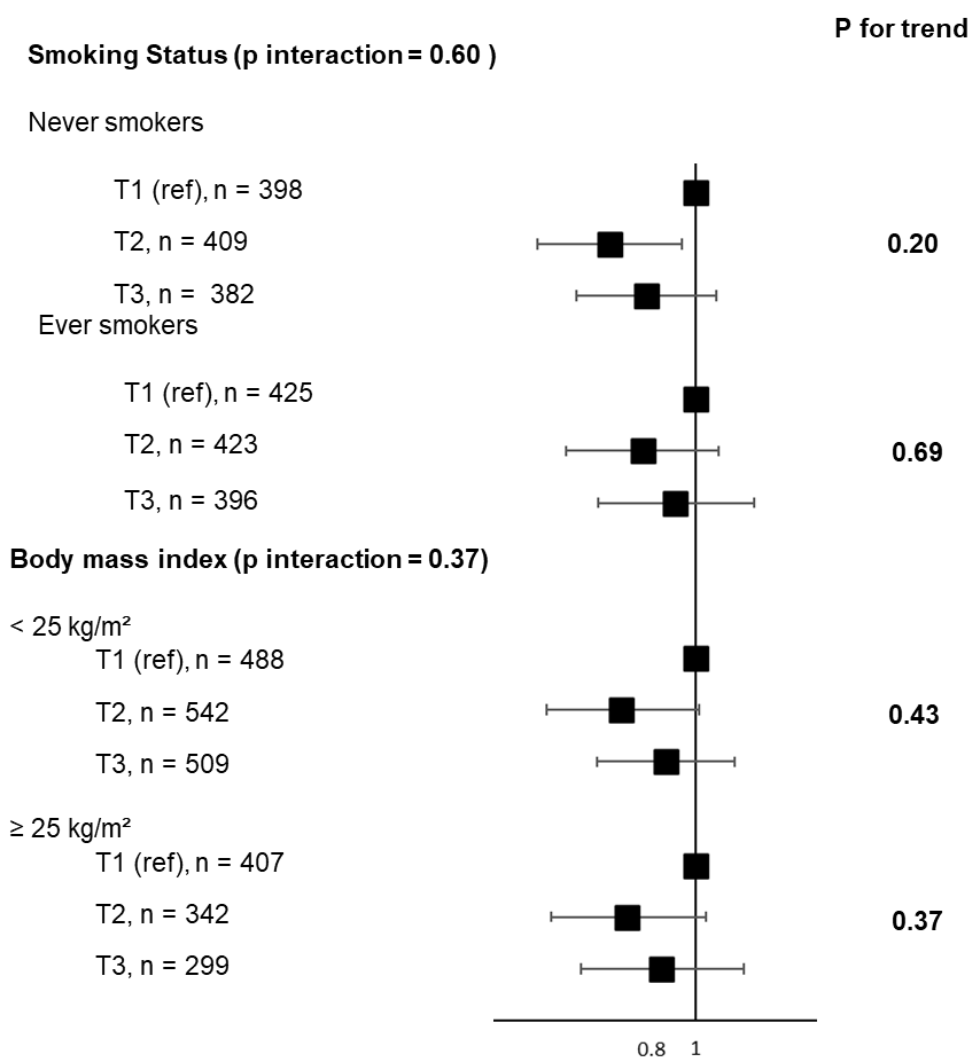**Figure 1**   Study design and flow chart of participants

Figure 2 Associations between quintiles of the AHEI-2010 diet score and the asthma symptom score, stratified according to smoking status, body mass index (BMI) and ever asthma

Models were adjusted for age, energy intake, physical activity, smoking (excepted in models stratified by smoking status), educational level, marital status, and having farmer parents. The first quintile (Q1) serves as reference. Asthma symptom score ranges from 0 to 5.
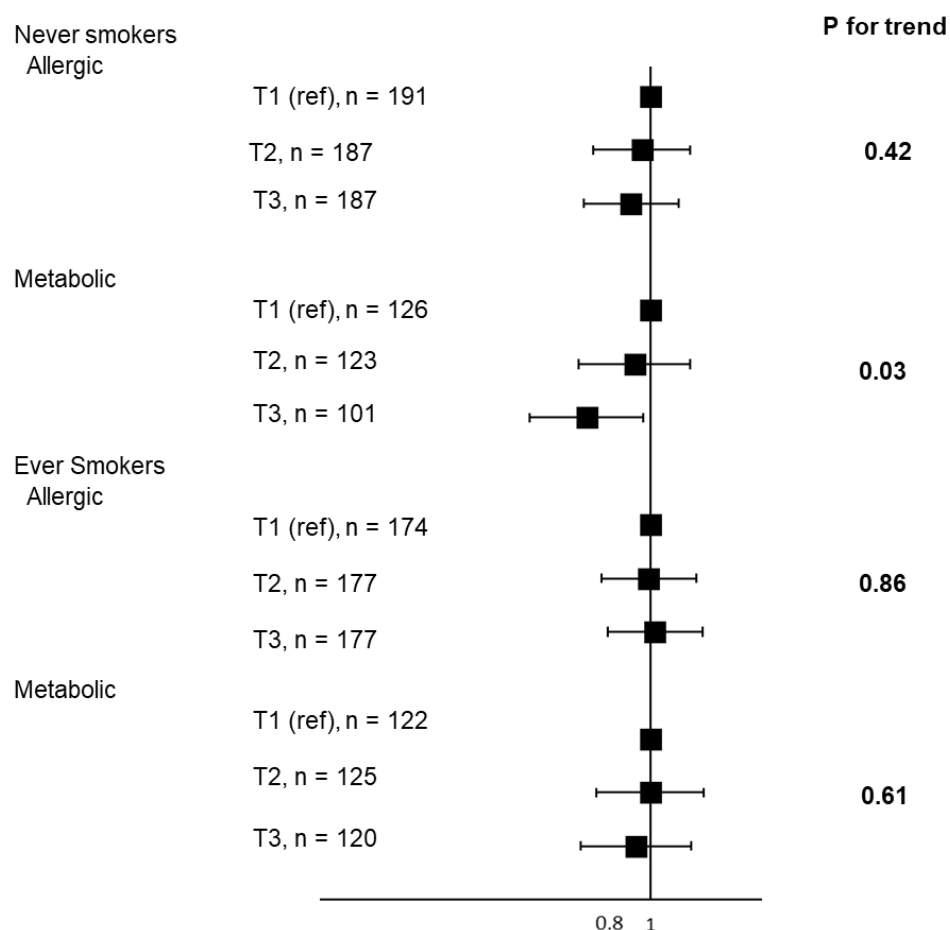
Figure 3   Associations between tertiles of the AHEI-2010 diet score and uncontrolled asthma, stratified according to smoking status and BMI

Models were adjusted for age, energy intake, physical activity, smoking (excepted in models stratified by smoking status), educational level, marital status and having farmer parents. The first tertile (T1) serves as reference

Figure 4   Associations between tertiles of the AHEI-2010 diet score and multimorbidity-related medication profiles, stratified according to smoking status

Models were adjusted for age, energy intake, physical activity, educational level, marital status and having farmer parents. The first tertile (T1) serves as reference.