

Title: Risk of asthma onset after natural and surgical menopause: Results from the French E3N**Cohort**

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Material

E3N is the French component of the European Prospective Investigation into Cancer and Nutrition (EPIC) 1. Information on smoking, weight, menopausal status, menopausal hormone therapy (MHT) and physical activity was updated over the follow-up.

Statistics

Each case of asthma onset was defined as pre-menopausal or post-menopausal incident case, based on the age of asthma onset and the age at menopause (figure E1). The person-years were calculated from the date of return of second questionnaire (1992) up to the date of first attack of asthma or to the date of last completed questionnaire, whichever comes first. In the Cox analysis, menopause was considered as a time-varying variable, since women could enter a survey as pre-menopausal and become post-menopausal (naturally or surgically) during the follow-up. Body mass index (BMI) was calculated as weight in kilogram divided by the square of height in meters, and was included in the analysis as a 4-level time varying categorical variable (<20, 20-24.9, 25-29.9 and ≥ 30 kg/m²) for adjustment, and as a 2-level categorical variable for stratified analyses (<25kg/m² (normal-weight) vs ≥ 25 kg/m² (overweight/obese)). When the analysis was stratified by baseline BMI, the Cox regression was further adjusted for BMI as a continuous variable treated as a time-dependent variable. Hazard-ratios were also adjusted for:

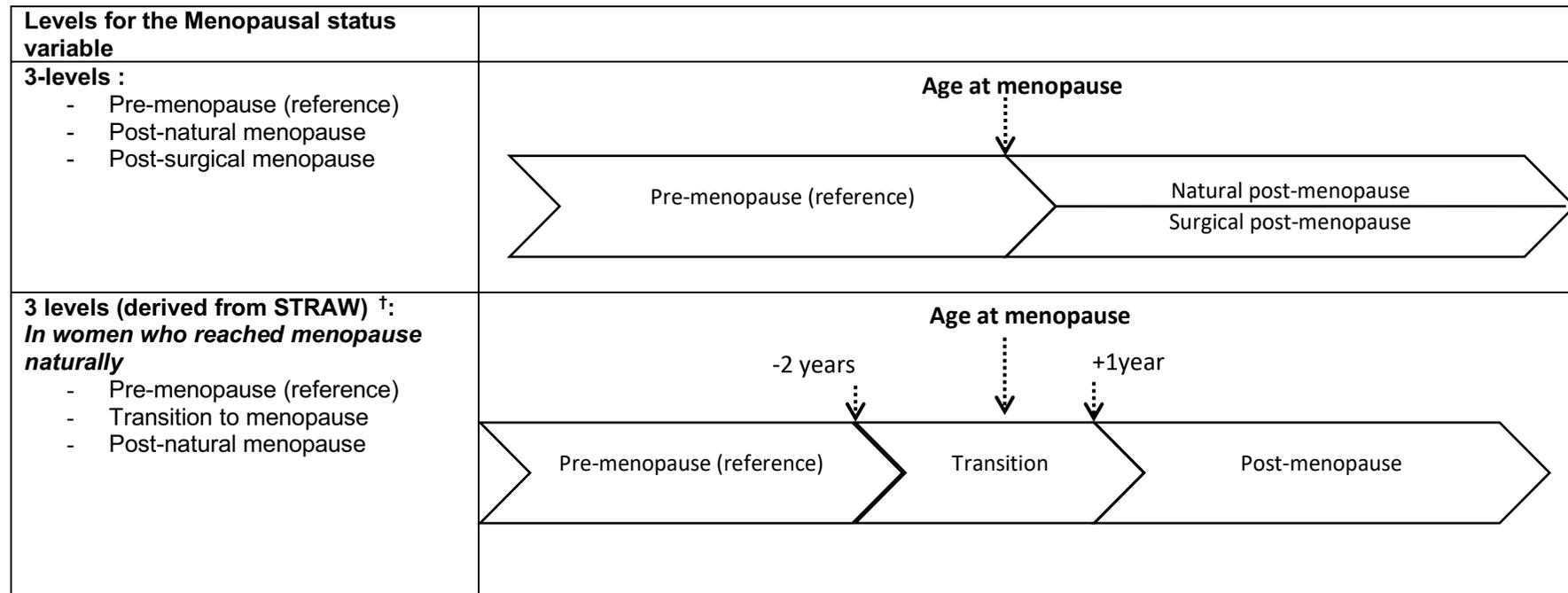
- Smoking status as a 4-level categorical variable (never, ex-smoker, current smoker with <15 cigarettes per day and current smoker with ≥ 15 cigarettes per day) included as a time varying covariate.

- Current use of MHT as a 5-level categorical variable (“estrogen alone”, “estrogen combine with micro progesterone or dydrogesterone”, “estrogen combined with other progestogen” or “other MHT”) included as a time varying variable.
- Physical activity: assessed using questions on several activities. Each activity was assigned an intensity code expressed as the metabolic equivalent of task (MET). Values of METs (hour/week) were added to yield the energy expended per week^{2,3}. A sum of METs was thereafter categorized into tertiles as lower, moderate and higher at each survey where questions on physical activity were available. The tertiles of physical activity were included as a time varying covariates in the Cox model.
- Birth cohort: women were classified in five cohort of birth according to the years of birth (≤ 1934 ,]1934-1939],]1939-1944],]1944-1946], >1946) for adjustment (as fixed covariate) and grouped into two cohorts (older cohort if they were born in or before 1945 and recent cohort otherwise) for stratified analyses.
- Allergic status (2-level categorical variable): assessed using question on hay fever and included in the model as a fixed covariate.
- Education level as a 3-level categorical variable.

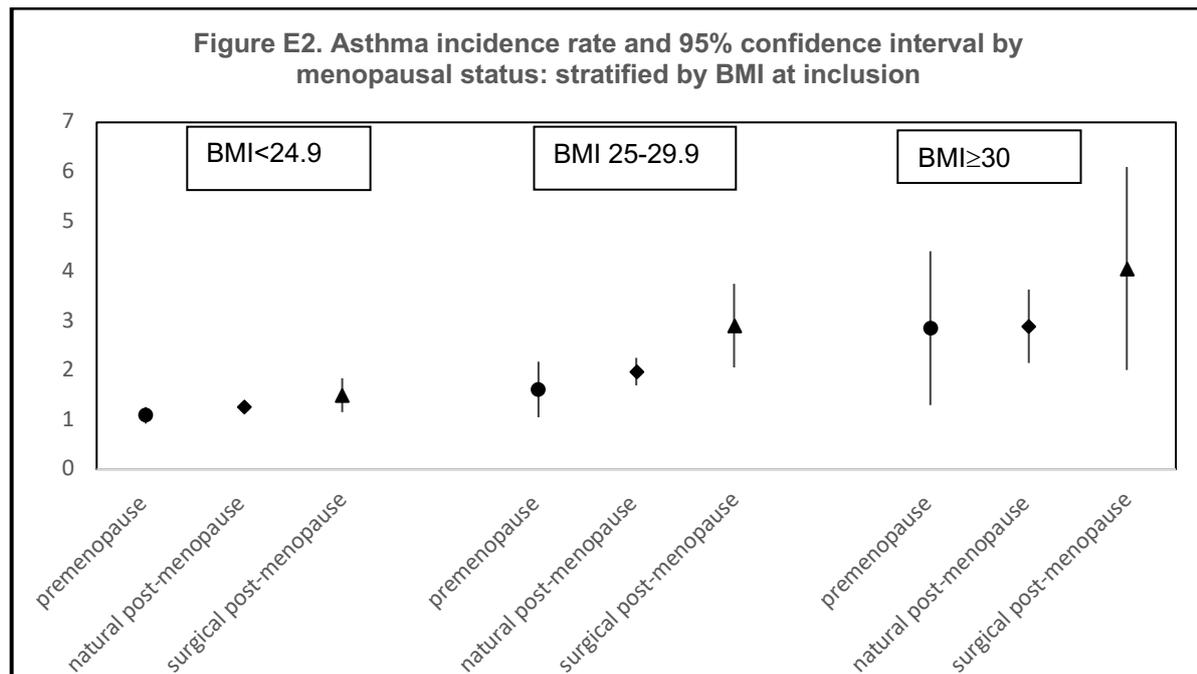
Comparison of women included and non-included in the analysis

At baseline (1992), 5212 women reported have ever had asthma. Among women not reporting asthma at baseline, those not-included in our analysis (n=25 911) were younger, had more frequently undergone surgical menopause, were more frequently smokers, had more frequently used MHT and had a lower education level as compared to women included in the present analysis (n=67 872).

Figure E1: Definition of menopausal status (time-varying variable) in cox-regression analyses



The age at menopause was defined as age at bilateral oophorectomy for surgical menopause and as age at the last menstrual period, or, in decreasing order of priority, self-reported age at menopause, age at start of menopausal hormone treatment (MHT) or age at start of menopausal symptoms for natural menopause † In this model *Pre-menopause* is defined as the period up to the 2 years before the age at menopause; *transition to menopause* is the period from 2 years before to 1 year after the age at menopause and *post-menopause* starts after 1 year of amenorrhea. Women who have undergone menopause surgically were excluded in this model.



Circle: in pre-menopausal women

Diamond: in naturally post-menopausal women

Triangle: in surgically post-menopausal women

BMI: body mass index

BMI < 25 kg/m²: normal-weight women

BMI ≥ 25 kg/m²: overweight/obese women

References

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3. Bedard A, Serra I, Dumas O, et al. Time-dependent associations between body composition, physical activity and current asthma in women using marginal structural models. *American journal of epidemiology.* 2017.