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Headache in girls and boys growing up from age 11 to 20 years: the Prevention and Incidence of Asthma and Mite Allergy birth cohort study

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Abstract

The striking difference between men and women in headache prevalence is suggested to develop in adolescence. Although headaches are common and affect quality of life and daily functioning, the evidence needed to develop effective counselling and preventive approaches is still limited. Using data collected at age 11, 14, 17, and 20 years in the Dutch Prevention and Incidence of Asthma and Mite Allergy birth cohort study (n = 3064 with ≥ 1 questionnaire), we assessed headache prevalence and incidence in girls and boys and explored associations with early life, environmental, lifestyle, health, and psychosocial factors. Associations were analysed longitudinally with generalized linear mixed models and discrete time hazard models. From age 11 to 20 years, the prevalence of headache increased from 9.4% to 19.8% in girls and hardly changed in boys (7.6%-6.1%). Headache commonly co-occurred with other unfavorable health and psychosocial conditions. Eighty-eight percent of the girls and 76% of boys with headache also reported at least one of the following at age 17: sleeping problems, asthma, hay fever, musculoskeletal complaints, fatigue, low mental health, or worrying. Results suggest higher headache prevalence in adolescents following lower educational tracks, in those who skip breakfast ≥2 days per week, and in boys exposed to tobacco smoke in infancy. In girls, sleeping problems and musculoskeletal complaints were associated with higher odds of incident headache and residential greenness with lower odds of incident headache. The high prevalence and strong female predominance of headache, already in adolescence and often with comorbidities, deserve recognition by professionals in (preventive) health care settings and schools.

Keywords: Headache, Pain, Adolescents, Sex differences, Comorbidity, Risk factors, Cohort study

1. Introduction

The striking difference between men and women in the reporting of headaches is suggested to develop in adolescence, when prevalence increases strongly among girls and changes little in boys.[2,13,17,32] According to a review published in 2013, 66% to 71% of 12 to 15 year olds have at least 1 headache every 3 months, and 33% to 40% have at least 1 per week.[26] The same review concludes that headaches are often associated with other physical and emotional complaints, such as pain in other parts of the body, tiredness, and mood disorders.[26] Especially long-lasting, recurrent and severe headaches among adolescents are affecting the quality of life, daily activities, social interaction, and school performance.[10,23,25]

Although headaches are common and affect quality of life and daily functioning, the evidence needed to develop effective counselling and preventive approaches is still limited. A systematic review of childhood and adolescent risk and prognostic factors of recurrent headaches concluded that "this is a research area at a very early stage of understanding."[13] A relatively small number of longitudinal studies explored a wide variety of potential risk factors for onset of recurrent headache, of which 85% were addressed in only 1 or 2 of the 19 studies included in the review. The review found high-quality evidence that negative emotional states manifested through anxiety, depression, or mental distress are not risk factors for developing headache and moderate-quality evidence suggesting that the presence of comorbid negative emotional states in children with headaches is associated with increased risk of headache persistence. For other potential risk factors that have been investigated, the authors consider the quality of the currently available evidence as low. They emphasize that "Because of the small number of studies, further investigation is needed to increase confidence in existing evidence and to explore new risk and prognostic factors."[13]

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Longitudinal studies are needed to evaluate the prevalence and development of headache during adolescence and to identify associated factors. For our study, we used data collected at ages 11, 14, 17, and 20 years in the ongoing Dutch Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort. Our study objectives were (1) to assess the prevalence and incidence of headache from age 11 to 20 years and (2) to explore associations of headache prevalence and incidence with a number of factors in different domains (early life, environment, lifestyle, health, and psychosocial wellbeing) to gain insight into factors that co-occur with headache and to identify risk factors that are associated with incident headache. In view of known sex and gender differences in headache, we conducted all analyses separately for girls and boys.

2. Materials and methods

2.1. Study design and study population

We used data from the Dutch population-based PIAMA birth cohort study that has been described in detail elsewhere.[31] Pregnant women were recruited from the general population in 3 different parts of the Netherlands. Their children (n = 3963), born in 1996/1997, have been followed from birth onwards. The study protocol was approved by the medical ethics committees of the participating institutes, and all parents gave written informed consent. For this study, data were mainly used from the questionnaires completed by the adolescents when they were 11 (n = 2651), 14 (n = 2522), 17 (n = 2094), and 20 years (n = 2206) old. Data on headache at at least one of these ages were available for 3064 adolescents. Early life characteristics were derived from questionnaires completed by the parents during pregnancy, at the child's ages of 3 months and 1 to 8 years (annually).

2.2. Headache

Presence of headache was assessed in the questionnaires with the following introductory question: "Please indicate whether you had one of the following diseases or disorders in the past 12 months, yes/no," followed by a list of 15 conditions. Headache, described as "regular occurrence of migraine or serious headaches," was one of the conditions on this list. For better readability, we refer to the condition(s) described in this question as "headache," rather than using the full "regular occurrence of migraine or serious headache over the past 12 months" every time we mention this condition. Incident headache was defined as a report of headache at age 14, 17, or 20 years and no headache reported at any preceding age(s). Recurrent headache was defined as headache reported in at least 3 of the 4 questionnaires among those with questionnaires at each of the 4 timepoints (n = 1575).

2.3. Factors potentially associated with headache

We explored a large number of factors potentially associated with headache prevalence or incidence. Based on the literature, we selected variables in 5 domains (early life, environment, lifestyle, health, and psychosocial wellbeing). Selection was based on mainly 2 criteria: First, we included factors that have previously been studied in relation to headache (reviewed by Huguet et al.[13] and Straube et al.[26]), so that we would be able to compare our results with those of earlier studies. These are the factors in the domains social environment, lifestyle, health, and psychosocial wellbeing. Second, we included factors that have not commonly been included in headache studies so far, but that we considered as plausible potential risk factors based on evidence from studies in related fields. Early life factors were included based on the so called Developmental Origins of Health and Disease (DOHAD) hypothesis that proposes that the risk of developing chronic disease later in life is associated with prenatal and early postnatal factors, referred to as "early programming."[4] Urbanization and residential greenness were included in the physical domain based on their associations with stress and mental ill-being,[1,12,21] conditions that tend to co-occur with headache. Also, data availability had to be taken into account in the selection of variables. The variables included in the analyses are described briefly here; more detailed definitions are provided in supplementary table S1 (available at http://links.lww.com/PAIN/B225).

2.4. Early life and childhood factors

Based on questionnaires administered during pregnancy and at the child's ages of 3 months and 1 year, we defined dichotomous variables for low birth weight (<2500 g), preterm birth (<37 weeks), maternal smoking during pregnancy, breast feeding (≥16 weeks), and secondhand smoke exposure at the child's age of 3 months. Maternal level and paternal level of education, obtained from the 1-year questionnaire, were combined into a variable with 3 categories: 0, 1, or 2 parents with a low level of education. As indicator of childhood health, we used the scores on the RAND 7-item general health rating index[6,19] that was completed by the parents at the child's ages of 4, 6, and 8 years. We created a "general health in childhood" variable by adding up the scores obtained at these ages, with higher scores representing a more favorable health state.

2.5. Social and physical environment

The social and physical environment factors included were the adolescent's level of education, neighbourhood socioeconomic status (SES), urbanization, residential greenness, and secondhand smoke exposure at home. The adolescent's level of education was categorized as low, intermediate, or high, using age-specific criteria (see Table S1, http://links.lww.com/PAIN/B225). We assessed neighbourhood SES with the "status scores" of 4-digit postal code areas (based on average income and percentages of low-educated residents, low-income residents, and unemployed persons).[16] Status scores represent a ranking and can range from roughly −8 to +2 with higher scores indicating higher SES. We categorized the level of urbanization as high (≥1500 addresses/km^2) or low. We used the average Normalized Difference Vegetation Index to assess greenness levels in a circular buffer of 1 km around the adolescents' home addresses.[30] Secondhand smoke exposure at home was obtained from parental questionnaires administered at ages 11, 14, and 17 years and the adolescents' questionnaire at 20 years and defined as smoking in the adolescent's home at least once a week (yes/no).

2.6. Lifestyle factors

Lifestyle factors included skipping breakfast on ≥2 days per week, use of energy drinks on ≥1 day per week, active smoking, and alcohol consumption. For the latter 2 factors, age-specific cutoff points were defined (see supplementary table S1, available at http://links.lww.com/PAIN/B225).

2.7. Adolescent health

Adolescents completed questionnaires at the ages of 11, 14, 17, and 20 years. From the question on different health conditions (described above under "headache"), we derived, besides headache, also the presence of asthma, hay fever, musculoskeletal complaints (complaints of back, upper extremities, or lower extremities), and fatigue in the last 12 months (yes/no). For "sleeping problems" (yes/no), a composite variable was constructed based on difficulties falling asleep and the frequency and duration of nighttime awakenings. This variable thus represents 2 of the criteria that are used to define insomnia. Using the Pubertal Development Scale (PDS),[7,22] we obtained adolescent-reported pubertal development scores at the ages of 11, 14, and 17 years. Higher scores on the PDS indicate more advanced pubertal development. We defined "early puberty" as a PDS score above the 75th percentile at age 11 (girls) or 14 (boys).

2.8. Psychosocial wellbeing

In the psychosocial wellbeing domain, we included mental health status, worrying, and being bullied. To assess mental health, we used the Mental Health Inventory-5,[5] a commonly used instrument that asks about the frequency of feeling nervous, calm, downhearted, happy, and "so down in the dumps that nothing could cheer you up" during the last 4 weeks. Response categories ranging from never to all the time were rescaled on a score from 0 to 100, with higher scores indicating better mental health. We used the commonly applied cutoff of <60 to define poor mental health.[15] "Worrying" was based on the question "do you have a problem that keeps you busy day and night? (yes/no)." Furthermore, participants were asked if they had been bullied in the last 12 months (yes/no).

2.9. Statistical analysis

First, we assessed associations between potentially associated factors and the overall prevalence of headache throughout the 11- to 20-year period for boys and girls separately with generalized linear mixed models using a logit link. A random subject-specific intercept was included to account for within-subject correlation across the repeated headache measurements. In these analyses, associations between the presence or absence of headache and the potentially associated factors at each of the 4 measuring points (ages 11, 14, 17, and 20 years) were used to estimate the overall association between the factors studied and headache during the 11- to 20-year period. If a participant failed to complete 1 or more of the 4 questionnaires, the participant was not excluded from the analyses, but his/her data from the other questionnaires were used in the analyses. Second, we used discrete time hazard models to estimate associations between factors measured at ages 11, 14, and 17 years and incidence of headache (a first report of headache in adolescents who never reported headache before) in the subsequent questionnaire (ie, at ages 14, 17, or 20 years). In the analyses of headache incidence, only adolescents who reported no headache at age 11 were included to identify risk factors for incident headache (ie, new cases of headache) at later ages. Those who reported headache at age 14 were excluded from further analyses ("censored"), so that associations between risk factors at age 14 and incident headache at age 17 could be assessed. Next, participants who reported headache at age 17 were excluded to assess associations between risk factors at age 17 and incident headache at age 20. Associations of potential risk factors at ages 11, 14, and 17 years with the presence or absence of incident headache at ages 14, 17, and 20 years were used to estimate the overall association between the factors studied and headache incidence during the 11- to 20-year period. The analyses of headache incidence were conducted in girls only, as the number of boys with incident headache was too low for meaningful analyses. A graphical presentation of the statistical models is provided in the supplement (Figures S1A and S1B, available at http://links.lww.com/PAIN/B225).

For both headache prevalence and headache incidence, we first assessed crude associations (adjusted for age only) with each of the individual factors (model 1). Then, within each of the domains, we conducted multivariable analyses including only variables in that domain with a P-value <0.10 in model 1 (model 2). In a final step, we ran a model across the domains including all the variables with a P-value <0.10 in model 2 (model 3). Odds ratios are presented with their 95% confidence intervals.

Statistical Analysis System, SAS software 9.4 (SAS Institute, Inc., Cary, North Carolina) was used to analyse the data.

3. Results

3.1. Prevalence and incidence of headache in boys and girls

At the age of 11 years, 7.6% of the boys and 9.4% of the girls reported headache. In girls, the prevalence increased to 14.4% at age 14, to 20.4% at age 17, and then remained at that level (19.8%) at age 20. In boys, the prevalence of headache hardly changed with age and was slightly lower at ages 17 (6.4%) and 20 (6.1%) years than at age 11 (**Fig. 1A**). After the age of 11 years, headache incidence (first time report of headache at age 14, 17, or 20 years) was 3% to 4% in boys and 10% to 13% in girls (**Fig. 1B**). Headache was reported in at least one of the 4 questionnaires by 14.9% of the boys and by 36.0% of the girls. The prevalence of recurrent headache (headache reported in at least 3 of the 4 questionnaires) was 3.0% in boys and 6.5% in girls.

3.2. Factors potentially associated with headache

Table 1 shows the prevalence of the factors potentially associated with headache at ages 11 and 17 years, the period in which the headache prevalence gap between boys and girls widens. In general, lifestyle, health, and psychosocial wellbeing tended to be less favorable at age 17 than at age 11. The environmental factors were similar at ages 11 and 17 years. With respect to differences between girls and boys, the prevalence of unhealthy lifestyles increased more in boys than in girls, whereas the prevalence of unfavorable health and psychosocial conditions tended to increase more strongly in girls than in boys.

3.3. Correlates of prevalent headache at ages 11 to 20 years

Table S2 shows (http://links.lww.com/PAIN/B225), for girls and boys, the prevalence of headache at ages 11, 14, 17, and 20 years, according to the presence or absence of each of the potential correlates. Odds ratios for the associations between the potential correlates and the overall prevalence of headache at 11 to 20 years are shown in **Table 2**.

The results shown in **Table 2** suggest that headache commonly co-occurs with other unfavorable health and psychosocial conditions. In post hoc analyses, we assessed the percentage of adolescents with headache who had at least one of the conditions in the health or psychosocial domains. At age 17, this was the case in 88% of the girls and in 76% of the boys with headache. In girls and boys without headache, these

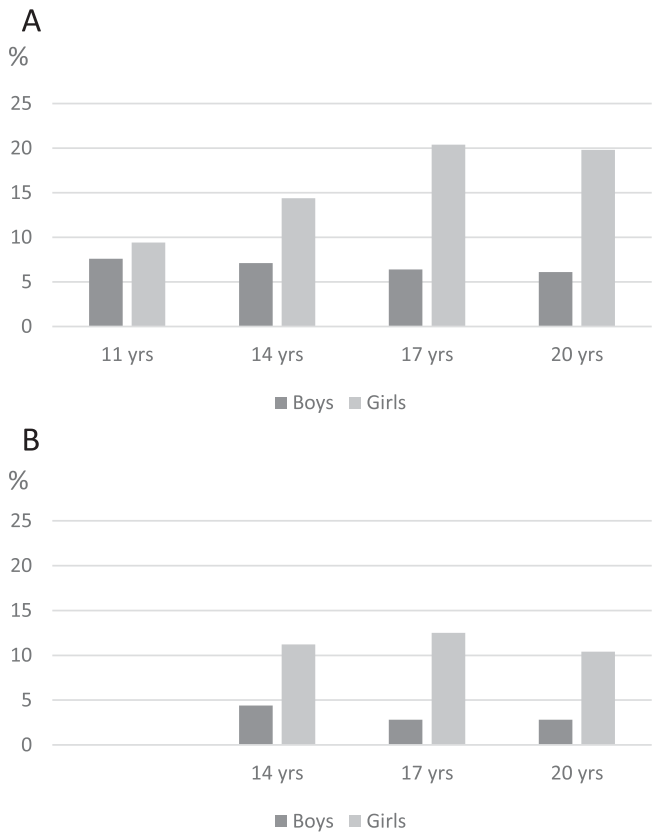

Figure 1. Prevalence (A) and incidence (B) (%) of headache by age in boys and girls.

percentages were 67% and 58%. The association of poor general health in childhood with prevalent headache at 11 to 20 years (statistically significant in model 2, but no longer in model 3) suggests that already at an early age, parents perceive health problems in their children that are associated with headache in adolescence. In the early life, environmental, and lifestyle domains, only few of the factors studied were associated with headache. In model 3, only skipping breakfast on 2 or more days per week by boys was associated with headache independently of all other factors in the study. Considering the possibility of overadjustment in model 3, as lifestyle and environmental factors may be on the pathway from (parental) education to headache, associations observed in model 2 may also be relevant. Results of model 2 suggest that headache is more likely in boys and girls following the lower educational tracks, in boys and girls who skip breakfast on 2 or more days per week, and in boys who are exposed to tobacco smoke in infancy.

3.4. Potential risk factors at ages 11, 14, and 17 years for incident headache in girls

Incidence of headache was studied in girls only because the number of boys with incident headache was too low for a meaningful analysis. Numbers available for girls (girls with complete data and no headache reports at earlier ages) were n = 1005 at age 14, n = 742 at age 17, and n = 604 at age 20.

The early life factors were not included in these analyses because they were already shown not to be related to the presence of headache at 11 to 20 years.

After adjustment for all other potential risk factors, we found sleeping problems and musculoskeletal complaints to be associated with higher odds of incident headache. Residential greenness was associated with lower odds of incident headache. Associations of low education, early puberty, and being bullied with incident headache lost statistical significance after inclusion of potential risk factors from other domains in the model (**Table 3**).

4. Discussion

4.1. Main findings

We observed a widening gap in headache prevalence between adolescent girls and boys from age 11 to 20 years, with 20% of the girls and 6% of the boys reporting headache at ages 17 and 20 years. The prevalence of headache recurring over the years was 6.5% in girls and 3.0% in boys.

Our results show common co-occurrence of headache with other unfavorable health and psychosocial conditions, with 88% of the 17-year-old girls and 76% of the 17-year-old boys with headache also reporting at least one of the following: sleeping problems, asthma, hay fever, musculoskeletal complaints, fatigue, poor mental health, or worrying. Only a few of the factors studied were identified as independent risk factors for incident headache in girls: Sleeping problems and musculoskeletal complaints were associated with higher odds of incident headache, and residential greenness was associated with lower odds of incident headache. The association of poor general health in childhood with prevalent headache at 11 to 20 years suggests that already at an early age, parents perceive health problems in their children that are associated with headache in later years. We observed no evidence that in utero conditions, as indicated by low birth weight, preterm birth and maternal smoking during pregnancy predispose to headache in adolescence.

4.2. Results of this study in relation to findings from earlier studies

Our observation of the widening gap in headache prevalence between girls and boys during adolescence is in line with observations from earlier studies.[2,13,32] Several mechanisms have been proposed for the increase of pain during adolescence among girls, but not boys, including increasing differences in hormone profile and physiology between males and females during puberty. A recent study in mice suggests that different immune cells play a role in pain pathways in male and female mice.[8] Apart from biological mechanisms, gender-based differences in risk factors such as sociocultural role expectations between boys and girls may play a role, not only in relation to pain, but possibly also in relation to factors such as fatigue and poor mental wellbeing.[9] It has also been hypothesized that it is socially more accepted for girls to report pain than for boys.[11]

The comparison of findings from different studies on factors associated with headache is difficult because of the large variation between studies in definitions and types of headache studied, the specific factors included, methods used, and (in longitudinal studies) duration of follow-up. Although specific indicators differ between studies, co-occurrence of headache with other somatic and psychological conditions is commonly observed.[3,18,26,29] Our finding that poor psychosocial wellbeing co-occurs with headache, but is not a risk factor for incident headache is in line with the review by Huguet et al. that found that negative emotional states are not a risk factor for developing headache.[13] Sleep problems were associated with incident headache in our study. Another study on headache and sleep among adolescents, using path analysis, observed a bidirectional association: Insomnia was associated with headache 1 year later,

Table 1

Characteristics of the study population at ages 11 and 17 years, by sex.

Characteristics	n (%) or median (25th to 75th percentiles)			
	Girls		Boys	
	11 years	17 years	11 years	17 years
N	1302	1074	1321	1009
Early life				
No. of low-educated parents				
0	866 (67.3)	737 (69.4)	904 (69.0)	734 (73.1)
1	283 (22.0)	220 (20.7)	280 (21.4)	189 (18.8)
2	138 (10.7)	105 (9.9)	127 (9.7)	81 (8.1)
Prematurity	59 (4.5)	44 (4.1)	67 (5.1)	44 (4.4)
Low birth weight	39 (3.0)	28 (2.6)	44 (3.4)	27 (2.7)
Maternal smoking during pregnancy	207 (16.0)	137 (12.8)	191 (14.6)	122 (12.2)
Breast feeding ≥16 weeks	493 (38.2)	429 (40.2)	458 (35.0)	382 (38.2)
Secondhand smoke exposure at home at 3 months	338 (26.0)	240 (22.4)	333 (25.2)	235 (23.3)
General health age 4-8 years, range 0-96	83 (77-89)	84 (77-89)	84 (77-88)	84 (77-88)
Social and physical environment				
Adolescent level of education*				
High	466 (37.5)	545 (52.8)	436 (34.8)	434 (44.8)
Intermediate	379 (30.5)	159 (15.4)	325 (25.9)	193 (19.9)
Low	399 (32.1)	329 (31.9)	492 (39.3)	342 (35.3)
Neighbourhood SES, range −8 to +2	0.50 (0.00-0.98)	0.21 (−0.52-0.96)	0.53 (0.01-0.95)	0.30 (−0.47-0.97)
Highly urbanized	511 (39.6)	465 (43.3)	524 (40.6)	423 (42.1)
Residential greenness, range 0-1	0.58 (0.51-0.64)	0.58 (0.51-0.65)	0.58 (0.51-0.65)	0.58 (0.52-0.64)
Secondhand smoke exposure at home	174 (13.7)	77 (8.2)	172 (12.9)	89 (9.7)
Lifestyle				
Smoking†	13 (1.0)	127 (11.9)	49 (3.7)	151 (15.0)
Alcohol consumption‡	75 (5.8)	63 (5.9)	104 (8.0)	230 (22.8)
Energy drinks ≥1x/wk	36 (2.8)	165 (15.5)	108 (8.3)	269 (26.7)
Skipping breakfast ≥2x/wk	51 (3.9)	2017 (20.4)	35 (2.7)	180 (17.9)
Health				
Early puberty§	(317) 24.8		(333) 26.6	
Sleeping problems (past 12 months)	266 (20.5)	187 (17.5)	242 (18.3)	92 (9.1)
Asthma (past 12 months)	66 (5.1)	79 (7.4)	85 (6.4)	65 (6.4)
Hay fever (past 12 months)	121 (9.3)	216 (20.1)	173 (13.1)	208 (20.6)
Musculoskeletal complaints (past 12 months)	225 (17.3)	382 (35.6)	187 (14.2)	190 (18.8)
Fatigue (past 12 months)	64 (4.9)	285 (26.5)	56 (4.2)	87 (8.6)
Psychosocial wellbeing				
Being bullied (past 12 months)‖	409 (31.4)	198 (15.9)	507 (38.3)	191 (15.2)
Poor mental health	87 (6.7)	274 (25.5)	67 (5.1)	110 (10.9)
Worrying	90 (6.9)	224 (20.9)	103 (7.8)	131 (13.0)

* At age 11, children are still in primary school. The percentages shown for the type of education in the column "11 years" are the percentages at age 14.
† Smoking was defined at age 11 as "ever smoked" and at age 17 as "smoking ≥1x per week."
‡ Alcohol consumption was defined at age 11 as "ever drank a whole glass" and at age 17 as "drinking ≥7 glasses per week."
§ Early puberty was defined for girls at age 11 and for boys at age 14.
‖ At age 17, being bullied was not asked in the questionnaire. The percentages shown for being bullied in the column "17 years" are the percentages at age 14.
SES, socioeconomic status.

and headache was associated with insomnia 1 year later, the strengths of these 2 associations being similar.[24] A systematic review addressed sleep problems in paediatric pain populations and proposed a model in which pain perception and sleep quality have a bidirectional relationship and together interact with physiology/biology and mood to influence functional outcomes, including health-related quality of life.[27] Evidence on the role of lifestyle factors in relation to headache is still inconsistent. For example, in our study, skipping breakfast was associated with headache prevalence, but smoking and use of alcohol were not, whereas opposite findings were reported in a German study.[20] Interpretation of the lifestyle-headache association in observational studies is complicated by the possibility of reverse causation, ie, adolescents with headache avoiding (active and passive) smoking and alcohol consumption. As lifestyle is a modifiable factor, more insight into its association with headache is, however, important because it could contribute to preventive approaches. To the best of our knowledge, early life factors have not been studied in relation to headache before. Green space exposure has been studied in relation to adolescents' mental health, so far with mixed results,[28] but, to the best of our knowledge, has not been studied in relation to headache.

4.3. Strengths and limitations

Strengths of the PIAMA birth cohort study include the high retention rate, with 3064 of the 3963 (77%) participants included at birth having completed 1 or more of the questionnaires at ages 11, 14, 17, and 20 years. Also, the long follow-up period from birth up to young adulthood with 4 measurement points for

Table 2

Odds ratio with 95% confidence interval (OR [95% CI]) for the associations between factors in different domains (early life, environment, lifestyle, health, and psychosocial wellbeing) and the prevalence of headache at 11 to 20 years (for continuous variables, ORs are estimated per interquartile range [IQR]).

	Girls n = 1079			Boys n = 1089		
	Model 1, OR (95% CI)	Model 2, OR (95% CI)	Model 3, OR (95% CI)	Model 1, OR (95% CI)	Model 2, OR (95% CI)	Model 3, OR (95% CI)
Early life						
No. of low-educated parents						
0	1.00	1.00	1.00	1.00	1.00	1.00
1	1.17 (0.82-1.67)	1.18 (0.80-1.73)	1.06 (0.69-1.62)	1.27 (0.74-2.18)	1.06 (0.59-1.89)	1.04 (0.51-2.09)
2	**1.71 (1.08-2.71)**	**1.61 (0.97-2.67)**	1.21 (0.68-2.17)	0.81 (0.77-1.75)	0.56 (0.24-1.35)	0.51 (0.18-1.51)
Prematurity	0.97 (0.47-1.99)			0.65 (0.21-2.01)		
Low birth weight	0.76 (0.30-1.92)			0.73 (0.19-2.73)		
Maternal smoking during pregnancy	1.02 (0.68-1.54)			1.44 (0.79-2.60)		
Breast feeding ≥16 weeks	**0.70 (0.51-0.94)**	0.76 (0.55-1.06)		0.84 (0.53-1.34)	0.97 (0.59-1.59)	
Secondhand smoke exposure at home at 3 months	1.09 (0.77-1.52)	1.03 (0.71-1.50)	0.97 (0.64-1.48)	**1.87 (1.16-3.03)**	**1.99 (1.17-3.39)**	1.77 (0.92-3.41)
Poor general health, age 4-8 years (per IQR)*	**1.49 (1.20-1.86)**	**1.45 (1.17-1.81)**	1.14 (0.90-1.43)	**1.43 (1.04-1.96)**	**1.45 (1.05-1.99)**	1.00 (0.68-1.47)
Social and physical environment						
Adolescent level of education						
High	1.00	1.00	1.00	1.00	1.00	1.00
Intermediate	**1.60 (1.14-2.25)**	**1.76 (1.24-2.51)**	**1.65 (1.14-2.40)**	1.43 (0.85-2.42)	1.51 (0.88-2.57)	1.40 (0.76-2.58)
Low	**1.83 (1.31-2.57)**	**1.86 (1.30-2.66)**	1.45 (0.97-2.17)	**1.61 (0.95-2.71)**	**1.63 (0.95-2.79)**	1.48 (0.79-2.78)
Neighbourhood SES (per IQR)	0.95 (0.81-1.11)			0.85 (0.66-1.08)		
Highly urbanized	0.96 (0.74-1.26)			1.15 (0.76-1.73)		
Residential greenness (per IQR)	0.89 (0.74-1.06)			1.02 (0.75-1.37)		
Secondhand smoke exposure at home	1.26 (0.84-1.90)	1.34 (0.85-2.09)	1.27 (0.75-2.17)	**1.83 (1.07-3.15)**	**1.75 (0.96-3.20)**	1.33 (0.65-2.73)
Lifestyle						
Smoking	1.32 (0.92-1.89)			1.18 (0.70-1.99)		
Alcohol consumption	0.93 (0.65-1.34)			1.10 (0.71-1.70)		
Energy drinks	**1.39 (1.00-1.94)**	1.30 (0.93-1.82)		1.19 (0.79-1.79)	1.09 (0.72-1.65)	
Skipping breakfast	**1.55 (1.16-2.05)**	**1.50 (1.13-2.00)**	1.16 (0.81-1.66)	**1.97 (1.24-3.13)**	**2.00 (1.25-3.20)**	**2.02 (1.08-3.78)**
Health						
Early puberty	**1.46 (1.01-2.10)**	1.17 (0.83-1.66)		0.75 (0.43-1.30)	0.66 (0.38-1.17)	
Sleeping problems	**2.16 (1.66-2.81)**	**1.79 (1.34-2.39)**	**1.48 (1.06-2.06)**	**2.16 (1.39-3.35)**	**1.67 (1.01-2.74)**	1.41 (0.80-2.47)
Asthma	**1.90 (1.23-2.94)**	**1.53 (0.96-2.44)**	1.63 (0.98-2.71)	**4.51 (2.42-8.40)**	**3.11 (1.55-6.25)**	**2.98 (1.34-6.63)**
Hay fever	**1.95 (1.43-2.66)**	**1.49 (1.07-2.10)**	**1.52 (1.05-2.20)**	**2.04 (1.32-3.14)**	**1.45 (0.89-2.37)**	1.47 (0.84-2.58)
Musculoskeletal complaints	**3.18 (2.54-3.99)**	**2.67 (2.08-3.43)**	**2.86 (2.17-3.77)**	**3.40 (2.34-4.94)**	**2.41 (1.58-3.67)**	**2.28 (1.39-3.74)**
Fatigue	**4.86 (3.77-6.27)**	**3.71 (2.80-4.89)**	**3.30 (2.41-4.52)**	**12.41 (7.57-20.35)**	**11.05 (6.44-18.97)**	**10.35 (5.50-19.47)**
Psychosocial wellbeing						
Being bullied	**1.56 (1.13-2.15)**	**1.34 (0.98-1.85)**	1.13 (0.78-1.63)	**2.20 (1.39-3.45)**	**1.94 (1.22-3.09)**	1.37 (0.80-2.35)
Poor mental health	**2.11 (1.62-2.73)**	**1.78 (1.33-2.37)**	1.41 (0.99-2.00)	**5.10 (3.16-8.25)**	**4.26 (2.48-7.31)**	**2.81 (1.45-5.44)**
Worrying	**2.12 (1.62-2.77)**	**1.72 (1.28-2.32)**	1.31 (0.91-1.87)	**2.84 (1.82-4.46)**	**1.61 (0.96-2.69)**	0.88 (0.47-1.66)

Model 1: adjusted only for age.

Model 2: includes all variables within the same domain with $P < 0.10$ (indicated in bold) in model 1.

Model 3: includes all variables in the table with $P < 0.10$ (indicated in bold) in model 2 (associations in model 3 are only printed in bold when $P < 0.05$).

* A high score on the RAND general health index defines a more favorable health state. For the analyses, we multiplied the total score by −1 to create a variable "poor general health" with higher scores defining poorer health.

CI, confidence interval; SES, socioeconomic status.

headache in adolescence is a strength of the study. Another strength is the availability of data on a large range of factors that could be studied in association with headache.

Limitations of the study should also be taken into account. Presence of headache was assessed based on the question on "regular occurrence of migraine or serious headaches in the last 12 months." No standard question on (recurrent) headache for use in questionnaire-based studies in the general population was available when this question was first developed. By labelling the type of headache, we were interested in as "migraine or serious headache," we aimed to avoid that participants would report any mild "head discomfort" that they might have experienced over the past 12 months. By including "regular" in the question, we aimed to avoid reports of an occasional headache due to, eg, a late night. A limitation of our headache assessment is that we do not have data on headache characteristics (frequency and disability) and that we are unable to distinguish between migraine, tension-type headache, and other types of headache. Prospective studies, however, challenge the meaning of headache classification in this age group because adolescent headache is a highly variable disorder and changes in the type of headache diagnosed are frequently observed.[14] We assumed that participants would be able to recall regular occurrence of migraine or serious headaches over a 12-month period, but recall error cannot be excluded. We assume, however, that recall error has not been differential, and we expect therefore that it may have weakened the associations we observed (if anything), but would not have led to spurious significant results. Another limitation is that our questionnaires were administered with 3-year intervals and asked about headache in the past 12 months, so that we do not have

Table 3

Odds ratios (95% confidence intervals) for the associations between factors in different domains (environment, lifestyle, health, and psychosocial wellbeing) at ages 11, 14, and 17 years and incidence of headache in the age periods 11-14, 14-17, and 17-20 years, in girls (for continuous variables, ORs are estimated per interquartile range [IQR]).

	Model 1, OR (95% CI)	Model 2, OR (95% CI)	Model 3, OR (95% CI)
Social and physical environment			
Adolescent level of education			
High	1.00	1.00	1.00
Intermediate	1.29 (0.94-1.78)	1.31 (0.95-1.80)	1.35 (0.97-1.87)
Low	**1.39 (1.02-1.88)**	**1.40 (1.03-1.90)**	1.33 (0.97-1.83)
Neighbourhood SES (per IQR)	0.98 (0.84-1.15)		
Highly urbanized	0.97 (0.75-1.25)		
Residential greenness (per IQR)	**0.85 (0.72-1.02)**	**0.84 (071-1.01)**	**0.82 (0.69-0.99)**
Secondhand smoke exposure at home	1.15 (0.76-1.73)		
Lifestyle			
Smoking	1.20 (0.68-2.12)		
Alcohol consumption	1.44 (0.90-2.31)		
Energy drinks	1.33 (0.87-2.03)		
Skipping breakfast	1.34 (0.89-2.02)		
Health			
Early puberty	**1.40 (1.05-1.86)**	**1.32 (0.99-1.77)**	1.25 (0.93-1.69)
Sleeping problems	**1.68 (1.24-2.28)**	**1.53 (1.12-2.09)**	**1.56 (1.13-2.15)**
Asthma	1.15 (0.69-1.92)		
Hay fever	**1.41 (0.99-2.00)**	1.30 (0.90-1.85)	
Musculoskeletal complaints	**2.02 (1.53-2.66)**	**1.81 (1.36-2.41)**	**1.83 (1.37-2.44)**
Fatigue	**1.57 (1.06-2.31)**	1.27 (0.85-1.89)	
Psychosocial wellbeing			
Being bullied	**1.50 (1.12-2.01)**	**1.42 (1.05-1.92)**	1.31 (0.96-1.79)
Poor mental health	**1.43 (0.99-2.06)**	1.24 (0.83-1.84)	
Worrying	**1.41 (0.97-2.04)**	1.22 (0.81-1.82)	

Model 1: adjusted only for age.
Model 2: includes all variables within the same domain with $P < 0.10$ (indicated in bold) in model 1.
Model 3: includes all variables in the table with $P < 0.10$ (indicated in bold) in model 2.
(Associations in model 3 are only printed in bold when $P < 0.05$).
SES, socioeconomic status.

information on presence of headaches in the remaining 24 months of the interval.

Generalizability of the study findings also needs to be considered. Participants were recruited from the general population in 1996 to 1997, and most of the participants have parents born in the Netherlands (93%), implying that our results may not be generalizable to populations with different ethnic or cultural backgrounds. In long-term follow-up studies, selective loss to follow-up of low SES participants is a common phenomenon that was also observed in the PIAMA study. Supplementary table S3 (available at http://links.lww.com/PAIN/B225) shows the prevalence of low parental education and of a number of early life factors that tend to be associated with parental education for the baseline population and for those who participated in the follow-up at the age of 20 years. The prevalence of these characteristics in the study population of this specific study is also shown in this table. Comparison of participants included in this study with the participants originally included in the PIAMA cohort at birth suggests that the study population is somewhat, but not substantially different from the study population at baseline, and we consider it unlikely that we would have obtained substantially different findings if the population in the current study would have been more similar to the original PIAMA population. Headache itself was unrelated to loss to follow-up, ie, adolescents who did and who did not report headache were equally likely to be nonresponders in the subsequent questionnaire. Finally, given the possibility of chance findings due to multiple testing, risk factors identified in our study need to be considered with caution.

4.4. Practical implications and future research directions

The substantial prevalence and strong female predominance of regular occurrence of migraine or serious headaches among adolescents as well as the common co-occurrence with other unfavorable health and psychosocial conditions need to be recognized in (preventive) health care settings and schools. From a prevention perspective, skipping breakfast could be a relatively easily modifiable risk factor, but its potential for headache management needs to be confirmed in further studies. Also, our finding that residential greenness seems to protect against incident headache in girls, whereas it is not associated concurrently with headache, deserves further study.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/B225.

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