Bone 121 (2019) 227–231

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Full Length Article

Fractures in school age children in relation to sex and ethnic background: The Generation R Study

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ARTICLE INFO

Keywords:
Fracture risk
Ethnic differences
Sex differences
Pediatric cohort

ABSTRACT

Fracture rate in childhood is increasing and its consequences may affect health and developmental processes and cause school absence and restricted activity days. There are scarce epidemiologic studies regarding fractures in children. The aim of this study was to evaluate if pediatric fractures show disparities across sexes and ethnic groups. This study was conducted based on data from 3632 participants of the Generation R Study. Prevalent fractures were assessed using a questionnaire at a mean age of 9.7 years. Child's ethnicity was determined based on country of birth of the parents using questionnaires (geographic ancestry) or admixture analysis (genetic ancestry). Associations between fracture occurrence and sex or ethnicity were evaluated using logistic regression models adjusted for age, weight, lean mass fraction, bone mineral density (BMD) and sex/ethnicity. Fracture was reported for 525 (14.5%) children. The great majority of these children were classified as European (N = 3164), followed by African (N = 283) and Asian (N = 185) based on geographic ancestry. Similarly, the highest proportion of Europeans was observed based on genetic ancestry. Prevalence of fractures was not different between boys and girls, even after adjustment for possible confounders (OR: 1.03, 95% CI 0.84–1.27, p-value = 0.8). However, odds of prevalent fractures were two times higher in European when compared to Asian children (OR: 2.01, 95% CI 1.17–3.45, p-value = 0.01), and 1.5 times higher when compared to African children (OR: 1.50, 95% CI 1.00–2.26, p-value = 0.05). Overall, in this study, European children showed a highest risk of prevalent fractures independently of factors such as body composition and BMD, while no difference in the prevalence of fractures between boys and girls was observed.

1. Introduction

Fractures in the elderly result in substantial mortality, morbidity and socio-economic costs, and have, therefore, been comprehensively studied [1–3]. However, only few studies have focused on the incidence of fractures in children. As in the adult population [4,5], nowadays, the rate of fracture in childhood is increasing [6–9], and is similar to that described in adults [6,10]. Pediatric fractures may affect the health and diverse developmental processes of children [6,11,12] and result in time-off school and restricted activity days [13]. While studies in the elderly population show that fracture risk is higher in women than in men [14,15], studies in younger adult populations show that men suffer more fractures than women [4]. In addition, ethnic differences in fracture risk have been described, showing that individuals of European descent have higher risk than non-Europeans [16,17].

The incidence of childhood fractures also varies depending on age, sex and ethnicity [18]. While the peak of fracture incidence occurs earlier in girls (~11 years) than in boys (~14 years) [6,19], boys are more susceptible to fracture than girls [18,20–27]. Also, a higher incidence of fractures has been reported in children of European background as compared to those of African, Asian or mixed background [18,23,24]. Nevertheless, the extent to which differences in bone

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https://doi.org/10.1016/j.bone.2019.01.019
Received 9 August 2018; Received in revised form 7 January 2019; Accepted 16 January 2019
Available online 22 January 2019

mineral density (BMD), body composition and/or physical activity contribute to explain pediatric fracture disparities in relation to sex and ethnicity remains unclear [23,28–30].

The aim of this study is to assess the determinants of childhood fractures in the Generation R Study, a multiethnic pregnancy cohort in The Netherlands, and to determine the contribution of sex and ethnicity variations in the risk of pediatric fractures. The large sample size, multiethnic composition and restricted geographical area of the Generation R Study, provide a suitable setting to convey insight into the determinants of pediatric fractures.

2. Methods

2.1. Study population

The Generation R Study is a multiethnic population-based pregnancy cohort study established in Rotterdam, The Netherlands, at the Erasmus University Medical Center. This study follows participants from fetal life until young adulthood. Mothers who gave birth between April 2002 and January 2006 (9778 participants) were asked to be included from the period of pregnancy. The Generation R Study was designed to assess early influences of environment and genetics on health, growth and development as described in detail elsewhere [31]. All measurements used in this research were registered in the third phase of the study, including questionnaires and visit of the participants to the research center at a mean age of 9.7 years. The Medical Ethics Committee of the Erasmus Medical Centre (MEC-2012-165) in Rotterdam, The Netherlands, gave approval for the study. Children and their parent(s) provided written informed consent before the beginning of each phase.

2.1.1. Participant characteristics

Information about sex and date of birth of every child were taken from the medical records and hospital registries. Age of a child was calculated as the difference between the dual-energy X-ray absorptiometry (DXA) visit date and the birth date. Trained personnel at the research center measured children's height (standing position without shoes to the nearest millimeter by a Harpenden stadiometer, Holtain Limited, Dyfed, UK) and weight (by a mechanical personal scale SECA, Almere, The Netherlands).

2.1.2. Geographic ancestry

Child's ethnicity was determined in the phase of enrolment using questionnaires and based on country of birth of the parents (according to the classification of Statistics Netherlands) [32]. All the children were categorized into European (Dutch, Turkish, American, Oceanic, North African and other European), Asian (Indonesian, Surinamese-Hindu and other Asians) and African (Surinamese-Creole, Antillean, Sub-Saharan African including Cape Verdian, and other African), as previously described [33].

2.1.3. Genetic ancestry

For the subset of children for whom genome-wide genotyping data was available, genetic ancestry was determined using the ADMIXTURE software [34], as previously described [35,36]. Briefly, this software models the probability of observed genotypes using ancestry proportions and ancestral population allele frequencies. Participants were grouped into three ancestral populations (European, Asian and African) based on their highest percentage (> 50%) of estimated ancestry proportions. Children who did not have 50% or more of certain ancestry proportion were classified as mixed ancestry group. Details about blood sample collection and genotyping of The Generation R cohort have been described elsewhere [37,38].

2.1.4. DXA measurements

Participants underwent whole body DXA, during their visit to the research center at a mean age of 9.7 years, using the same GE-Lunar iDXA device (GE Healthcare Lunar, Madison, WI). All scans were analyzed by well-trained research assistants using the same manufacturer's proprietary software (enCORE V. 13.60). Lean mass (LM) was obtained from the scans and used to calculate lean mass fraction (LMF) as the division of LM by weight. Total body less head BMD (TBLH-BMD) was the preferred phenotype to evaluate bone density as recommended by the International Society for Clinical Densitometry for the measurements in children [39].

2.1.5. Fracture assessment

Fractures were assessed based on questionnaires filled in by the parents. Questions were designed to inquire of fractures occurring since birth. In addition to fracture occurrence, those questionnaires also considered age when the first, second and third fracture occurred (in case of recurrent fractures), localization and severity of fractures.

2.1.6. Physical activity assessment

Parental self-completed questionnaires also included items regarding the physical activity of the participants at a mean age of 9.7 years. Information on the number of hours per week the child spends doing sports (training and/or competing) was condensed as follows: a) < 1 h per week, b) 1–2 h per week, c) 2–4 h per week, d) > 4 h per week. Further, answers in this item were converted to average hours per week as follows: a) < 1 = 0.5, b) 1–2 = 1.5, c) 2–4 = 3.0, d) > 4 = 6.0. Based on the type of sport performed most frequently, children were classified in those mainly involved in: football/hockey, basketball/handball/netball, tennis, judo/karate/other martial arts, ballet/jazz ballet/(street) dance or other types of sports. The number of sports the child participated in was also recorded and details about the other sports the child was involved in (if so) were not assessed. Total weekly energy expenditure (EE) (kcal) was calculated as a product of time (hours) spent on sports per week, child's weight (kg), MET-score for the particular sport the child practiced the most and the basal metabolic rate (BMR) of the child ($kcal \cdot kg^{-1} \cdot h^{-1}$), as recommended for pediatric populations [40]. The MET score for the sport that the child practiced most frequently was extracted from a compendium of energy expenditures available for youth (moderate effort value was used) [40]. An average MET score value was assigned to groups which included more than one sport (e.g., football/hockey), while for the children who were allocated to the last group (i.e., other types of sports), the average MET score value of the study sample was employed. BMR was calculated based on the Oxford equation [41]. Since the standards for its calculation are given separately for children from 3 to 10 years and from 10 to 18 years, and our age range was 8.53–11.98 years, we used the average values obtained from these two groups.

2.2. Statistical analyses

Association between ever-fracture and sex/ethnicity of the participant was carried out using a logistic regression model adjusted for age, weight, LMF, TBLH-BMD, sex (to assess differences in fracture risk across ethnicities), and ethnicity (to assess differences in fracture risk across sexes). Odds ratios (ORs) and 95% confidence intervals (CI) were calculated to describe those associations. Sensitivity analyses were carried out in subsets of the study population as follows. First, in the subset of children (N = 2510) who had physical activity information (weekly energy expenditure [EE]), the association between ever-fracture and sex/ethnicity of the participant was evaluated adding log-transformed EE as a covariate. Second, for the subset of children who were genotyped, the ethnic background was assessed based on genetic data and evaluated in the model. To do this, the log-ratio transformation [42] was used with the European component of ancestry as reference, thus evaluating whether the percentage of Asian or African ancestry influenced the odds of sustaining a fracture. All statistical

Table 1
Descriptive characteristics of the study sample; N- sample size, SD- standard deviation, *Z*- standardized values, BMI- body mass index, LMF- lean mass fraction, TBLH-BMD- total body less head bone mineral density, N/A-not applicable, *Count (percentage), European- reference category; **Z scores are standardized values based on the Generation R population distribution.

N = 3632	Fracture (525) Mean (SD)	No_Fracture (3107) Mean (SD)	p-Value ΔFracture
*Sex:			
Females (N = 1840, 50.7%)	255 (13.90%)	1585 (86.10%)	0.30
Males (N = 1792, 49.3%)	270 (15.10%)	1522 (84.90%)	
*Ethnicity:			
European (N = 3164, 87.1%)	482 (15.20%)	2682 (84.80%)	N/A
Asian (N = 185, 5.1%)	15 (8.10%)	170 (91.90%)	**0.01**
African (N = 283, 7.8%)	28 (9.90%)	255 (90.10%)	**0.02**
Age (years)	9.76 (0.30)	9.75 (0.29)	0.56
Weight (kg)	34.95 (6.61)	34.80 (6.57)	0.61
**Z_Weight	0.12 (1.01)	0.10 (0.99)	0.69
Height (m)	1.42 (0.06)	1.42 (0.06)	0.33
**Z_Height	−0.03 (0.94)	−0.07 (0.98)	0.39
BMI (kg/m^2)	17.29 (2.42)	17.29 (2.48)	0.95
**Z_BMI	0.19 (1.01)	0.19 (1.00)	0.99
LMF (%)	62.23 (6.07)	62.01 (5.83)	0.44
TBLH-BMD (g/cm^2)	0.673 (0.06)	0.682 (0.06)	**0.002**

significant p-values (p-value ≤ 0.05) are presented in bold.

analyses were conducted using SPSS Statistics version 21 (IBM Corp, New York, USA), where statistical significance was set at p-value ≤ 0.05.

3. Results

This study included 3632 children (1792 boys and 1840 girls) at a mean age 9.7 (± 0.29) years with available fracture and ethnicity information, as well as anthropometric and DXA measurements (Table 1). The great majority of these children were classified as European (N = 3164), followed by African (N = 283) and Asian (N = 185) based on geographic ancestry (Table 2). Occurrence of at least one fracture was reported for 525 (14.5%) children, from whom 84 (16%) reported more than one fracture. Most of these children sustained the first fracture in the arm or wrist (54%), followed by 18% of fractures in leg or ankle, while the remaining fractures occurred at other body sites (25%), or had no localization reported (3%). Furthermore, the majority of the fractures reported were classified as of moderate severity (56%), followed by average (37%) and very low number of severe (3%) or unidentified severity (4%). Overall, there were no significant differences in age, weight, height or LMF between children who sustained a fracture and those who never fractured. In contrast, mean TBLH-BMD was 0.01 g/cm^2 lower in the group of children who sustained a fracture as compared to those who did not (95% CI 0.02–0.40, p-value = 0.002) (Table 1). The proportion of girls who sustained a fracture (13.9%) did not differ significantly (OR: 1.10, 95% CI 0.92–1.33, p-value = 0.3) from the proportion of boys who fractured (15.1%), while the proportion of European children who fractured (15.2%) was 2 times higher than the proportion of Asian (8.1%) and 1.6 higher than the proportion of African children (9.9%) in the fractured group (OR: 2.04, 95% CI 1.19–3.45, p-value = 0.01 and OR: 1.64, 95% CI 1.10–2.44, p-value = 0.02, respectively) (Table 1).

In our study population, the proportion of girls in the Asian (48.65%) or African (50.88%) groups did not differ significantly from the one in the European group (50.76%) (p-value > 0.5) (Table 2). Asian children were significantly shorter when compared to European children, and had significantly lower LMF and TBLH-BMD (p-value < 0.01). African children were significantly older (p-value = 0.02), heavier, had significantly higher BMI and TBLH-BMD and significantly lower LMF, as compared to the European children (p-value ≤ 0.001) (Table 2).

Sex differences in fracture occurrence were not observed after correction for age, weight, LMF, TBLH-BMD and ethnicity (OR: 1.03, 95% CI 0.84–1.27, p-value = 0.76). Conversely, ethnic differences were observed in the adjusted models. The odds of fracture were 2 times higher in European children when compared to Asian (OR: 2.01, 95% CI 1.17–3.45, p-value = 0.01) and 1.5 times higher when compared with African children (OR: 1.50, 95% CI 1.00–2.26, p-value = 0.05). Analyses performed in the subset of children with physical activity assessment (N = 2510) showed the same trend for Asian children as compared to Europeans (OR: 2.12, 95% CI 1.02–4.42, p-value = 0.05) and inclusion of EE in the model resulted in a 7% drop in the estimated OR (OR: 1.98, 95% CI 0.95–4.13, p-value = 0.07). On the other hand, in this subsample, the difference in odds of fractures between European and African children was not statistically significant even before the correction for EE (OR: 1.36, 95% CI 0.83–2.23, p-value = 0.23), likely due to the reduced sample size. Inclusion of EE in the model resulted in a 8% drop in the estimated OR (OR: 1.25, 95% 0.76–2.05, p-value = 0.39).

The evaluation of ethnic background as a risk factor for pediatric fracture was also performed in 2360 children employing a genetically determined ancestry assessment: 2171 Europeans, 62 Asians, 105 Africans and 22 children with mixed ancestry (Supplementary Table 1). We did not find significant differences in fracture risk across the three ancestral populations (p-value > 0.1, excluding admixed children).

Table 2
Descriptive characteristics of the study sample across different ethnic groups evaluated based on geographic data; N- sample size, SD- standard deviation, Z-standardized values, BMI- body mass index, LMF- lean mass fraction, TBLH-BMD- total body less head bone mineral density; *Count (percentage), European-reference category, **Z scores are standardized values based on the Generation R population distribution.

N = 3632	Europeans (3164) Mean (SD)	Asians (185) Mean (SD)	p-Value	Africans (283) Mean (SD)	p-Value
*Sex:					
Females (N = 1840, 50.7%)	1606 (50.76%)	90 (48.65%)	0.58	144 (50.88%)	0.97
Males (N = 1792, 49.3%)	1558 (49.24%)	95 (51.35%)		139 (49.12%)	
Age (years)	9.75 (0.29)	9.72 (0.29)	0.29	9.79 (0.32)	**0.02**
Weight (kg)	34.65 (6.31)	33.95 (6.72)	0.16	37.23 (8.64)	< **0.0001**
**Z_Weight	0.09 (0.97)	−0.05 (1.11)	0.06	0.39 (1.14)	< **0.0001**
Height (m)	1.42 (0.06)	1.40 (0.07)	**0.001**	1.42 (0.07)	0.36
**Z_Height	−0.05 (0.96)	−0.28 (1.06)	**0.002**	−0.03 (1.03)	073
BMI (kg/m^2)	17.20 (2.37)	17.23 (2.63)	0.90	18.32 (3.14)	< **0.0001**
**Z_BMI	0.16 (0.98)	0.14 (1.14)	0.70	0.55 (1.11)	< **0.0001**
LMF (%)	62.25 (5.72)	60.08 (5.90)	< **0.0001**	61.02 (6.93)	**0.001**
TBLH-BMD (g/cm^2)	0.678 (0.06)	0.665 (0.06)	**0.004**	0.714 (0.07)	< **0.0001**

significant p-values (p-value ≤ 0.05) are presented in bold.

Nevertheless, there was a trend for children with higher percentage of Asian ancestry having lower odds for fracture (OR $_{(\text{per log[Asian/European] proportions})}$: 0.94, 95% CI 0.89–1.01, p-value = 0.08). No differences in the risk of fracture were observed with the increase of African percentage of ancestry (0.96, 95% CI 0.903–1.03, p-value = 0.23).

4. Discussion

This study assessed sex and ethnic differences in fracture prevalence in 3632 children at a mean age of 9.7 years. There were no differences in the risk of fracture between boys and girls, while a significant difference in fracture risk was found across different ethnic groups. In European children, the odds of fracture were 2 times higher when compared to Asian and 1.5 times higher when compared to African children, even after the adjustment for age, sex, weight, LMF and TBLH-BMD.

Differences in fracture risk in boys and girls have been previously reported [18,20–27]. The higher risk in boys to sustain fractures has been attributed to their higher involvement in sports and the fact that they spend more time outdoors than girls [21,30]. In contrast with these reports, in a study by Rennie et al. [20] boys and girls showed a similar fracture incidence up to the age of 12, when a significant increase in the fracture rate in boys was noted. Likewise, in our study, where fracture prevalence was evaluated at a mean age of 9.7 years, no sex differences were observed even after adjustment of possible confounders, which could have biased this association towards the null.

The higher fracture susceptibility in European children as compared to the other ethnicities reported here is in line with previous studies from South Africa, USA and UK [18,23,24]. These studies all suggested that differences in BMD and physical activity across ethnicities partially explained the higher fracture risk sustained by European when compared to Asian or African children. In the present study, we observed higher BMD in African children, but lower BMD in Asian children when compared to Europeans (Table 2). European children had a higher risk of prevalent fracture than both Asian and African children even after the adjustment for BMD. Additionally, our sensitivity analyses, including a questionnaire-based assessment of physical activity for each child, did not suggest that exercise levels explained differences in fracture risk of Asian children as compared to European children. Nevertheless, these analyses were performed in a subset of the population (2510 participants, comprising 180 African and 109 Asian children). The reduced statistical power, as result of the limited sample size, restrained us from observing significant differences in the odds of fractures between European and African children, even before the adjustment for EE. However, it is worth noting that LMF could be considered as a proxy of physical activity and that, indeed, in our study, it was higher in European than in children of Asian or African background (Table 2). Yet, European children had a higher risk of prevalent fracture than both Asian and African children even after the adjustment for LMF. Overall, these findings imply that other factors, such as bone geometry, could also shape the differences in fracture risk in children across ethnicities [43], and hence, should be further investigated.

As the concept of ethnicity is framed in terms of both a cultural and a genetic context, we also evaluated whether genetic ancestry was associated with pediatric fracture. This approach is particularly important within the Generation R Study, where many of the participants classified as of Dutch ethnicity are the third generation of their family to be born in The Netherlands [38]. Consequently, the genetic ancestry of these children cannot be fully captured by the questionnaire-based ethnic classification. Although an increase in Asian genetic proportion showed a trend towards decrease in the odds of fracture, no significant differences were found across the three continental ancestries. The 65% reduction in sample size while performing the genetic ancestry analyses could be responsible for this negative result, as it affected the number of children classified as non-European notably (64.3% reduction). Therefore, to establish an effect of genetic ancestral components in the risk of fracture, a replication in a better powered setting is required.

Altogether, the large sample size, multiethnic composition and restricted geographical area of the Generation R Study, provide a suitable setting to convey insight into the etiology of pediatric fractures, particularly with regard to ethnic background. A strength of our study is that participants were all residents in the city of Rotterdam, within a similar age range and examined in the same research center, resulting in a relatively homogenous setting. Nevertheless, we were not able to assess sex and ethnic differences in the severity, localization, or number of fractures as this information was available only for a small number of the participants, resulting in poor statistical power. Our study has also other limitations. Information on fracture occurrence was collected from the parents and not radiographically confirmed, therefore, we could not exclude the presence of recall bias. Also, the limited statistical power in the assessment of physical activity prevents us to fully discard its role in the reported ethnic differences. Importantly, physical activity was assessed in terms of energy expenditure. EE does not distinguish between mild and vigorous/contact physical activities which are more likely to cause a fracture. Furthermore, the calculation of the EE was based on multiple assumptions, as described in the methodology section. However, a potential error in the BMR calculation would affect participants regardless of sex or ethnic background and, therefore, would not change our conclusions. The lack of information on other sport(s) a child may be practicing or the averaging of activities according to the questionnaire options could biased the calculated EE. The effect of both geographic and genetic ancestry on fracture risk needs to be replicated in other pediatric cohorts as the number of non-European children was small in our study.

5. Conclusion

In conclusion, our study corroborates the predisposition of European children to sustain fractures as compared to children from other ethnic backgrounds independently from BMD or body composition. However, given the small number of non-European children in the Generation R Study, caution is required in the interpretation of the current findings. The lack of association between sex and pediatric fracture - even in our well-powered study - could be specific to the age at which our assessment was made and should be addressed in future studies. The influence of other potentially important factors in fracture risk, such as bone geometry, remains unknown, and further investigations in this direction could provide new insight into ethnic disparities.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bone.2019.01.019.

Funding sources

The general design of Generation R Study is made possible by financial support from The Erasmus Medical Center, Rotterdam, The Erasmus University Rotterdam, The Netherlands Organisation for Health Research and Development (ZonMw), The Netherlands Organisation for Scientific Research (NWO), The Ministry of Health, Welfare and Sport. Additional grants from The Netherlands Organisation for Health Research and Development supported this study (ZonMw 907.00303, ZonMw 916.10159, ZonMw VIDI 016.136.361 to V.W.V.J., and ZonMw VIDI 016.136.367 to F.R. and C.M-G.).

Declarations of interest

None.

Acknowledgements

We gratefully acknowledge the contribution of children and parents, general practitioners, hospitals, midwives and pharmacies in Rotterdam, involved in the Generation R Study.

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