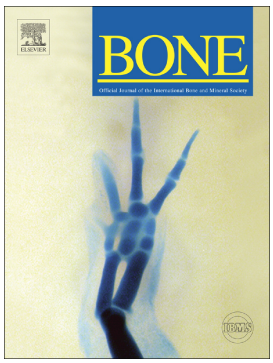

Maternal alcohol consumption during pregnancy associates with bone fractures in early childhood. A birth-cohort study of 6718 participants

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Maternal alcohol consumption during pregnancy associates with bone fractures in early childhood. A birth-cohort study of 6718 participants.

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Declaration of Interest

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Abstract

Fractures are common injuries in children, but their underlying biological and environmental risk factors are not well known. Maternal alcohol consumption during pregnancy is a known risk factor for bone malformations and impaired growth, in connection with Fetal Alcohol Spectrum Disorders (FASD). There is evidence that even lower doses of alcohol than what is needed for FASD can cause changes in the developing bone. Birth weight and length may also associate to childhood

fractures. The aim of this study was to find out whether there exist associations between maternal alcohol use during pregnancy, birth weight or length and fractures of the long bones in childhood.

A prospective birth cohort was performed, including all women in Northern Finland with an expected date of delivery between July 1985 and June 1986, and their offspring (N = 9432). The National Hospital Discharge Register (NHDR) provided the information on inpatient treated fractures. The subjects who declined participation or were treated as outpatient were excluded. The final study population consisted of 6718 children (71.2%). 98 (1.5%) of them suffered from inpatient treated fracture of a long bone (N = 105). Maternal alcohol consumption during pregnancy was inquired by questionnaires during late pregnancy or shortly after parturition. The birth length and weight were recorded immediately after birth.

Binomial regression analysis was used to determine the association between the potential explanatory variables and bone fractures. Gender, socioeconomic status of the family, maternal age, premature birth, body mass index (BMI) of the children and maternal smoking during pregnancy were taken as possible confounders.

In this study, the maternal alcohol consumption during pregnancy was associated to 2.22-fold (CI 1.09 – 4.12 , $p < 0.02$) increased risk of a long bone fracture before the age of eight. Birth weight or length did not associate to childhood fractures.

Bone fractures are an important cause of morbidity in childhood. Their prevention should start from the prenatal period by protecting the fetus from the alcohol exposure.

Key words: Prenatal alcohol consumption, Childhood fracture, Bone fracture, Birth weight, Birth length

1. Introduction

In general, childhood fractures are common injuries causing pain and suffering. According to literature, before the age of 18 approximately 27-50% of children suffer from a bone fracture [1,2]. The incidence of childhood fractures under five years of age has been shown to be 50-100/10 000 person years [3-5]. The risk of recurrent fracture may be as high as 20% [6]. These high rates show that children without known bone affecting diseases break them repeatedly. There may be several bone-affecting reasons behind this e.g. calcium intake, diet, smoking, physical activity and prenatal conditions.

There is evidence that the intrauterine environment affects the development of the fetus and causes physiological changes that increase the risk of adverse health outcomes later in life [7,8]. In utero, ethanol exposure is known to cause several health problems in the offspring, known as Fetal Alcohol Spectrum Disorder (FASD) [9-11]. The disorder is characterized by growth retardation and abnormalities in the craniofacial bones and central nervous system [10-12]. The minimum amount of alcohol needed to cause FASD is not exactly known, but from the literature can be found amounts as low as half a drink per day or three or more drinks per occasion (one drink equals approximately 14 grams of ethanol) [10,11].

Fetal ethanol exposure has also been shown to cause delayed bone maturation, lower bone age and short stature in children [13,14]. Simpson and associates have shown, with a rodent model, that even moderate alcohol consumption during pregnancy causes changes in the fetal skeletal development that are independent of the fetal growth [15]. In the study, the authors describe that

peak blood ethanol concentration of ≤ 50 mg/dL is a level accepted to represent moderate drinking and this was achieved when the rodent dams consumed 25% ethanol derived calories [15]. Simpson et al. found out that the ethanol disrupts ossification especially in ulna, radius, tibia and sacrum [15]. This effect was observed at lower doses of ethanol (25% ethanol derived calories) than what was required (36% ethanol derived calories) for actual growth retardation [15]. In other words, Simpson et al. showed that the impaired ossification of the bones is seen in lower doses of ethanol than what is needed for the length of the bone to be affected [15]. Snow and Keiver showed that alcohol decreases the total amount of bone in fetus, reduces the length of the diaphysis and corrupts the organization of the histological zones in the epiphyses [16].

Furthermore, birth weight and length may reflect the intrauterine circumstances, and thus these factors may be related to fracture risk in childhood. According to previous studies, birth weight is associated with bone mineral density (BMD) in children under the age of 10 [17,18]. However, with regard to the actual fracture risk, birth weight has not been found to be related [19,20]. Jones et al. found that birth weight had no association with fractures, but high birth length was associated with prepubertal bone fractures [21].

Further research is needed on the causes that explain bone fractures in children with no bone-affecting diseases. Previously we reported that maternal smoking during pregnancy increased the risk of childhood bone fractures [22]. The aim of this study was to analyze the association of maternal alcohol use, birth weight and birth length with fractures of the long bones in early childhood.

2. Materials and methods

2.1. The study population

The study population consisted of a comprehensive Finnish, pregnancy-birth cohort, which included all women (N = 9362) who were living in the two northernmost provinces of Finland and whose expected date of delivery was between July 1985 and June 1986. Regular follow-ups have been performed to the women and their 9432 live-born children since the children's birth. The detailed description of the cohort can be found in a study by Järvelin et al. [23]

The present study included 6718 persons (3363 girls and 3355 boys) who gave permission to use their information for research purposes and to link it to the national health register data and who did not meet the other exclusion criteria explained in section 2.6. Altogether 2711 individuals did not grant the permission to use their data for scientific research and there is no information available on these people.

The research was approved by the Ethics Committee of the Northern Ostrobothnia Hospital District. The cohort participation was voluntary and those who took part signed an informed consent document. The personal information was replaced with identification codes for anonymization purposes. In the analysis, we used individual level data, but report only group level data. The study followed the principles of the Declaration of Helsinki.

2.2.The fracture information

The fracture information was obtained from the National Hospital Discharge Register (NHDR) currently known as the Care Register for Health Care [24]. The register contains information of all hospital treated fractures, including discharge dates and diagnoses. The NHDR includes all inpatient treatment episodes in Finland, and it is coordinated by the Finnish National Research and Development Center for Welfare and Health. The register is the oldest nationwide discharge

register in the world [25]. In the study area, it is mandatory to report information of all injuries to the nationwide NHDR. Fracture patients treated outside the hospital were not included in this study. The treatment of simple fractures took place mainly in primary healthcare centers by general practitioners and these fractures were not included in the NHDR either. All in-hospital treated fractures were comprehensively included in the analysis (fracture yes/no) and the diagnose codes according to the International Classification of Diseases (ICD-9) were used to separate the fractures from each other in cases where the subject had several fractures. If there was more than one period of hospitalization with the same ICD code, the fractures were interpreted to be caused by separate injuries if the hospitalization dates were separated by more than six months.

Altogether 104 cohort participants had suffered from 112 inpatient treated fractures, before the age of 8. Out of these fractures six were other than long-bone fractures (four skull and two facial bone fractures). Given that these bones go through intramembranous ossification rather than endochondral, these patients were excluded to improve the coherency of the material. Further, it was deduced that at least some of these fractures may have been caused by high energy or intentional trauma, thus not giving reliable information on the potential underlying fragility of the bone. For the same reason, the only vertebral column fracture was removed from the material. Clavicle is a long bone that develops both by endochondral and intramembraneous pathways and the two clavicle fractures were included in the analysis. After these exclusions the study material comprised of 105 fractures. The included fractures and their ICD-9 codes are presented in Table 1

The NHDR data includes the external causes of every injury but the register was not inclusive in this respect. Out of a total of 105 fractures, an external cause was reported for 81 fractures; a large portion of them (N = 35) were low to moderate energy accidents such as tripping, slipping, falling

to the same level or falling from less than a meter height. For the rest of the fractures, the energy of the trauma could not be determined.

Fracture	ICD-9	Number of fractures in the population
Humerus	812	37
Radius or ulna	813	32
Tibia or fibula	823	19
Femur	820&821	9
Finger	816	6
Clavicle	810	2

Table 1. The in-hospital treated long bone fractures in the study population

2.3. Alcohol consumption

The information of the alcohol consumption was collected prospectively, before the fractures. The midwives at the communal maternity centers delivered structured questionnaires during the first antenatal visit, on average on the 10th gestational week, to the expectant mothers which they returned if still pregnant after 24th week. The time when the alcohol consumption took place was inquired in three parts: pregnancy weeks 1-16, 16-28 and after week 28. The amount of alcohol was inquired as a structured question with three categories: 1-5 alcoholic drink equivalents per week (14-70 grams of ethanol), 5-20 alcoholic drink equivalents per week (70 – 280 grams of ethanol) and over 20 alcoholic drink equivalents per week (over 280 grams of ethanol). One alcoholic drink equivalent equals approximately 14 grams of ethanol i.e. 40ml of distilled spirits or 150ml wine or 350ml beer. 418 mothers did not answer the questionnaire and they and their offspring were removed from the alcohol exposure analysis to reduce the bias. The exposure to alcohol was taken as a binary variable (yes/no) in the analysis.

2.4. Birth weight

All the cohort participants had their birth weight recorded. The participants were categorized into three groups according to their birth weight: low birth weight, high birth weight and a control group with regular birth weight. The low weight group consisted of those children (N = 216) whose birth weight was less than the mean weight minus twice the standard deviation (<2500g), and the high weight group included those (N = 117) who weighted more than the mean weight plus twice the standard deviation (>4637g). The remaining children formed the weight reference group (N = 6385).

2.5. Birth length

The cohort participants were also classified into three groups according to their birth length. Children whose birth length was less than the mean length minus twice the standard deviation were classified into the low birth length group (<46.1cm, N = 265). Those children, whose birth length was more than the mean length plus twice the standard deviation, were classified into the high birth length group (>54.9cm, N = 130). The remaining children formed the reference group for birth length (N = 6253).

2.6. Exclusions and confounders

The original cohort included 9432 live born children. After removing those who refused to participate, the data consisted of 6721 participants. Three cases were excluded from the study population since they were suffering from osteogenesis imperfecta or a possible bone affecting malignancy. There were no cases with diagnosed FAS or FASD cases among the study population. The question of the prenatal alcohol consumption was left unanswered by 418 mothers out of 6718. The reason for their refusal to answer this question was not available and their offspring were

removed from the alcohol analysis to reduce the bias. The children of these 418 mothers had suffered eight fractures and therefore in the alcohol analysis 90 fractures were taken into account. Those cohort participants (N = 57) whose birth length was not recorded were removed from the birth length analysis. The subjects with a skull, facial bone or vertebral column fracture, were removed from the analysis, as explained in Chapter 2.2.

The following parameters were assessed as potential confounders: gender, socioeconomic status of the family, mother's age at childbirth, the BMI of the child at 7 years of age, maternal smoking during pregnancy and prematurity (birth week <37). Boys are known to be more prone to fractures than girls [2]. The family's socioeconomic status has been shown to be a potential confounder and the education of the father is the most reliable indicator of the socioeconomic status of the family [1,26,27]. The father's education was classified as follows: basic education (1–10 years of grade school), secondary level (high school graduate or vocational school) and tertiary level (attended or graduated from college or university) [22]. Higher maternal age (≥ 35 years) has also been associated with an increased risk of childhood fracture [19]. The average age of the mothers at childbirth was 29.1 years (range 17-51 years). The mothers were categorized into three groups according to the age at childbirth: under 25, 25 to 35 and over 35. Previously it has been shown that the maternal smoking during pregnancy can affect the BMD of the child and that the smoking associates to higher fracture risk in childhood [22,28]. Therefore, maternal prenatal smoking was included as a confounder. Prematurity of the child was also taken as a confounder in the analysis, since it affects the birth weight and length, and may affect the development of the bone.

2.7. Statistical analysis

The main outcome variable was a fracture of a long bone before the age of eight. In the study country, all children are obliged to start primary school at the latest during the year they turn eight.

The association of maternal alcohol consumption during pregnancy, child's birth weight and birth length to fractures of the long bones was examined by binomial regression analysis with and without confounding variables. The results are presented as Odds Ratios (ORs) with their 95% confidence intervals (95% CIs) and P-values. The difference in fracture rates between the children whose mothers answered the alcohol question and the children whose mothers did not answer was tested using two-proportions Z-test. The statistical analyses were performed by using R software version 3.5.0 (2018-04-23, The R Foundation for Statistical Computing) and RStudio Software version 1.1.453 (RStudio Inc.).

3. Results

3.1.Patient characteristics

Altogether 98 children had suffered from an inpatient treated fracture of a long bone (Table 2). Of the children with a fracture 66 (67.3%) were boys and 32 (32.7%) were girls. In total there were 105 fractures, as seven children had suffered two fractures. The mean age was 4.6 years (ranging from less than one to 7, SD 2.0 years) at the time of the fracture.

	Girls (N = 3363) % (n)	Boys (N = 3355) % (n)
Childhood bone fractures before the age of eight		
No	99.0 (3331)	98.0 (3289)
Once	0.98 (33)	1.9 (63)

Twice	0.09 (3)	0.15 (4)
Maternal alcohol usage during pregnancy		
No	94.0 (3160)	94.5 (3172)
Yes	6.0 (203)	5.5 (183)

Table 2. Characteristics of the study population

3.2. Prenatal alcohol consumption

In the cohort, 765 (11.4%) mothers reported using alcohol during pregnancy weeks 1-16. Altogether, 535 of the mothers reported drinking 1-5 alcoholic drink equivalents per week (14 – 70g of ethanol), 18 mothers reported 5-20 alcoholic drink equivalents (20 – 280g of ethanol). The rest did not comment on the amount. 386 (5.8%) mothers reported that they had continued to use alcohol during pregnancy weeks 16-28 (Table 3). Out of these, 300 mothers reported having used a maximum of five alcoholic drink equivalents per week and 2 mothers stated that they had used 5-20 alcoholic drink equivalents per week. The rest did not comment on the amount. According to the questionnaires, 171 mothers still reported use of alcohol 1-5 alcoholic drink equivalents after the 28th week of pregnancy. The alcohol consumption reported by the mothers is presented in Table 3. 418 mothers did not answer the alcohol question and the fracture rate among their children was 1.9% (eight fractures), compared to the 1.4% fracture rate among the rest of the population (p=0.6).

Amount of alcohol	Pregnancy week 1-16 (N)	Pregnancy week 1-28 (N)	Pregnancy week, >28* (N)
1-5 drink equivalents	535	300	171
5-20 drink equivalents	18	2	-
Not known**	212	84	-

*The mothers who reported that they had continued to use alcohol after 28th pregnancy week
**Those mothers who declared that they had drunk alcohol, but did not specify the amount

Table 3. The reported alcohol consumption during pregnancy.

The mother's alcohol consumption during weeks 1-28 of pregnancy was associated with a 2.21-fold (CI 1.10 – 4.01, p = 0.02) increase in the offspring's risk of suffering a hospital-treated fracture of a long bone before the age of eight. When the confounders described in section 2.6. were included in the analysis, the result did not change significantly; the adjusted odds ratio was 2.22 (CI 1.09 – 4.12, p = 0.02) (Table 4). The alcohol usage during pregnancy weeks 1-16 was associated with slightly increased risk of a long bone fracture (OR 1.20), but the result was not statistically significant (CI 0.65 – 2.03, p = 0.5). The risk of a long bone fracture was elevated (OR 1.67) also for those subjects, whose mother had continued to use alcohol after pregnancy week 28, but the result was not statistically significant (CI 0.51 – 4.01, p = 0.3).

		OR	95% CI	p-value
Alcohol consumption, weeks 1-16				
Without confounders		1.20	0.65 – 2.03	0.5
Alcohol consumption, weeks 1-28				
Without confounders		2.21	1.10 - 4.01	0.02
Adjusted with confounders*		2.22	1.09 - 4.12	0.02
Alcohol consumption, weeks > 28				
Without confounders		1.67	0.51 – 4.01	0.3
Birth weight**				
	Low	0.72	0.19 – 2.30	0.61
	High	$1.6x10^{-6}$	$1.25x10^{-65}$ – 0.56	0.97
Birth length**				
	Low	0.47	0.10- 1.55	0.26

High	0.54	0.03 - 2.44	0.54

* sex, socioeconomic status of the family, maternal age at the time of giving birth, the BMI of the child at 7 years of age, maternal smoking during pregnancy, prematurity.
** prematurity as a confounder

Table 4. The association of maternal alcohol use during pregnancy, child's birth weight and birth length with childhood bone fractures. Odds ratios (OR) with 95% confidence intervals (CI) and p-values.

3.3. Birth weight

The mean birth weight of all the children, was 3568g (range from 1050g to 5560g, SD 534g)**.** The prematurity was taken as a confounder in the analysis. The fracture risk of the low (N = 207) and high weight group (N = 117) was compared to the reference group (N = 6381) separately and no statistically significant association with fractures was found from either of the groups (Table 4).

3.4. Birth length

The mean birth length was 50.5cm (range 35cm to 59cm, SD 2.20cm). Information of birth length was missing for 57 and they were removed from the material, as well as the prematurely born children. The prematurity was taken as a confounder in the analysis. The fracture risk of both low (N = 265) and high length (N = 130) group was compared to the reference group (N = 6253). No statistically significant association was found between low or high birth length and fractures (Table 4).

4. Discussion

In this comprehensive birth cohort study, linked to the National Hospital Discharge Register, we found out that even a moderate maternal alcohol consumption (approximately 1-5 alcoholic drink

equivalents i.e. 14 – 70 grams of ethanol per week) during pregnancy is associated with over two-fold increase in the risk of suffering a hospital-treated fracture of a long bone within the first seven years of life. The risk is independent of gender, maternal age, child's BMI, maternal smoking during pregnancy, premature birth and the socioeconomic status of the family. Previously, the association of fracture risk of the children and maternal prenatal alcohol consumption has not been thoroughly studied. A study by Orton et al. found no association between bone fractures of the children and harmful alcohol consumption of the parents, but this study did not investigate the maternal alcohol usage during pregnancy [29].

In our analysis, we did not find a statistically significant association between childhood long bone fractures and birth weight or birth length.

Disadvantageous effects of prenatal alcohol exposure are widely known; Fetal Alcohol Spectrum Disorder (FASD) is a common term used to describe health issues caused by ethanol exposure in utero. Growth retardation of the fetus and craniofacial dysmorphology are clinical consequences of FASD [12]. In humans, the growth deficits are found already at low levels of alcohol consumption (< 1 drink/day) [13]. There is also evidence that the fetal skeletal ossification is affected by ethanol in lower doses than what is needed for actual growth retardation of the fetus [15]. In their rodent study, Simpson et al. showed that the ethanol has effects on the fetal skeletal ossification at lower doses than what is required to affect the body weight or length of the fetus [15]. It is known that the effect of ethanol is more severe on the bones that go through a greater part of their development in utero and start the ossification of cartilage model early during prenatal period (ulna, radius, tibia) [15]. Simpson et al. have hypothesized that the pathways by which ethanol affects the skeletal development of the fetus, in particular the endochondral ossification of the cartilage model, are not the same that affect the general growth of the fetus [15]. The pathology behind the abnormal

osteogenesis is not well understood. In rodent models, there is evidence that the ethanol exposure causes decreases in total bone and diaphysis lengths and disrupts the organization of the resting, proliferative and hypertrophic zones within epiphysis [16]. On the other hand, evidence from a study with chick embryos showed that the exposure to ethanol decreased the length of the proliferative and hypertrophic zones in the epiphysis [30]. In the study by Li et al. the gastrulating chick embryos were treated with ethanol dose varying from 5 – 20 mg/egg during days 1.5 - 10 of incubation, which comprises approximately the first half of the incubation time, and then harvested for investigation [30]. Li et al found out that ethanol exposure inhibits chondrogenesis, produces excess reactive oxygen species (ROS) and alters the osteogenesis-related gene expression [30]. These studies by Li et al., Snow et al. and Simpson et al. have shown that in-utero alcohol exposure can harm the architecture of the developing bone in a subtle way that causes the bone to be more fragile, even though the growth of the fetus and later the general development of the child may not be affected [15,16,30]. Thus, bones may be more prone to fractures and even to osteoporosis through early exposure to alcohol.

Simpson et al deduced from their rodent model that the ethanol appeared to have the most effect on bones in which the ossification had advanced rather than on bones whose ossification was only beginning [15]. Therefore, Simpson et al. deduced, using rodent study, that the ethanol's effect on the ossification is the most dramatic to bone development stages after the cartilage calcification [15]. In human embryos, the ossification centers form in the long bones during pregnancy weeks 8 – 12, but the majority of the mineralization occurs during the third trimester [31]. Snow et al found out in a rodent study that the effects on hypertrophic zone support the hypothesis that ethanol in utero affects the later stages of long bone development [16]. This is in line with our finding that the fracture risk of the long bones is associated to maternal alcohol consumption after the first trimester.

The development of long and flat bones takes different paths. The long bones go through endochondral ossification where a hyaline cartilage template forms first and is later ossified, whereas in flat bone (e.g. craniofacial bones) the mesenchymal cells are directly ossified. Li et al have shown that the ethanol can inhibit the osteogenesis during flat bone development [30]. These effects take place very early on in the development of the embryo and are dose dependent in Li's analysis [30]. On the other hand, Muggli et al. have established that prenatal exposure to alcohol can influence the craniofacial development, even though the used amounts of alcohol are low (< 20 g – 70g of ethanol per week) [32]. However, in our research, the main focus was to find out the explanatory factors of the in-hospital treated bone fractures. Since the large majority of the fractures in our material were long bone fractures, the flat bone fractures were excluded from the analysis. The number of skull, face bone and vertebra fractures in this cohort was low and it was not possible to perform any subgroup analysis for the fractures of these different types of the bones. Further, we acknowledge that at least some of them might have been a consequence of child abuse or other intentional injuries and therefore they may not represent the underlying bone fragility reliably. In the future studies, it is important to address this issue in a larger set of data to achieve satisfactory number of flat bone fractures to analyze their association with alcohol exposure. It should be noted that among the 6718 cohort participants included in this study, there were no diagnosed fetal alcohol syndrome cases.

It has been observed that birth weight is related to BMD in children, but no association with the fracture risk has been found [17,18]. In this respect, our results are in accordance with previous findings. I.E. Jones et al found that high birth length is associated with a higher risk of fracture in prepubertal children, but this association was not found in our material [21]. We deduced that the difference is based on the different age of the patients between the studies. While Jones et al

counted the fractures in girls aged <9 years, and boys, aged <11 years, we counted the fractures in children until the age of eight. Environmental factors, such as recreational activities and general living conditions, may be more important in older children. In children below the school age the biological factors may have a greater effect.

The main strengths of the study are the large birth cohort and the reliable fracture data from the National Hospital Discharge Register. We took into account only the more severe, hospital-treated inpatient fractures, as we deduced that these may provide a better indication of the bone fragility than the very common and conventional, less serious fractures. The literature suggests that up to 30-50% of children get a bone fracture before the age of 18. In our current study only the more severe, inpatient treated, long bone fractures were taken into account. These accounted only 1.5% of the entire cohort. Therefore, it would be beneficial to replicate the analysis in the future with another population including all fractures: the less serious fractures should be included in the studies also and the results compared to our current findings.

As strength of our study, it should be noted that in the study country, health care system is based on high-standard public services. The private sector has minimal or lacking role in the inpatient treatment of childhood fractures. Therefore, high-standard treatment resources were available for all, regardless on their social status. As a conclusion, there is no inclusion bias as regarding the place of treatment.

In our study, we focused only on fractures before the age of eight. This is because the older the children get, the more their fracture risk is affected by recreational activities, personal behavior and other external reasons. This phenomenon has been observed by G. Jones et al., who found out that the association between maternal smoking during gestation and bone density disappeared during

late childhood and puberty [33]. In the study country, all children start their elementary school at the latest the year they turn eight, which we used as an age limit.

As a weakness, the study database of NFBC1986 does not include bone density measurements and therefore comparisons with other studies that have focused on bone quality rather than bone fractures cannot be made. In the future studies this aspect should be taken into consideration, since the bone mineral density can give additional information of the quality of the bone.

One limitation of our study is that the total amount of fracture cases was too low to enable subgroup analysis between different bones, fracture locations and subgroups of age and sex. The lack of information on injury types made it impossible to distinguish the high-energy injuries from other injuries. However, the fractures of the flat bones were excluded, and the material was coherent in this regard.

It should be kept in mind that the alcohol consumption of the mothers was recorded using questionnaires and this causes uncertainty to the actual amount of alcohol that was used. In addition, 418 mothers did not comment the alcohol consumption and it remains unclear whether this group included the heaviest alcohol consumers. It is possible that these mothers had used great amounts of alcohol and did not give an answer at all for modesty. The proportion of the fractures was not significantly different between those who answered the alcohol question (1.4%) and those who left it unanswered (1.9%). In order to avoid the potential selection bias, the offspring of these mothers were removed from the alcohol analysis.

Further, we didn’t have any information about the 2711 cohort cases that didn’t give permission to use any information in scientific purposes. We deduce that the remaining 6718 cases that comprised

the study population represented well the average maternal age and social class structure of Northern Finland at that time, however, we don't know if they differed from participants as regarding their alcohol use during pregnancy.

5. Conclusion

This prospective, large birth-cohort study presented over two-fold risk of fractures of the long bones in children who had been exposed to alcohol in utero, as compared to the children whose mothers did not consume alcohol during their pregnancy. This result was independent of the potential confounders.

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Highlights

- The association of maternal alcohol usage during pregnancy on children's fractures was studied
- The material was taken from a birth cohort including 6718 subjects
- Maternal prenatal alcohol usage was associated with increased risk of in-hospital-treated fractures