DURATION OF BREASTFEEDING AND PRESENCE OF CHILDHOOD OVERWEIGHT AT 3 YEARS OF AGE

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ABDELLA ROUN: DURATION OF BREASTFEEDING AND PRESENCE OF CHILDHOOD OVERWEIGHT AT 3 YEARS OF AGE
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ABSTRACT

Background: Breastfeeding is considered to protect against childhood obesity; however, the evidence remains inconsistent.

Objective: The aim of this study is to assess how the duration of exclusive and total breastfeeding are related to overweight at the age of 3 years.

Methods: A birth cohort of 3719 singleton infants carrying increased genetic susceptibility to type 1 diabetes was recruited in 1997-2004 from Pirkanmaa, southern Finland. Information on both breastfeeding and anthropometrics at 3 years was available for 2110 singletons. Overweight (obesity inclusive) was defined using International Obesity Task Force (IOTF) cut-offs for BMI. Logistic regression was used to model the relationship of duration of exclusive and total breastfeeding as well as potential confounders to child overweight.

Results: The durations of exclusive (median 1.6, range 0-8 months) and total (7.0, 0-25 months) breastfeeding were similar in boys and girls. The prevalence of overweight was higher in girls (15%) than in boys (8%, $p<0.001$). Shorter duration of exclusive (<3 months) and total (<3 months) breastfeeding were associated with higher risk for of overweight at 3 years of age. When adjusted for maternal weight, educational level, smoking during pregnancy and gestational diabetes, child's sex, birth weight and gestational, location of residence and paternal diabetes, only exclusive breastfeeding remained significantly related to overweight (<1 vs. ≥3 months OR 1.02 (95%CI 0.70-1.48), 1-2 vs. ≥3 months OR 1.64 (95%CI 1.09-2.47)).

Conclusion: There was no clear dose-response relationship between duration of breastfeeding and risk of child overweight when potential confounders were taken into account.

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REFERENCE TO THE ORIGINAL PAPER

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LIST OF COMMONLY USED ABBREVIATIONS

BMI	Body Mass Index
CDC	Center for disease control and prevention
DIPP	Type one diabetes prediction and prevention project
DEXA	Dual energy x-ray absorptiometry
IOTF	International Obesity Task Force
MRI	Magnetic resonance imaging
SPSS	Statistical Package for the Social Sciences
UNICEF	United Nations Children Fund
WHO	World Health Organization
WHtR	Waist circumference to height ratio

1 INTRODUCTION

Obesity is one of the major public health concerns of the 21st century. The prevalence is increasing in children and adolescents worldwide (11,12). Overweight and obesity are important determinants of health and may lead to different metabolic disorders. Many studies showed that childhood obesity is a major cause for metabolic disorders such as early type-2 diabetes, increased blood pressure, coronary heart disease, osteoporosis, increased cholesterol level, cancers of the colon, breast and ovaries (18,20,26). Breastfeeding is considered among one of the several factors that reduces the risk of overweight in children.

Over the past decades evidence for the advantage of breastfeeding has continued to increase. WHO and UNICEF recommend exclusive breastfeeding for the first 6 months, followed by continuing breastfeeding with complementary foods for 2 years of life (56). Breast milk is nutritious food for the baby as it provides energy and all the nutrients that the baby needs for the first months of life (56).

Many researchers have studied the association between breastfeeding and childhood obesity. Breastfeeding is generally considered to be one of the factors that are associated with a lower prevalence of obesity in children. However, the evidence remains inconsistent. A meta-analysis (57), reviewing 14 studies published between 2003 and 2006, reported no clear association between breastfeeding and childhood obesity. Three studies reported a protective effect of breastfeeding on obesity, four reported a partial protective effect, six reported no protective effect, and one reported a protective effect in children but not in adults (57).

Several studies have been conducted since then; the majority of them suggesting that breastfeeding would protect against childhood obesity (58-63). However, a range of studies

also reported that being breastfed does not affect the risk of becoming overweight later in childhood (64-66).

Beyerlein and Von Kries (72) recently conducted a review based on previous meta-analysis in this area. They concluded that there is no clear and concrete evidence for or against potential protective effect of breastfeeding against childhood overweight. The three meta-analyses and the interventional study in this review with overweight and obesity as an outcome reported a protective effect after adjusting for potential confounders. However, one meta-analysis with mean BMI as outcome found no significant association between breastfeeding and childhood overweight after adjusting for potential confounders. (72)

The aim of the present study is to assess whether duration of breastfeeding lowers the risk of childhood obesity or has no protective effect against it. Specifically, this question is addressed in a cohort study where detailed information on child feeding and anthropometrics as well as several potential confounding factors have been prospectively collected since the birth of the child.

2 LITERATURE REVIEW

The search strategy for this review involved identification of studies of breastfeeding and childhood obesity. Systematic search of electronic databases such as World Health Organization (WHO) web pages, Medline (Ovid) and Pub Med were conducted by using the following key words; ‘child’, ‘overweight’, and ‘breastfeeding’. Inclusion criteria for the studies were that they should have been published between 2006 and 2012 in English. Additionally, references cited in other articles relevant for the current study were included. In total about 100 studies were retrieved and around 70 of them met the criteria and were included in this review.

2.1 Definitions and methods of adiposity measurements

By definition overweight is the excessive accumulation of body fat that may cause impaired health (1). Adiposity is fat stored in adipose tissue. Measurement of this fat helps to identify the amount of the overall fat accumulated in a person. This consequently determines whether the person is overweight or obese.

There are two groups of measurement used to measure adiposity: sophisticated and simple. The first group consists of Magnetic resonance imaging (MRI), Dual energy x-ray absorptiometry (DEXA), densitometry and isotope dilution which is good measures of body fat and lean tissues. However, due to their complexity, lack of accessibility, need for professionals and expense they are not used for large populations. The second group, on the other hand, consists of anthropometric measurements such as skin fold thickness, body mass index and waist circumference. These are simple, quick and cheep measures of adiposity and are used for population based studies. (2)

One of the measures for body fat distribution is the ratio of waist circumference to height/length (WHtR). This is the ideal anthropometric measure for central (abdominal) obesity in children. Additionally it is a good indicator of children at a risk of developing type 2 diabetes and cardiovascular diseases (3). In contrast to BMI, WHtR measurements do not depend on age and sex however; no commonly accepted standard has yet emerged.

Skin fold thickness is used to estimate a body fat composition. It can be measured using different standard anatomical sites around the body to mention some; triceps, biceps, sub-scapular, abdominal, thigh and calf. The procedure starts when the tester pinches skin at the appropriate site to raise a double layer skin and the underlying adipose tissue. The clips are then applied to the pinch, and the results reported in millimeters (mm) are compared using the general guidelines. However, skin fold thickness does not have a validated general guideline for children. This is maybe due to lack of estimates for fat mass in children as they are in continuous development. (74)

Body mass index is a widely accepted measure of adiposity in children and adolescents. It is a type of anthropometric measure that can be calculated from a weight of a person in kilograms divided by his/her height in square meters. It is a good indicator for changes of weight that are greater than what is normally considered healthy for a given height (4).

Even though BMI cannot measure the actual fat distribution of the body since it uses both the lean and fat tissues for measuring the weight of a body (5), it is a good indicator for child overweight/obesity and other metabolic diseases as well as age and sex specific growth in children (6,7).

2.2 Classification of overweight and obesity

Different BMI cut off points are used in order to differentiate obesity in children. The most commonly used cut off points are the center for disease control and prevention (CDC), international obesity task force (IOTF) and the world health organization (WHO) references. Since children are in a continuous process of development, the BMI cut off depends on the age and sex of the child. The CDC classify child overweight and obesity as 85 and 95 percentiles based on age and gender respectively from a reference derived from five national surveys conducted in the USA (8). Whereas the IOTF cut offs classify child overweight and obesity (starting from the second year of life) as BMI cut offs equivalent to the adult cut off values (25 kg/m^2 and $30kg/m^2$ respectively) at the age of 18 years based on the surveys conducted in six countries (Brazil, Hong Kong, Singapore, the Netherlands, the United Kingdom and the United States) (9).

The 2006 WHO standard growth chart includes child overweight and obesity starting from birth up to 19 years based on data collected from six geographically different countries (Brazil, Ghana, India, Norway, Oman and the USA).(10)

2.3 Trends and prevalence of child obesity

Obesity is one of the major public health concerns of the 21^{st} century. The prevalence is increasing in children and adolescents worldwide (11,12). Previously, obesity was a problem of developed nations as undernutrition was for developing nations. However this concept is changing now since obesity is appearing in developing nations as well due to life style changes and urbanization.

Globally over 14.4% (92 million) of children aged 0-5 years were estimated to be at risk of overweight in 2010. Out of these 15 million live in developed and 78 million in developing countries. (13) The prevalence of overweight and obesity in preschool children increased from 4% in 1990 to 7% in 2010 worldwide (13). The trend increased both in developed and developing countries (11,13). However, the rate of increase in percent of prevalence is higher in developing nations (13). If the trend continues without intervention, the estimated number of overweight and obesity in preschool children will be 9% (9% in developing and 14% in developed countries) by 2020. The prevalence is higher in Africa (9%) compared to Asia (5%). However, the number of affected children is higher in Asia (18 million). (13)

In Africa the prevalence of overweight and obesity in children aged 0-5 years changed from 4% in 1990 to 9% in 2010. If the trend continues without intervention, the estimates for 2015 and 2020 will be 10% and 13% respectively. The number of prevalence differs according to sub region. The highest prevalence of overweight and obesity is in the northern region and the lowest prevalence in the western region. (13)

In Asia (excluding Japan) the prevalence of overweight and obesity in children aged 0-5 years increased from 3% in 1990 to 5% in 2010. Without intervention the trend is estimated to be 6% in 2015 and 7% in 2020. The prevalence is higher in the western part (15%) and lower in the south central parts of Asia. (13)

The prevalence of overweight and obesity in Latin America and the Caribbean did not show a significant increase in children aged 0-5 from 1990 to 2010. In this region the highest prevalence was in the Caribbean and Central America and the lowest was in Oceania (excluding Australia and New Zealand). There was a decrease in the prevalence of child overweight and obesity in South America from 8% in 1990 to 7% in 2010. (13)

A recent systematic review conducted in Australia indicated that the prevalence of overweight and obesity in children aged 2-18 years was high from 1985 to 1996 both in boys (10%-22%) and girls (12%-24%) (14). However, the trend did not show a rapid increase after 1996 to 2008 (boys 22%-24%, girls 24%-25%) respectively (14).

In Europe the prevalence of child overweight and obesity showed a significant increase between 1998 and 2007. The highest prevalence being in Southern Europe and the lowest in Central Europe. The range of prevalence in, 4 years old children, 2001 varied from 32% in Spain to 12% in the Czech Republic. In addition to this, a similar prevalence was observed in 4 years old children from 2000 to 2002 in Sweden (25%), Portugal (23%), Poland (23%), England (21%) and Northern Ireland (21%). From 2002 to 2005 the prevalence of overweight and obesity in 4 years old children was higher in Greece (27%) and Italy (22%) compared to The Netherlands (15%) and Romania (12%). (15)

In Finland, Kautiainen et al reported a slight increase prevalence of overweight in 12 years old boys (21% to22%) compared to girls (20% to 22%) from 1977 to 1999 respectively using a self-reported data (16). A recent study conducted in Finland based on measured data reported similar findings that the prevalence of overweight continued to increase significantly in 12 year old boys (10% to 19%) and girls (11% to 16%) from 1986 to 2006(17).

2.4 Effect of childhood obesity on health

Globally overweight and obesity are the fifth leading risk of deaths. Annually around 2.8 million adults die as a result of overweight and obesity (1). Obesity is known to be risk factor for metabolic disorders, such as increased blood pressure, type 2 diabetes, coronary heart disease, increased cholesterol level and hyperlipidemia (1,18-22). In addition to

metabolic disorders, childhood obesity is also a risk factor for such chronic diseases as arthrosclerosis, nonalcoholic fatty liver disease, asthma, cholelithiasis, osteoporosis, and cancers of the colon, breast and ovaries (23-26).

Childhood obesity also results in hormonal imbalance in both males and females. Due to this imbalance the body facilitates sexual maturity in girls, resulting being sexually active before the actual age of puberty. However, the reverse is true in case of overweight boys, who become sexually mature later than their non-overweight counterparts (27).

Being overweight/obese may result in psychological problems such as anxiety and depression as a result of stigma and discrimination among peer groups (28). Overweight children are considered lazy, naughty and stupid by their peer groups (28). In addition to this, obese adolescents have a lower chance of going to college, having jobs and getting married compared to their non-obese counterparts (28).

Overweight children have a higher risk of being obese in adulthood (23,29,30). A study conducted to assess the relationship between childhood obesity and the risk of coronary heart disease showed a strong relationship of being overweight in childhood and having coronary heart disease later in life. In this study, out of 186 obese children (BMI > 95 percentile), 144 were obese also as adults (BMI of > 30) (29).

2.5 Factors influencing childhood obesity

2.5.1 Diet and physical activity

The world's type of diet has changed significantly through time with a shift from healthy foods such as vegetables, grains and fruits to processed foods in which animal source foods

comprise the highest proportion of all calories (31). The major shift has been with an increased consumption of vegetable oils, added caloric sweeteners, an increase intake of dairy sourced foods and a decreased consumption of vegetables, fruits and whole grains (31). For example, a study based on the national representative household survey data in China reported that the consumption of animal foods tripled from 1952 to 1992. The rate of intake was smaller (5.6kg) per capita before 1979 whereas there was a steady increase of 21kg per capita between 1979 and 1999 (32).

World nutrition is highly influenced by globalization and a wide access to processed and ready to go foods. Due to high expense of healthy foods (fruits and vegetables) people are shifting to cheap but energy rich foods such as fast foods, sweetened beverages and salty snacks. Thus the consumption of those energy rich foods frequently leads to overweight and obesity in children and adolescents (33-35). For example, in the USA, energy dense fast food provides more than one third of the daily energy, total fat and saturated fat. Consumption is increasing because they are easily accessed due to low prices. In addition to this, in the USA the consumption of calorie added beverage sweeteners has been increasing for the past two decades. The national representative data from 1994 to 1998 estimates an intake of 318kcal/day for the average US resident aged ≥2 year. Moreover, it was reported that large amount of non-diet carbonated sweetened beverages are consumed at fast food places (34,35).

A study conducted in Norway shows that lack of proper eating; for example, missing breakfasts and not attending family meals, increases the prevalence of overweight in children. The study reported that children who eat breakfast five times or less per week have a higher prevalence of overweight compared to those having breakfast six times or more per week. (36)

Children who spend their leisure time watching television for more than four hours per day have a higher prevalence of being obese in later ages (36-38). In another study, it was

observed that lack of sleep, hours spent watching television and eating snacks have significant associations with childhood obesity at 5 years of age (39).

Moreover, decreased physical activity is also a predisposing factor for later obesity. This is because the energy rich food that is consumed by the child is not going to be used; instead it will be converted to fat to be stored in the body. As a result, the more energy consumed and the fewer physical activities performed in a day, the more accumulation of fat in the body, resulting in obesity in later life.

2.5.2 Socioeconomic and demographic factors

Many diseases are known to be affected by socioeconomic and demographic factors of society. Areas with lower socioeconomic status are high risk factors for overweight and obesity. The socioeconomic statuses of the parents also influence the type of nutrition and duration of breastfeeding. Mothers who have a low socioeconomic status are more often obese. As a result they do not breastfed their children as often compared to their counterparts in high social classes. Moreover, they consume energy rich snacks rather than healthy food due to a lack of knowledge and income. (40)

Studies conducted in Sweden reported that children living in semi-urban and rural parts of the country have a higher prevalence of overweight and obesity compared to children living in urban areas (41,42). The same result was reported in a study conducted in Finland showing that overweight in adolescents was associated with living in a rural area, both in Western and Eastern Finland, with lower educational achievement as well as with a father who is not employed outside home. Among girls, overweight was also associated with living in non nuclear families or with a mother who is unemployed (17,43). In addition to the above being a girl, being from a family with lower educational status or having fewer siblings increases the prevalence of childhood overweight and obesity (41,44).

2.5.3 Parental BMI

Parental obesity is one of the main predicting risk factors for childhood obesity. Several studies showed that being born of an overweight or obese mother increases the chance of being overweight in childhood and later in life (45,46). Moreover, the chance increases if both parents are obese (45-47).

A retrospective cohort study conducted in the USA in 2004, reported that children of obese mothers were twice as often large-for-gestational-age than children of normal weight mothers (48). Large-for-gestational-age babies are more likely going to continue as obese in their childhood compared to appropriate for gestational age babies (37). Similarly children of obese mothers had 2.4 to 2.7 times higher prevalence of obesity at the ages of 2 to 4 years compared to children born of normal weight mothers, with the risk increasing in children whose mothers were obese in the first trimester of pregnancy (48).

2.5.4 Maternal smoking status

Maternal smoking during pregnancy increases the risk of being overweight or obese in childhood and later in life (48,49). For example, a longitudinal study conducted in Quebec (Canada) observed that normal weight infants born from smoking mothers gained the highest amount of weight in the first five months of life. This in turn results in a higher BMI at the age of 4.5 years compared to children born to non-smoking mothers (50). A similar result was reported in a cross sectional study conducted in Bavaria (Germany) showing that children of smoking mothers had increased risk of being overweight or obese later in life (51).

The association between smoking status during pregnancy and childhood overweight depends largely on the duration of smoking, the number of cigarettes smoked and gestational age when exposed to smoking (40,49,51). For example, a cohort study

conducted in the United Kingdom reported that smoking at 28 to 32 weeks of pregnancy increases the prevalence of childhood overweight at the age of 7 years (37). On the other hand, in a study conducted in 2002, it was observed that children born with mothers who quit smoking before pregnancy showed a slight decrease in prevalence of obesity later in life compared to children who were born of smoking mothers during pregnancy (52).

2.5.5 Gestational age, gestational weight gain and birth weight

Studies have shown that infants born small for gestational age have a higher prevalence of overweight and obesity in childhood compared with infants born normal for gestational age (53). Moreover, a Dutch prospective cohort study conducted in infants born at less than 32 weeks of gestation discovered that, infant prematurity and the catch-up growth in the first years of life were associated with increased height, weight and BMI in later life (54). Crozier et al (55) reported that gestational weight gain was positively associated with birth weight: for every 5 kg increase in gestational weight there was a 76g increase in the weight of the infant (55). This complements further findings that there is a positive association between infant weight at birth and risk of childhood obesity at the age of seven years (37).

2.5.6 Breastfeeding

Over the past decades evidence for the advantage of breastfeeding and recommendation for its practice has continued to increase. WHO and UNICEF recommend exclusive breastfeeding for the first six months, followed by continuing breastfeeding with complementary foods for the first two years of life (56). Breast milk is nutritious food for the baby and it provides all the energy and nutrients that the baby needs for the first months of life. It promotes sensory and cognitive development, protects the infant against infectious and chronic diseases and contributes to the health and wellbeing of mothers (56).

Many researchers have studied the association between breastfeeding and childhood obesity. Breastfeeding is generally considered to be one of the factors that are associated with a lower prevalence of obesity in children. However, the evidence remains inconsistent. A systematic review (57), reviewing 14 studies published between 2003 and 2006, reported no clear association between breastfeeding and childhood obesity. Three studies reported a protective effect of breastfeeding on obesity, four reported a partial protective effect, six reported no protective effect, and one reported a protective effect in children but not in adults (57).

Several studies have been conducted since then, the majority of them suggesting that breastfeeding would protect against childhood obesity (58-63). However, a range of studies also reported that being breastfed does not affect the risk of becoming overweight later in childhood (64-66).

Most of the studies compared breastfed subjects with formula-fed subjects(60,63,67,68) and some of them compared the duration of breastfed subjects (58,65,67,69,70). For example, a cross sectional Canadian study conducted on preschool children found a decreased risk of overweight at the age of 4 years in children who were exclusively breastfed up to 3 months as compared to formula feeding and mixed feeding (a combination of breastfeeding and formula feeding) to 3 months after adjusting for the child's gender and age, whether the child was preterm or full term, the mother's education and current smoking status (63). Formula-fed children have a higher risk of overweight or obesity compared to breastfed counterparts. This may be due to an inability to self-regulate the amount of milk intake by the child in the case of formula feeding (bottle), or due to a higher protein content of the formula milk as compared to breast milk (71).

Similar results were reported in a German prospective cohort study, where children with longer duration of both exclusive and total breastfeeding had lower risk of overweight at

the age of 2 years taking into account maternal nationality, age, BMI, level of education, smoking during pregnancy and child birth weight (67).

Breastfeeding is also recommended for children at high risk of diabetes in order to decrease the prevalence of overweight and obesity (60). Crume et al. (58) reported that children from diabetic mothers that adequately breastfed (≥6 breast-milk months) showed smaller sub scapular-to-triceps ratio compared to less breastfed (<6 breast-milk months) counterparts. The same study reported that adequately breastfed (≥6 breast-milk months) children aged 6 to 13 years had lower BMI and waist circumference compared to inadequately breastfed (<6 breast-milk months) counterparts (58).

On the other hand, some studies argue that breastfeeding is not associated with a prevalence of childhood obesity. In an Australian birth cohort study, higher risk of overweight at the age of 8 years was observed in those children who were breastfed for less than 4 months compared to longer breastfed counterparts. However, the association was no longer statistically significant when maternal BMI, smoking status during pregnancy, level of education, as well as the birth weight, gestational age, sex, ethnicity and parity of the child were taken into account (69).

Similar results were reported from Sweden where a weak association was reported between duration of exclusive breastfeeding and child overweight at 5 years of age, but the association was lost when adjusted for potential confounders (65). Similarly, a study conducted in Kansas USA reported no association between duration of breastfeeding and child overweight at the age of 4 years after adjusting for ethnicity, gender, birth weight, maternal BMI and mixed feeding (70). Furthermore, a study conducted in Hong Kong reported lack of association between duration of exclusive breastfeeding and the child's BMI at the age of 7 years when adjusting for possible confounders (64).

The authors of a recent review (72) summarized four previous meta-analyses as well as the interventional study on breastfeeding and childhood overweight. They concluded that there is no clear and concrete evidence for or against a protective effect of breastfeeding against childhood overweight. The three meta-analyses which had overweight or obesity as an outcome reported a protective effect after adjusting for potential confounders. In the contrary, the interventional study and one meta-analysis with mean BMI as the outcome found no significant association between breastfeeding and childhood overweight after adjusting for potential confounders.(72) In order to clarify the above controversies researchers' recommended further study in this area.

2.6 Factors related to breastfeeding in Finland

The duration of breastfeeding in Finland is shorter than recommended by the WHO. The duration of breastfeeding has been found to associate with several socio-demographic factors, such as maternal age, educational status, smoking status and place of residence. The duration of exclusive breastfeeding was longer in southern Finland, whereas total breastfeeding was longer in Northern Finland. Duration of breastfeeding was longer in children of more educated parents, of mothers who were 30 years old or older at the time of giving birth or non-smoking during pregnancy, and also in children born vaginally.(73)

3 AIMS OF THE STUDY

3.1 General aim

The main aim of the present study is to test the hypothesis “duration (length) of breastfeeding decreases the risk of child overweight” by assess the relationship of duration of breastfeeding to childhood overweight at the age of 3 years.

3.2 Specific aims

- To assess the relationship of duration of exclusive breastfeeding to child overweight at the age of 3 years.
- To assess the relationship of duration of total (overall) breastfeeding to child overweight at the age of 3 years.

4 WORK DESCIPTION

I had the interest of doing my thesis in the field of child health before joining the master's degree program. I started searching for my thesis topic during the 'Introduction to Masters Thesis' course. As it was my interest to work in malnutrition in children of developing countries, I approached professor Per Ashorn, who, at the time, had a project on underweight children in Malawi. He was willing to give me the materials which are used for measuring underweight children, indicating data can be collected from my country, Ethiopia. Unfortunately, I didn't have the funding for the data collection and traveling to Ethiopia. Therefore I started looking for other topics around child health.

In one of several seminars conducted for the 'Introduction to Masters Thesis' course, Professors from different departments presented available topics for master's thesis. During the presentation our epidemiology Professor, Patrik Finne, mentioned a study in the area of child health. After the seminar, I contacted Professor Patrik Finne through email to inform him about my interest in this study area. He then forwarded my request to Susanna Kautiainen, who then informed me about the topic "breastfeeding and childhood obesity" and requested that I write one page report on the topic. This is when I started reviewing the literature.

I wrote the study plan for the thesis between spring and summer of 2010 with the help of my supervisor, Susanna Kautiainen. In this stage everything what I am going to do for the literature review were clear. During autumn 2010 I continued working on my literature review. However I didn't get the data for analysis until February 2011 when I was assigned as full time visiting researcher in THL and started working on my thesis.

The data was based on the ongoing type 1 Diabetes Prediction and Prevention study (DIPP) project, a prospective population based Finish birth cohort. It consists of children born between 1997 and 2004, in the catchment area of Tampere University Hospital (N=3719).

The study variables are gestational diabetes, mode of delivery, parity, duration of gestation, number of siblings, maternal smoking status during pregnancy, location of residence area, birth weight and height of child, duration of exclusive breastfeeding, maternal and paternal diabetes, pre-pregnancy BMI of the mother, paternal BMI, maternal and paternal educational level, weight and height of child at age of 3.These variables were obtained from the National Medical Birth Registry and from food frequency questionnaire.

I started the analysis with the description of the data in frequencies, percentages, mean, median and missing values. At first, the age of the study subjects were 5 years but was changed to 3 years at a later stage, based on the suggestion from my second supervisor Suvi Virtanen. This change was due to high dropout rates and caused me an extra work doing the whole analysis for a second time. The main exposures for the study are both duration of exclusive breastfeeding and total breastfeeding and the outcome variable is childhood overweight. I started analyzing the association of duration of exclusive breastfeeding and total breastfeeding as well as background variables to childhood overweight using chi x^2 test and logistic regression. I also stratified the analysis by age. In the logistic analysis my supervisor Susanna recommended I start with the univariate analysis to see the effects of the background variables one by one. In the multivariate analysis I adjusted for the possible confounders (maternal BMI, duration of gestation, birth weight, infant sex, maternal basic education, maternal smoking status during pregnancy, paternal diabetes, location of residence area and gestational diabetes).

At the beginning of autumn 2011 I started writing the draft for the manuscript. I completed the manuscript with the continuous support and several invaluable comments from my supervisor Susanna Kautiainen and the co-authors from the second draft to the last one.

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7 A COPY OF THE ORIGINAL PAPER

Duration of breastfeeding and presence of childhood overweight at 3 years of age

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ABSTRACT

Objective: To assess the relationships between duration of exclusive or total breastfeeding and overweight at 3 years of age.

Design: Prospective birth cohort.

Setting/subjects: 3719 singleton newborn infants carrying increased HLA-conferred susceptibility to type 1 diabetes were recruited in 1997-2004 from Pirkanmaa, southern Finland. Information on both breastfeeding and anthropometrics at 3 years was available for 2110 children. Overweight (obesity inclusive) was defined using the International Obesity Task Force (IOTF) cut-offs for BMI and logistic regression was used for statistical analyses.

Results: The durations of exclusive (median 1.6, range 0-8 months) and total (7.0, 0-25 months) breastfeeding were similar in both sexes. The prevalence of overweight was higher in girls (15%) than in boys (8%, $p<0.001$). Shorter duration of exclusive (<3 months) and total (<3 months) breastfeeding were associated with a higher risk for overweight at 3 years. When adjusted for potential confounders (maternal weight, educational level, smoking during pregnancy and gestational diabetes, child's sex, birth weight and gestational age, location of residence and paternal diabetes), only exclusive breastfeeding remained statistically significantly related to overweight ($p=0.030$, OR 1.64 (95%CI 1.09-2.47) for 1-2 vs. ≥3 months).

Conclusion: There was no clear dose-response relationship between duration of breastfeeding and risk of child overweight when potential confounders were taken into account.

Key words: breastfeeding, childhood, overweight

Introduction

Most of the studies assessing the relationship between breastfeeding and childhood overweight have compared never breastfed children with ever breastfed children[1-6]. A majority of these studies suggest that breastfeeding reduces the risk of childhood overweight[1-3,5] while some found no association[6]. The duration of breastfeeding has been protectively associated with childhood overweight in some[6-8] although not in all[9-12] studies. The evidence remains inconsistent[13,14] potentially because of heterogeneity of study populations and methods.

The aim of the present study was to assess whether duration of breastfeeding is associated with the risk of childhood overweight and obesity at the age of 3 years. Specifically, this question is addressed in a cohort of children where detailed information on feeding, anthropometrics and several potential confounders were prospectively collected since birth.

Subjects and methods

This study is part of the ongoing type 1 Diabetes Prediction and Prevention (DIPP) project, where newborn infants with increased HLA-DQBI-conferred susceptibility to type 1 diabetes were recruited from the catchment areas of three university hospitals in Finland (Oulu, Tampere and Turku)[15] The DIPP Nutrition study is conducted within the framework of the DIPP study in Oulu and Tampere[16,17].The study protocol was approved by the local ethics committees and signed informed consent was obtained from the parents.

The source population of the present study comprised 3719 singletons born in 1997-2004 in Tampere University Hospital (catchment area Pirkanmaa in Southern Finland). Out of these children, 33 had no information on breastfeeding, 633 had no information on growth at the age of 3 years, and 943 on neither measure. Thus, the study population included 2110 singleton children.

When the child was 3, 6, 12 and 24 month-old, the parents filled in information about the duration of breastfeeding, the age of introduction of infant formula, cow's milk, and other complementary foods. In the 3-month questionnaire, the parents were additionally asked whether the child was breastfed, had received donated breast milk or infant formula in the maternity ward.

Exclusive breastfeeding was defined as the period in which the child received, in addition to breast milk, only drops of water, vitamins and/or mineral supplements. The type of infant feeding in the maternity ward was taken into account when calculating the duration of exclusive breastfeeding. Total breastfeeding was defined as the period in which the child was either exclusively breastfed or received in addition to breast milk infant formula or other foods and fluids.[18]

Children's weight and length/height were measured during the regular study clinic visits. Body mass index (BMI, kg/m^2) was calculated and the International Obesity Task Force (IOTF) criteria[19] was used to classify children at the age of 3 years as normal weight, overweight (obesity inclusive) and obese.

Mothers were asked to record the results of the height and weight measurements during their first (median 9 weeks, range 3-36 weeks) and last (median 39 weeks, range 8-44 weeks) visit to the antenatal clinic. BMI was calculated based on the weight at the first visit, if that visit took place during the first 10 weeks of pregnancy. For mothers who had their first antenatal clinic visit after the 10^{th} week of pregnancy, weight at week 10 was estimated from the difference between weight at the first and last visits, assuming linear weight gain during the second and third trimesters of pregnancy[20,21]. Information on paternal height and weight, maternal age and parental education was acquired by structured questionnaires after delivery. Information on gestational diabetes was obtained from an additional question on special diets during pregnancy (including diet due to disturbance of glucose metabolism) in the food frequency questionnaire. Data on number of siblings, maternal smoking during pregnancy, location of residence, duration of gestation, mode of delivery, parity, birth weight and length of the children were obtained from the National Medical Birth Register. Table 1 shows the variables as categorized for the present analysis.

Statistical methods

The associations between background factors and the duration of breastfeeding variables (continuous) were examined using the non-parametric Mann-Whitney U and Kruskal-Wallis tests, while the associations between background factors and overweight were assessed using the χ^2 test. The associations between the categorized duration of breastfeeding variables and overweight were assessed using the x^2 test. The associations of explanatory variables with overweight where further studied by univariate and multivariate logistic regression analyses. All explanatory variables that were significantly ($p<0.05$)

associated with overweight in the univariate analyses were simultaneously included in the final logistic regression model, apart from paternal BMI which had a high number of missing values. In addition, duration of gestation was included in the multivariate models to adjust birth weight for gestational age. Statistical significance of interaction terms between duration of exclusive and total breastfeeding, respectively, and sex of the child, maternal BMI and gestational diabetes were assessed. The x^2 test was used to assess the proportion of missing anthropometric data at the age of 3 years (loss to follow-up) in relation to the duration of exclusive and total breastfeeding, respectively, and to compare children with and without anthropometric data in relation to sex, birth weight, maternal BMI and maternal smoking during pregnancy. All reported p-values were based on two-sided tests and the level of statistical significance was set at $p<0.05$. SPSS version 19.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

Results

The proportion of infants exclusively breastfed for less than 1 month, 1-2 months and 3 months and longer were 39%, 24% and 37%, respectively. The proportions of infants with total breastfeeding for less than 3, 3-5, 6-11 and 12 months and longer were 21%, 20%, 39% and 20%, respectively. At the age of 3 years, 11% of the children were overweight (obesity inclusive) and 2% obese.

Duration of exclusive and total breastfeeding were longer in children with more siblings, older mothers, or parents with higher basic education; and shorter in children born by caesarean section, with mothers who were smoking during pregnancy or who were

overweight or obese (Table 1). In addition, higher birth weight of the child and maternal diabetes (type 1 and 2) were statistically significantly associated with shorter total breastfeeding, and higher paternal BMI with shorter exclusive breastfeeding (Table 1).

The prevalence of overweight was higher in girls and in children with higher birth weight; mothers with gestational diabetes, shorter education or who were smoking during pregnancy; diabetic fathers; overweight or obese parents; and rural location of residence (Table 1).

Association between duration of exclusive breastfeeding and overweight

The prevalence of overweight was lower in children who were exclusively breastfed for at least 3 months as compared to children exclusively breastfed for less than a month or for 1-2 months (Fig 1).

Shorter duration of exclusive breastfeeding was associated with a higher risk of overweight at the age of 3 years in the univariate logistic regression analysis (Table 2). When adjusted for potential confounders, the association was weaker; children exclusively breastfed for 1 to 2 months had a higher risk of overweight than those exclusively breastfed for at least 3 months (Table 2). No statistically significant interactions were observed between duration of exclusive breastfeeding and sex of the child, maternal BMI or gestational diabetes.

Association between duration of total breastfeeding and overweight

The prevalence of overweight was higher in children who were breastfed for <3 months compared to children with total breastfeeding for >6 months (Fig 1). Duration of total

breastfeeding was statistically significantly inversely associated with the risk of overweight at the age of 3 years in the univariate analysis, but not in the multivariate model (Table 2). No statistically significant interactions were observed between duration of total breastfeeding and sex of the child, maternal BMI or gestational diabetes.

Drop-out analysis

Loss to follow-up was more common among children with shorter exclusive breastfeeding compared to children exclusively breastfed for 3 months or longer (30% vs. 22%, $p<0.001$).Likewise, the shorter the duration of total breastfeeding, the higher the loss to follow-up (increasing from 17% to 36%, $p<0.001$). Maternal smoking during pregnancy (11% vs. 7%, $p<0.001$) and lower maternal basic education (52% vs. 40%, $p<0.001$) were more common among children lost to follow-up than in children with BMI values available.

Discussion

In this prospective birth cohort study, the crude risk of overweight at 3 years was higher in children with shorter duration of both exclusive and total breastfeeding compared to longer breastfed counterparts. When adjusted for potential confounders, the association remained significant for exclusive but not for total breastfeeding. However, no clear dose-response relationship was observed for exclusive breastfeeding either.

Our results are in accordance with an intervention study conducted in Belarus in 2007[9] , the meta-analysis by Owen et al[10], a recent prospective cohort study in Southeast Sweden[11], and three other studies[12,20-21]. Owen et al. suggest that the differences in previous studies may be due to residual confounding and publication bias[10]. In contrast to our results, a meta-analysis conducted by Harder et al[7] and some recent cohort studies found that longer breastfeeding was associated with a lower risk for childhood overweight[6,8,22]. In the meta-analysis, however, potential confounders were not taken into account. Also differences in the study populations and in the definitions of the exposure and outcome variables between the studies could explain the variation in the results. We had no reference group of never breast-fed children, as there were only few never breast-fed children in the DIPP Nutrition Study population[18]. It is also possible that the type of feeding during the very first weeks of life is more important than the duration of breastfeeding.[23]

Major strengths of the present study are a large sample size and the prospective birth cohort design where detailed information on infant feeding and anthropometrics were routinely collected by trained nurses. The diversified data enabled us to evaluate potential confounding by several important factors[9,10,13].

However, there are also limitations: The number of missing values for paternal BMI was high; therefore, it could not be considered in the analysis. Infant growth, child's physical activity and feeding beyond infancy were not assessed. Loss to follow-up was associated with shorter breastfeeding, lower maternal basic education and maternal smoking during pregnancy, which could bias our estimates of relative risk towards one. However,

considering the rather small differences in the magnitude of loss to follow-up in the different exposure categories and the effect sizes of maternal smoking and education on child obesity together, the effect of potential selection bias should be small.

The participants of the present study represent longer breastfeeding[24] and healthier lifestyle habits overall[25] than all Finnish parturient, which may restrict the generalizability of the results. Also, all children carried increased HLA-conferred susceptibility to type 1 diabetes. In Finland, 15% of the newborn infants carry such a risk but only 3-4% of the children at risk present with clinical type 1 diabetes by the age of 15 [15]. A few previous studies have reported inconsistent results on the associations of risk HLA-genotypes with fetal and early growth [26-31]. In the current study, the genetic risk level (high or moderate) for type 1 diabetes was not associated with the duration of exclusive or total breastfeeding, nor with overweight (data not shown).

In conclusion, we found no clear dose-response relationship between duration of breastfeeding and risk of child overweight when potential confounders were taken into account, suggesting the importance of other aspects, such as maternal BMI and smoking during pregnancy, in the prevention of childhood overweight and obesity. Further studies with thorough consideration of potential confounders, including eating and physical activity of the child, and of loss to follow-up, are warranted.

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Conflict of interest: None of the authors had any conflict of interest to declare.

Author's contribution: R.A, S.K and S.M.V planned the present study concept and design.R.A analyzed the data with the help of S.K, W.K, H.M.T. and S.M.V. R.A and S.K drafted the manuscript and revised it based on comments given by W.K, H.M.T, M.E, P.L, M.K and S.M.V. M.K and O.S designed the DIPP study, and S.M.V the nutrition study within the DIPP. R.V is responsible for the clinical work of the DIPP study in Oulu.

Table 1. The background characteristics and their associations with exclusive and total breastfeeding as well as overweight.

			Duration of exclusive breastfeeding (months)*,†		Duration of total breastfeeding (months)†		Overweight at the age of 3 years ‡	
Characteristic	n	%	Median	Range	Median	Range	N	%
Infant sex								
Boy	1921	52	1.6	0-8	7.0	0-25	86	8
Girl	1798	48	1.6	0-8	7.0	0-25	151	15
P-value			p=0.760		p=0.474		p<0.001	
Birth weight(kg)								
1st quantile	1241	33	1.4	0-6.5	6.5	0-25	41	6
2nd quantile	1224	33	1.8	0-8	7	0-25	76	11
3rd quantile	1253	34	1.5	0-8	7	0-25	120	16
P-value			p=0.340		p=0.005		p<0.001	
Number of siblings§								
No	1888	51	1.4	0-6.5	6.0	0-25	124	11
One	1158	31	1.8	0-8	7.0	0-25	67	10
Two and more	624	17	2.3	0-6.5	9.0	0-25	43	12
Missing	49	1						
P-value			p<0.001		p<0.001		p=0.574	
Maternal age (years)§								
<25	673	18	1.2	0-6.5	5.0	0-25	38	13
25-29.9	1271	34	1.5	0-6	6.5	0-25	75	10
30-34.9	1102	30	2.0	0-8	7.5	0-25	72	11
≥35	673	18	1.8	0-8	8.0	0-25	52	12
P-value			p<0.001		p<0.001		p=0.506	
Route of delivery								
Vaginal	3290	88	1.8	0-8	7.0	0-25	203	11
Caesarean section	429	12	1.0	0-6	5.5	0-25	34	14
P-value			p<0.001		p=0.001		p=0.190	
Maternal basic education§								
Less than high school	1624	44	1.4	0-8	5.0	0-25	114	14
High school graduate	1997	54	2.0	0-8	8.0	0-25	115	9
Missing	98	2						
P-value			p<0.001		p<0.001		p=0.001	
Maternal higher education								
None or vocational education or course	1440	39	1.2	0-6	4.6	0-25	99	13
Secondary vocational education	1466	39	1.8	0-8	7.0	0-25	89	10
University studies or degree	781	21	3.0	0-8	9.5	0-25	48	10
Missing	32	1						
P-value			p<0.001		p<0.001		p=0.041	
Paternal basic education§								
Less than high school	2145	58	1.4	0-8	6.0	0-25	142	12
High school graduate	1355	36	2.0	0-8	8.0	0-25	84	10
Missing	219	6						
P-value			p<0.001		p<0.001		p=0.111	
Paternal higher education								
None or vocational education or course	1841	50	1.4	0-6.5	6.0	0-25	125	12
Secondary vocational education	960	26	2.0	0-6.5	7.5	0-25	60	10
University studies or degree	746	20	1.8	0-8	8.0	0-25	43	9
Missing	172	4						
P-value			p<0.001		p<0.001		p=0.110	
Maternal smoking during pregnancy								
No	3303	89	1.8	0-8	7.0	0-25	199	10
Yes	329	9	1.0	0-5	3.0	0-25	32	21
Missing	87	2						
P-value			p<0.001		p<0.001		p<0.001	

(To be continued)

(Table 1 continued)

			Duration of exclusive breastfeeding (months)*,†		Duration of total breastfeeding (months)†		Overweight at the age of 3 years ‡	
Characteristic	n	%	Median	Range	Median	Range	N	%
Maternal diabetes**								
No	3595	97	1.6	0-8	7.0	0-25	225	11
Yes	124	3	1.1	0-6.5	6.0	0-25	12	15
P-value			p=0.144		p=0.030		p=0.252	
Gestational diabetes¶								
No	2616	70	1.6	0-8	7.0	0-25	204	11
Yes	144	4	1.0	0-6.5	7.0	0-25	19	18
Missing	959	26						
P-value			p=0.107		p=0.477		p=0.018	
Location of residence area								
Rural	375	10	1.4	0-6	6.5	0-25	38	18
Semi-urban	412	11	1.4	0-6	7.0	0-25	30	12
Urban	2931	79	1.6	0-8	7.0	0-25	169	10
Missing	1	0						
P-value			p=0.725		p=0.887		p=0.001	
Maternal BMI ||								
Normal	1699	46	1.8	0-8	7.0	0-25	101	8
Overweight	642	17	1.4	0-6.5	6.5	0-25	61	13
Obese	279	7	1.0	0-6.5	5.0	0-25	48	24
Missing	1099	30						
P-value			P<0.001		P<0.001		P<0.001	
Paternal BMI								
Normal weight	749	20	1.6	0-6.5	7.0	0-25	40	7
Overweight	782	21	1.4	0-6	7.0	0-25	80	14
Obese	233	6	1.0	0-6	7.0	0-25	37	21
Missing	1955	53						
P-value			p=0.018		p=0.879		p<0.001	
Paternal diabetes								
No	3532	95	1.6	0-8	7.0	0-25	220	11
Yes	81	2	1.7	0-6	7.0	0-25	11	21
Missing	106	3						
P-value			p=0.839		p=0.502		p=0.017	

*Exclusive breastfeeding includes information about hospital feeding.

†If the child was breastfed for more than 2 years, 25 months was taken as the length/duration of total breastfeeding. P-values based on Mann-Whitney U and Kruskal-Wallis tests. Missing values were not taken into account in the analysis.

‡ The IOTF reference[19] was used to define overweight at the age of 3 years. Overweight includes obesity.

§ At the time of birth.

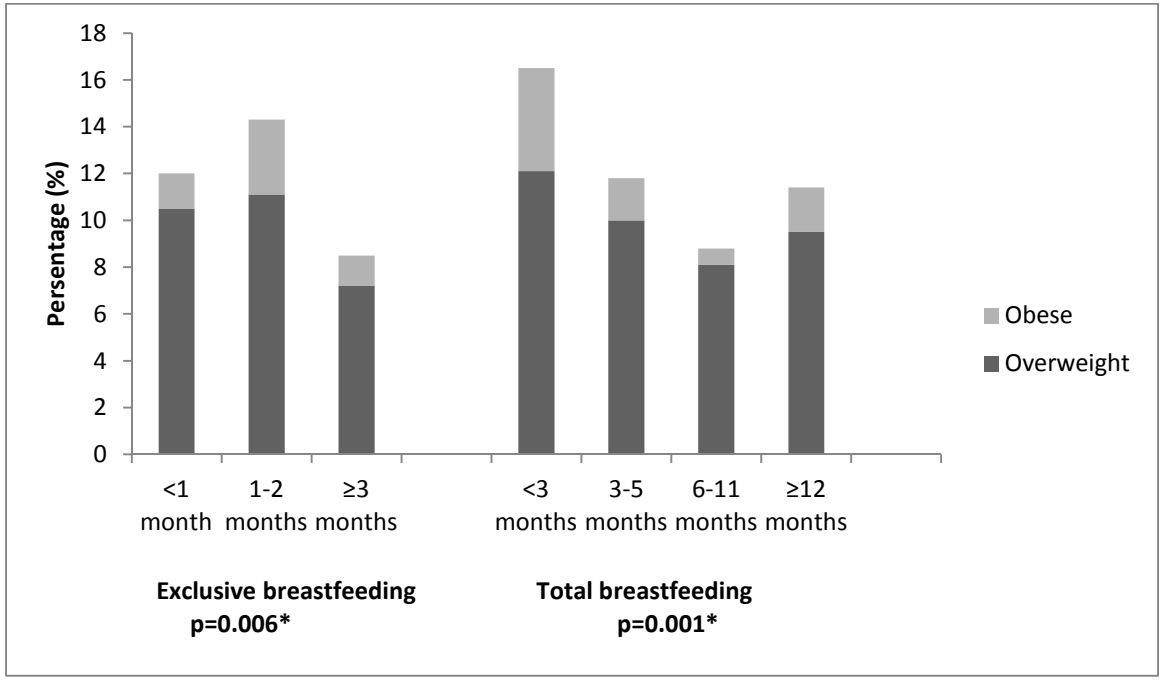
||BMI of mothers was calculated using their weight at the first antenatal clinic visit. Regarding mothers who had their first antenatal clinic visit after the 10th week of pregnancy, weight at week 10 was estimated based on the difference between weight at the first and last antenatal visit and assuming linear weight gain during the second and third trimesters of pregnancy.

¶ Obtained from food frequency questionnaire by asking about any special diets during pregnancy that the mother had due to disturbance of glucose metabolism.

** Maternal diabetes includes both type 1 and type 2 diabetes

Legend for Figure 1:

Fig 1. Prevalence of overweight and obesity at the age of 3 years according to duration of exclusive and total breastfeeding



* x^2 test for the association between the duration of breastfeeding and overweight.

Table 2. Associations of breastfeeding and background variables with the risk of child overweight at the age of 3 years.

		Exclusive breastfeeding*						Total breastfeeding		
		Unadjusted			Adjusted‖			Adjusted‖		
Characteristic	N	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Exclusive breastfeeding*				0.005			0.030			
Less than one month	1138	1.45	(1.05, 2.01)		1.02	(0.70, 1.48)				
1-2 months	701	1.77	(1.24, 2.53)		1.64	(1.09, 2.47)				
3 and more months	1064	1			1					
Total breastfeeding				0.002						0.204
<3 months	570	1.53	(1.03, 2.28)					1.04	(0.64, 1.68)	
3-5 months	536	1.03	(0.68, 1.57)					0.87	(0.54, 1.41)	
6-11 months	1079	0.75	(0.52, 1.08)					0.69	(0.46, 1.04)	
≥12 months	558	1						1		
Maternal BMI†	2620	1.12	(1.09, 1.15)	<0.001	1.09	(1.06, 1.13)	<0.001	1.08	(1.05, 1.12)	<0.001
Duration of gestation	3701	1.03	(0.95, 1.12)	0.457	0.89	(0.79, 1.01)	0.065	0.88	(0.78, 0.99)	0.045
Birth weight (kg)	3718	2.44	(1.85, 3.23)	<0.001	2.96	(2.05, 4.27)	<0.001	2.97	(2.06, 4.28)	<0.001
Infant sex				<0.001			<0.001			<0.001
Boy	1921	1			1			1		
Girl	1798	2.03	(1.53, 2.68)		2.12	(1.54, 2.93)		2.07	(1.50, 2.86)	
Maternal basic education‡				0.001			0.318			0.339
Less than high school	1624	1.57	(1.19, 2.07)		1.18	(0.85, 1.64)		1.18	(0.84, 1.64)	
High school graduate	1997	1			1			1		
Maternal smoking during pregnancy				<0.001			0.001			0.001
No	3303	1			1			1		
Yes	329	2.32	(1.53, 3.51)		2.33	(1.39, 3.89)		2.41	(1.44, 4.03)	
Paternal diabetes				0.020			0.100			0.105
No	3532	1			1			1		
Yes	81	2.24	(1.13, 4.42)		2.02	(0.87, 4.66)		1.99	(0.86, 4.58)	
Location of residence area				0.001			0.107			0.104
Rural	375	2.04	(1.38, 2.99)		1.58	(0.99, 2.51)		1.56	(0.98, 2.48)	
Semi-urban	412	1.24	(0.82, 1.88)		1.31	(0.82, 2.08)		1.35	(0.85, 2.14)	
Urban	2931	1			1			1		
Gestational diabetes§				0.020			0.685			0.707
No	2616	1			1			1		
Yes	144	1.85	(1.10, 3.11)		1.13	(0.62, 2.07)		1.12	(0.61, 2.05)	

* Exclusive breastfeeding includes information about hospital feeding.

† BMI of mothers was calculated using their weight at the first antenatal clinic visit. However, regarding mothers who had their first antenatal clinic visit after the 10th week of pregnancy, weight at week 10 was estimated based on the difference between weight at the first and last antenatal visit and assuming linear weight gain during the second and third trimesters of pregnancy.

‡ At the time of birth of the child.

§ The information about gestational diabetes was obtained from the food frequency questionnaire by asking about any special diets during pregnancy that the mother had due to disturbance of glucose metabolism.

‖ Adjusted for maternal BMI, duration of gestation, birth weight, infant sex, maternal basic education, maternal smoking during pregnancy, paternal diabetes, location of residence area, gestational diabetes.

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