行うことの利点は乏しい。むしろ，現時点では，積極的な栄養管理により発育や神経予後を向上させることと引き替えにメタボリックシンドロームのリスクをもつことになってもやむをえないと考えるべきかもしれない。

極低出生体重児は年齢を経るとともにNCDsへと進展するリスクが高いと考えられるが，個々の児についてのリスク予知の手段は確立されていない。これらの点を明らかにしていくためには，長期にわたるフォローアップ体制の整備が欠かせない。また，極低出生体重児や超早産児出身の小児や成人は，physical activityが低いことが指摘されており[12]，これはメタボリックシンドロームや生活習慣病の重要なリスク要因の一つである。NCDsのリスク予知が困難であったとしても，physical activityを高めるための支援は欠かせないと思われる。

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わが国における低出生体重児の現状と小児歯科診療の関わり

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Key word 低出生体重児、早産児、エナメル質形成不全

はじめに

わが国では早産児や低出生体重児の出生率が増加傾向にある。一般に低出生体重児の出生率が高い国ほど乳児死亡率が高い。しかし、様々な周産期医療技術の導入や周産期医療の地域化などによって、わが国は、未熟性の強い極低出生体重児（出生体重1,500g未満）や超早産児（在胎28週未満の早産児）であっても生存率の高さは先進諸国の中ではトップレベルである。そのため、このような児を含む多くの低出生体重児や早産児も小児科のみならず歯科を受診する機会が以前に比べて増えてきている。本稿では、低出生体重児や早産児を中心に、わが国の現状および予後について解説するとともに、歯科診療との関わりについて述べることとする。

主な用語について

1）低出生体重児と早産児

低出生体重児は、在胎期間にかかわらず出生体重が2,500g未満の児をさす。出生体重が1,500g未満の児を極低出生体重児、出生体重が1,000g未満の児を超低出生体重児と呼ぶ。その原因は、早産で出生する場合と、早産でなくとも胎児発育が抑制された状態で出生する場合に分けられる。

早産児とは在胎22週以上37週未満で出生した児をいう。在胎28週未満の児は超早産児、在胎34～37週未満の児はlate preterm（後期早産）児という。なお在胎37週～42週未満の児は正期産児という。在胎期間と出生体重の関係は図1[1]のごとくである。

2）SGAと胎児発育不全

ICD-10においてはsmall for gestational age（以下SGA）は出生体重および出生時の身長が在胎期間別出生時体格値の10パーセンタイル未満と定義されている。しかしながら、重症な児では出生時の身長測定が困難なこともあり、必ずしもICD-10の定義でSGAと判定されるとは限らない。出生体重だけが10パーセンタイル未満の場合、light for gestational ageと呼ぶこともある。一方、胎児発育不全（fetal growth restriction、以下FGR）は胎児超音波検査で計測された値をもとに推測された胎児発育が胎児発育基準値を下回っている状態をさし、胎児発育のポテンシャルが阻害された病的状態である。SGAはしばしばFGRと同義的に使用されるが、元来比較する基準が異なっており、厳密に言えば異なるものである。

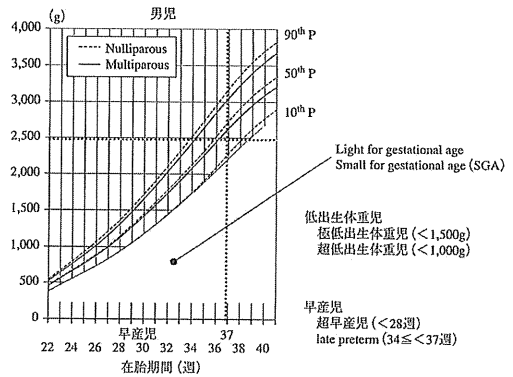

図1 在胎期間別出生時体格曲線（出生体重、男児）
Itabashi K, et al. Pediatr Internat [1]より作図。実線は初産、点線は経産を示す。

最近のわが国の現状

1）低出生体重児・早産児の推移

2010年の母子保健統計[2]では低出生体重児の出生率は9.6％である。OECD加盟国（平均は6.8％）のなかでは、第一位のトルコ（11.0％）、第二位のギリシャ（10.0％）に次ぐ高さである[3]。わが国の低出生体重児と早産児の出生率に関する年次的な推移をみると、1980年の早産出生率は4.1％、低出生体重児の出生率は5.2％であったが、1990年以後増加し2010年にはそれぞれ5.7％、9.6％に達している（図2）。この間、早産児の出生率が1.4倍の増加であるのに対して、低出生体重児は1.9倍であり、早産ではない低出生体重児、すなわち正期産低出生体重児の増加率が高いことが推測される。おそらく正期産で出生した低出生体重児の多くがFGRによるものと推測される。したがって、このような児の増加は、胎児を取り巻く子宮内環境の悪化に関連しているのではないかと懸念される。

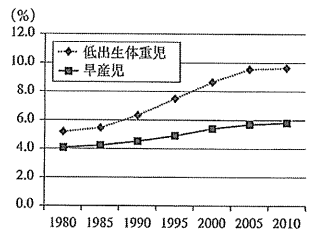

図2 低出生体重児（low birth weight）と早産児（preterm）の出生率の変化

2）出生体重別・在胎別分布

2010年に出生した低出生体重児の出生体重別分布は、約80％近くが出生体重2,000g以上で、極低出生体重児は8％である（図3）。早産児の分布を見ると late preterm（後期早産）児は早産児の約80％を占め、超早産児は5％

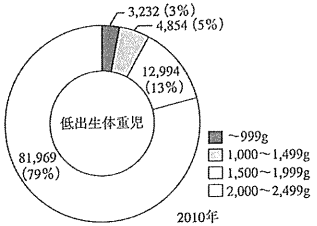

図3　低出生体重児の出生体重別分布（2010年）

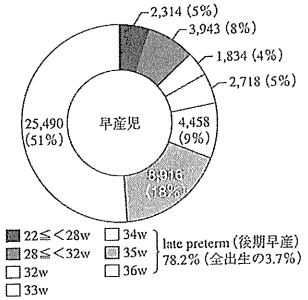

図4　早産児の在胎期間別分布（2010年）

を占めている（図4）。

低出生体重児、早産児の予後

1）超低出生体重児の死亡率の変遷

一般に低出生体重児の死亡率は、出生体重が少ないほど高い。その最たるものは超低出生体重児である。日本小児科学会新生児委員会では1980年より5年ごとに超低出生体重児の死亡率について全例調査を行ってきた。調査のたびにNICUに収容される超低出生体重児数が増加しているが、それにもかかわらず死亡率は減少傾向にある。2005年調査では全体の死亡率は17％で、5年前の2000年調査の21％からわずか5年で4％も低下している。出生体重別にみると出生体重800g未満の児の死亡率が、在胎週数別では超早産児の死亡率の低下が有意に低下している[4]

2）超低出生体重児の神経学的予後

一般に発達遅滞や神経学的異常は、より未熟な児ほど、またより出生体重が小さく生まれた児ほど出現率が高い。わが国の超低出生体重児の3歳時点の神経学的予後は、表1に示したように総合発達評価では2005年出生の児で異常と判定されたのが17.1％で、境界と判定された児は20.3％であった[5]。これらの児では脳性麻痺や発達遅滞に加えて聴力障害や視力障害、慢性呼吸器障害など様々な異常を合併している。調査対象症例数は、死亡率を20％として計算しても予想される対象のわずか3割程度であり、この結果をもってわが国の超低出生体重児の長期予後とするのは困難である。このようにわが国では信頼性の高い長期予後調査結果が得られておらず、今後の大きな課題となっている。

3）後期早産児の予後

早産児の約80％を占める後期早産児は、出生体重が比較的大きいにもかかわらず死亡のリスクは正期産児に比べて明らかに高い（相対リスク2.9～4.5）[6]。さらに脳性麻痺のリスクは2.7倍、発達遅滞は1.6倍と高いことが報告されている[7]。

4）早産児の発育と栄養

未熟性の強い早産児ほど予定日になっても体重や身長、頭囲が在胎別出生時体格値の10パーセンタイルに届かないことが多く、このような状態は子宮外発育不全（extrauterine growth restriction、以下EUGR）と呼ばれる。2002年に出生した在胎32週以下の児を対象として筆者らが行った国内調査では、その発生率は図5[8]に示したごとくで、在胎26週以下の超早産児では体重および身長において90％以上がEUGRであった。EUGRは、少ない栄養素の備蓄に加えて消化吸収・代謝機能の未熟性や出生後の様々な合併症による栄養摂取不足、FGRが主な要因である。

NICU入院中の成長の程度と神経学的予後の関連性が指摘されており[9]、最近ではEUGRを回避すべく、急性期においては極低出生体重児に対し出生直後から蛋白質を主体として胎児必要量を積極的に与えるためのearly aggressive nutrition（EAN）が導入されつつある[10]。また、安定期には母乳単独では不足する蛋白質やエネルギー、カルシウム、リンを中心に補充する強化母乳栄養が行われる。これは、早産出生やFGRでは母体からの蛋白質やカルシウム、リンなどの供給が不十分であるという背景に加えて、急速な発育に伴いこれらの栄養素の供給が需要を上回

表1　超低出生体重児の3歳予後

	1990	1995	2000	2005
症例数	853	757	790	701
総合発達評価				
境界	10.9％	14.9％	18.2％	20.3％
異常	14.1％	14.9％	19.6％	17.1％
脳性麻痺	12.0％	14.3％	16.3％*	12.4％
視力障害	8.3％	6.9％	9.0％	8.5％
両眼失明	2.2％	1.2％	0.6％	0.4％
片眼失明	0.6％	0.7％	0.0％	0.3％
弱視	5.5％	5.0％	6.1％	3.6％
聴力障害	2.2％	2.1％	2.4％	1.7％
てんかん	4.3％	3.8％	3.7％	3.2％
反復性呼吸障害	11.1％	8.1％	4.4％	4.0％
喘息	8.0％	9.2％	7.2％	8.8％
在宅酸素療法	3.6％	3.7％	5.1％	4.6％

*P＜0.05
上谷良行．超低出生体重児の予後全国調査．厚生労働科学研究「周産期母子医療センターネットワークによる医療の質の 評価とフォローアップ・介入による改善・向上に関する研究」平成21年度報告書．[5]

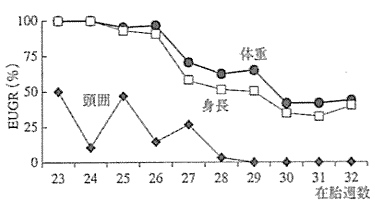

図5　在胎期間別にみた子宮外発育不全（EUGR）の発症率

表2　強化母乳パウダーの栄養組成

母乳100mL あたりの添加量	HMS-1®	HMS-2®
熱量（kcal）	9	20
蛋白質（g）	0.7	1
脂質（g）	0	1
炭水化物（g）	1.5	1.8
Ca（mg）	70	100
P（mg）	40	60
Na（mg）	9	18

り、発育不良や低蛋白血症、未熟児くる病や骨減少症などの未熟児代謝性骨疾患の発症リスクが高くなるためである。

EAN導入以前の極低出生体重児の小児期の成長をみると、NICU退院後2～3歳までは急速に増加するが、その後は小児期を通じて変化はなく出生体重が小さい児ほど標準値を下回る程度が大きい[11]。最近導入されるようになってきたEANは、NICU入院中の成長を促進することは明らかであるが、長期的な成長や発達予後が改善されるかどうかは、現時点では明らかでない。

強化母乳栄養に使用される母乳強化パウダーは1990年代半ばより筆者らの開発したHMS-1®がわが国で導入され、2013年よりさらに強化された新しい母乳強化パウダーHMS-2®が普及しつつある（表2）。強化母乳栄養はEANと同様に短期的な発育に対する効果が認められるものの、長期予後への効果は明らかでない。

SGAで出生した児は低身長となるリスクが高いことが知られており、このような児に認められる成長ホルモン分泌不全によらない低身長はSGA性低身長症と呼ばれ、成人の低身長症の約20％を占めている。わが国の調査でも欧米の報告と同じように2～3歳以後になってもSGA児の約10％に身長のキャッチアップがみられない。在胎期間あるいは出生体重別にみると、在胎32週未満あるいは出生体重が1,000g未満で出生したSGA児ではキャッチアップ率はそれぞれ74％、70％と低い[12]。

低出生体重児や早産児と歯科診療

Seowら[13]の総説によれば、早産児には表3に示したような歯や口腔形態のような変化が報告されている。また、井上によれば、形成不全歯や癒合歯の発現率が高く、歯列の狭窄や高口蓋なども起こりやすいという。さらに咀嚼能力も低いが、加齢とともにキャッチアップすると述べている。これらの変化が顕著であるのは、とくに極低出生体重児であるが、一般に混合歯列期になると咬合力や咀嚼力はキャッチアップしていく[14]。最近のシステマティックレビューでも、早産児の乳歯列ではエナメル質形成不全が、極低出生体重児ではエナメル斑のリスクが高いと報告されている[15]。早産児や低出生体重児にエナメル形成不全が発症する理由としては、子宮内や出生後の低栄養やそれに関連して起こる未熟児代謝性骨疾患、低酸素血症、気管挿管チューブによる圧迫など様々な要因が指摘されている[13-16]。

エナメル質形成不全は、早産児や低出生体重児におけるう歯のリスクを増加させると考

表3　早産が口腔構造へ与える影響

歯冠の構造変化
エナメル：エナメル斑、エナメル低形成
気管挿管による歯冠の裂隙
口蓋のゆがみ
高口蓋
歯列のゆがみ
歯の成長と発達の遅れ
乳歯の萌出の遅れ
永久歯の発育の遅れ

Seow WK. Aust Dent J. 1997;42:85-91.[13]

えられるが、必ずしも意見の一致を見ていない。最近の福岡県からの報告では、3歳時点のう歯の発生率には低出生体重児やSGA児、早産児ともに対照に比べて高くないことが報告されている[17]。早産児、低出生体重児の呼吸管理法や栄養管理法などは時代とともに変遷しており、今後もより詳細な検討が必要であろう。

おわりに

新生児科医は、早産児、低出生体重児の後遺症なき生存を目指して日々新生児集中治療室（NICU）で働いている。発育や発達についての関心が強いが、これまで口腔内の問題については無関心であったことは否めない。また、エナメル形成不全はいったん発症してしまうと元に戻すことができないことを考えると、NICU入院中のケアにおいても口腔内の異常のリスクを考えながら対応する必要がある。さらに、NICU退院後のフォローアップについても適時小児歯科医との連携をはかりながら協働していくことが重要と思われる。

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Original Article
PEDIATRIC OBESITY

Latent Protective Effects of Breastfeeding on Late Childhood Overweight and Obesity: A Nationwide Prospective Study

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Objective: To investigate the latent effect of breastfeeding on overweight and obesity in late childhood.
Methods: Data on breastfeeding and child anthropometric measurements were collected annually from a nation-wide population-based prospective cohort study in Japan (21,425 boys and 20,147 girls). Breastfeeding status (exclusiveness and duration) was assessed when the child was 6 months old. Mixed effects models were used to evaluate trajectories of body mass index (BMI), together with overweight and obesity status, from 1.5 to 8 years of age.
Results: Mixed-fed boys and exclusively breastfed boys showed lower BMI as the main effect, as well as a slower increase of inclination in BMI as interaction term between feeding type and age, than exclusively formula-fed boys. Breastfed boys had lower BMI at the ages of 7 and 8, in comparison with exclusively formula fed boys ($P = 0.002$ and $P < 0.001$, respectively). A similar association was found for girls, although the main effect of feeding type was not statistically significant. The analysis of breastfeeding duration had similar results.
Conclusions: Breastfeeding, even if partial or for short duration, has a latent protective effect against overweight and obesity in late childhood, especially for boys.

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Introduction

The number of overweight and obese children has been rapidly increasing worldwide (1). In Japan, the prevalence of obesity among 6- to 11-year-olds was around 10% in 2007, a percentage that doubled from 1978 to 2007 (2). Childhood obesity is a known risk factor for adulthood obesity (3), hypertension, hyperlipidemia, diabetes mellitus, cardiovascular disease (4), or even premature death (5). Therefore, the prevention of childhood obesity is a major public health issue for long-term prevention of chronic disease.

Breastfeeding has been shown to have a protective effect against childhood and adolescent obesity (6,7). Previous systematic reviews repeatedly showed that breastfeeding had a significant protective effect against childhood obesity (8,9) and was associated with decreased body mass index (BMI) throughout life (10). However, recent studies showed inconsistent findings. A cluster randomized controlled trial of a breastfeeding promotion intervention reported no significant difference in both mean BMI and the prevalence of overweight between the intervention and control groups at the age of 6.5 (11) and 11.5 (12) years. Recent observational studies for children aged 3 and 5 years also showed no significant association between breastfeeding and childhood obesity (13,14).

These inconsistent results may be due to the differences in the ages at which BMI was measured in the subjects (15). Poulton and Williams empirically showed that the effect of breastfeeding might be non-significant for early childhood, but the relationship between breastfeeding and obesity became clear with growth, suggesting that breastfeeding has a latent protective effect against childhood obesity (16). Bergman et al. also showed that the prevalence of childhood obesity became significantly higher in bottle-fed children compared with breastfed children after the age of 5 years, although this difference was not statistically significant before the age of 5 years (17). In summary, these studies suggest that breastfeeding may have a long-term, latent effect on the development of overweight or obesity in late childhood. Another reason for the inconsistency in existing findings could be that the studies had limited power to detect the effects of breastfeeding on the BMI trajectory. Using trajectory analysis in a sample of 434 boys and girls in total, Buyken et al. failed to find a difference in BMI at 5.5 years of age among breastfed and formula-fed children. Thus, it is necessary to investigate the latent effect of breastfeeding on BMI during childhood, including late childhood, but before puberty, using a large representative sample.

Another major weakness in previous studies on breastfeeding and childhood obesity is that they are limited to Western countries, and there are few reports from Asian countries. Since there are noteworthy differences in the distribution of BMI, prevalence of obesity, and duration of breastfeeding among races and ethnicities (18,19), the association between breastfeeding and childhood obesity may differ across countries and ethnicities. Thus, this association should be investigated in Asian countries to generalize the evidence of the protective effect of breastfeeding against childhood obesity.

Against this background, the purpose of the present study is to investigate the effect of breastfeeding exclusiveness and duration on overweight and obesity in late childhood (5.5-8 years), with BMI trajectory analysis, using data from a Japanese nationwide prospective cohort study.

Methods

Study sample

The data used for this study were from the Longitudinal Survey of Babies in 21st Century, conducted by the Ministry of Health, Labour, and Welfare in Japan from 2001 to 2009. Institutional Review Board approval was not obtained, because the entire data was collected by the Ministry of Health, Labour, and Welfare and does not include any identifiable parameters. The study sample included all babies born between January 10 and 26 and between July 10 and 26 in 2001. Potential subjects were identified using the birth record list of vital statistics for Japan ($n = 53,575$). Questionnaires were mailed to parents when the children were 0.5, 1.5, 2.5, 3.5, 4.5, 5.5, 7, and 8 years old. Parents were considered to agree to participate in the study if they returned the questionnaire to the Ministry of Health, Labour, and Welfare. There were a total of 47,015 respondents at 6 months (response rate: 88%). Because this study focused on the effect of breastfeeding on growth trajectories for singleton and term babies, the following exclusion criteria were employed: multiple birth ($n = 976$), preterm deliveries (i.e., delivery < 37 weeks of gestation, $n = 1,890$), unknown gestational age ($n = 104$), and missing data on breastfeeding status at 6 months ($n = 231$). This yielded an eligible sample of 43,814 children (93% of all respondents). An additional 2,242 children were excluded because their parents did not report their weight and height throughout the follow-up period. Thus, the total sample size for this study was 41,572 (21,425 boys and 20,147 girls), which was 95% of the eligible sample. The response rates for the follow-up questionnaires at 1.5–8 years ranged from 73% to 89%. As the weight and height of one child at 3.5 years of age were reported as 40.0 kg and 90.0 cm respectively (i.e., BMI = 49.4), this case was considered an outlier and treated as a missing value.

Anthropometry

In each questionnaire, parents were required to provide anthropometric measurements, including weight (to the nearest 0.1 kg) and height (to the nearest 0.1 cm) at that time. BMI was calculated using the following formula: weight [kg]/height [m]^2. Childhood overweight and obesity were defined using the International Obesity Task Force BMI cut points (20), which were derived from six large, nationally representative cross-sectional surveys on growth. The cut points of age-sex-specific BMI corresponded to a BMI of 25 for overweight and 30 for obesity at age 18 (20).

Duration and exclusiveness of breastfeeding

When the children were 6 months old, their parents were asked about breastfeeding status via the questionnaire. First, parents had to choose from one of the following options: 1) breastfed, 2) never breastfed, and 3) only colostrum. Parents who chose "breastfed" were asked to report the number of months for which the child was breastfed. Second, parents were asked whether they gave formula milk, with the following options: 1) formula fed and 2) never formula fed. The duration of formula fed was asked if participants chose "formula fed." Subsequently, we categorized breastfeeding exclusiveness into three classes regardless of duration: exclusive breastfeeding (children who were fed only breast milk), mixed feeding (children who were fed both breast milk and formula milk), and exclusive formula-feeding (children who were fed only formula milk, and never fed breast milk except colostrum). Duration of breastfeeding was categorized into four classes regardless of the status of formula feeding: never, 1–2 months, 3–5 months, and over 6 months.

Covariates

Information on children's birth weight and maternal age were obtained from birth records. Data on parental smoking status, total household income, and presence of older siblings were collected when at the age of 6 months (i.e., first survey) and on parental educational status were collected at the age of 1.5 years (i.e., second survey).

Statistical analysis

To consider the correlated-data structure due to repeated measurements within persons, we used a multilevel mixed effects model to investigate the effect of exclusiveness and duration of breastfeeding on trajectories of BMI from 1.5 to 8 years as a dependent variable. Variables modeled as fixed effects were breastfeeding status, child age, and potential confounders (birth weight, having elder sibling(s), maternal age, parental educational level, total household income, and parental smoking status at 6 months of age). Child age was used as dummy variables for time as previous study found nonlinearity in the trajectory of BMI (20,21). Then, we evaluated the associations between breastfeeding status and changes in BMI over time, using interaction terms between child age and exclusiveness or duration of breastfeeding. We assumed an autoregressive correlation structure between the time points in the measurement of BMI in each individual. Finally, crude and adjusted odds ratios (ORs) and 95% confidence intervals (CI) of obesity and overweight at the age of 5.5, 7, and 8 years were calculated using multiple logistic regression analysis. Trends across breastfeeding status were tested by treating the level of exposure to breastfeeding as a continuous, ordinal variable in the regression model.

There were no missing data for birth weight, maternal age, presence of elder sibling(s), and total household income at 0.5 years, but there were missing values in parental education levels and parental smoking status (Table 1). For these variables, missing values were coded into additional indicator variables in the analysis. Because there were missing values among confounders, we also conducted a sensitivity analysis excluding the data with missing values. All analyses

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TABLE 1 Demographic, perinatal, and socioeconomic characteristics of sample population[a]

Characteristics	Boys ($n = 21,425$)	Girls ($n = 20,147$)
Birth variables		
Gestational age (weeks)	39.5 (1.1)	39.6 (1.1)
Birth weight (g)	3128 (377)	3037 (368)
<2,500	833 (3.9)	1234 (6.1)
2,500-3,999	20279 (94.7)	18731 (93.0)
≧4000	313 (1.5)	182 (0.9)
Birth length (cm)	49.5 (1.9)	48.9 (1.9)
Having elder sibling(s)	10873 (50.8)	9953 (49.4)
Breastfeeding exclusiveness		
Exclusive formula feeding	1261 (5.9)	1123 (5.6)
Mixed feeding	15444 (72.1)	14392 (71.4)
Exclusive breastfeeding	4720 (22.0)	4632 (23.0)
Breastfeeding duration[b]		
Never	1,261 (5.9)	1,123 (5.6)
1-2 months	4,086 (19.1)	3,783 (18.8)
3-5 months	4,059 (19.0)	4,073 (20.2)
Over 6 months	11,774 (55.0)	10,958 (54.4)
Maternal variables		
Maternal age at birth (years)	30.2 (4.4)	30.1 (4.4)
Maternal educational level[b]		
Junior high school	1,062 (5.0)	1,084 (5.4)
High school	8,114 (37.9)	7,700 (38.3)
Some college or vocational school	8,779 (41.0)	7,990 (39.7)
College or more	2,868 (13.4)	2,817 (14.0)
Maternal smoking at 0.5 years old[b]	3,475 (16.2)	3,269 (16.2)
Paternal variables		
Paternal age at birth (years)[b]	32.3 (5.6)	32.3 (5.5)
Paternal educational level[b]		
Junior high school	1,658 (7.7)	1,567 (7.8)
High school	8,202 (38.3)	7,660 (38.0)
Some college or vocational school	3,266 (15.2)	3,020 (15.0)
College or more	7,487 (35.0)	7,116 (35.3)
Paternal smoking at 0.5 years old[b]	13,230 (61.8)	12,391 (61.5)
Total annual household income at 6 months of age (million yen)		
<2.5	2,542 (11.9)	2,364 (11.7)
2.5-<5	7,702 (36.0)	7,196 (35.7)
5-<7.5	7,151 (33.4)	6,837 (33.9)
7.5-<10	2,576 (12.0)	2,371 (11.8)
≥10	1,454 (6.8)	1,379 (6.8)

[a]Data are shown mean (standard deviation) for continuous variables and *n* (%) for dichotomous variables.
[b]Missing values in boys (in girls): Birth length, 26 (28); Breastfeeding duration, 245 (210); Maternal educational level, 602 (556); Maternal smoking at 0.5 years old, 114 (98); Paternal age at birth, 222 (247); Paternal educational level, 812 (784); Paternal smoking at 0.5 years old, 394 (403).

were performed with the STATA SE statistical package, version 12.1 (Stata Corp., College Station, TX).

Results

Overall, for boys and girls, 22% and 23% were breastfed exclusively, and 55% and 54% were breastfed for over 6 months, whereas 5.9% and 5.6% were exclusively formula-fed, respectively. Mean gestational age of delivery was similar between boys (39.5 weeks, standard deviation [SD] = 1.1) and girls (39.6 weeks, SD = 1.1), but the rate of low birth weight was higher among girls (6.1%) than boys (3.9%), a finding consistent with previous studies (22). At 6 months of age, 62% of the fathers and 16% of the mothers smoked tobacco.

Mixed-fed boys (coefficient = −0.09, 95% confidence interval [95% CI], −0.16 to −0.02) and exclusively breastfed boys (coefficient = −0.10, 95% CI, −0.18 to −0.03) showed lower BMI as a main effect compared to those who were exclusively formula-fed

TABLE 2 Mixed effects models to evaluate trajectories of body mass index (BMI) in each age of children by breastfeeding exclusiveness among boys ($n = 21,425$) and girls ($n = 20,147$).

	Boys				Girls			
	Adjusted model[a]		Adjusted + Interaction term[b]		Adjusted model[a]		Adjusted + Interaction term[b]	
	Coefficient (SE)	*P* value	Coefficient (SE)	*P* value	Coefficient (SE)	*P* value	Coefficient (SE)	*P* value
Breastfeeding exclusiveness								
Exclusive formula feeding	Reference		Reference		Reference		Reference	
Mixed feeding	−0.09 (0.04)	0.01	0.001 (0.05)	0.99	−0.02 (0.04)	0.64	0.05 (0.05)	0.28
Exclusive breastfeeding	−0.10 (0.04)	0.009	−0.09 (0.05)	0.08	−0.01 (0.04)	0.80	−0.01 (0.05)	0.83
Age								
1.5 years old	Reference		Reference		Reference		Reference	
2.5 years old	−0.31 (0.01)	<0.001	−0.36 (0.05)	<0.001	−0.16 (0.01)	<0.001	−0.15 (0.05)	0.005
3.5 years old	−0.69 (0.01)	<0.001	−0.67 (0.05)	<0.001	−0.46 (0.01)	<0.001	−0.50 (0.05)	<0.001
4.5 years old	−0.99 (0.01)	<0.001	−0.96 (0.05)	<0.001	−0.69 (0.01)	<0.001	−0.66 (0.05)	<0.001
5.5 years old	−1.07 (0.01)	<0.001	−0.98 (0.05)	<0.001	−0.78 (0.01)	<0.001	−0.71 (0.05)	<0.001
7 years old	−0.91 (0.01)	<0.001	−0.68 (0.05)	<0.001	−0.73 (0.01)	<0.001	−0.60 (0.05)	<0.001
8 years old	−0.54 (0.01)	<0.001	−0.29 (0.05)	<0.001	−0.41 (0.01)	<0.001	−0.19 (0.05)	<0.001
Age*Breastfeeding exclusiveness								
2.5 years old* Mixed feeding			0.03 (0.05)	0.54			−0.02 (0.05)	0.70
3.5 years old* Mixed feeding			−0.05 (0.05)	0.32			0.01 (0.05)	0.83
4.5 years old* Mixed feeding			−0.06 (0.05)	0.24			−0.07 (0.05)	0.22
5.5 years old* Mixed feeding			−0.12 (0.05)	0.02			−0.10 (0.05)	0.07
7 years old* Mixed feeding			−0.26 (0.05)	<0.001			−0.17 (0.06)	0.003
8 years old* Mixed feeding			−0.27 (0.05)	<0.001			−0.24 (0.06)	<0.001
2.5 years old* Exclusive breastfeeding			0.14 (0.06)	0.01			0.03 (0.06)	0.61
3.5 years old* Exclusive breastfeeding			0.06 (0.06)	0.30			0.12 (0.06)	0.03
4.5 years old* Exclusive breastfeeding			0.05 (0.06)	0.36			0.07 (0.06)	0.22
5.5 years old* Exclusive breastfeeding			−0.009 (0.06)	0.87			−0.005 (0.06)	0.94
7 years old* Exclusive breastfeeding			−0.18 (0.06)	0.002			−0.07 (0.06)	0.27
8 years old* Exclusive breastfeeding			−0.23 (0.06)	<0.001			−0.20 (0.06)	0.001
Birth weight (g)								
<2,500	Reference		Reference		Reference		Reference	
2,500-3,999	0.58 (0.04)	<0.001	0.58 (0.04)	<0.001	0.56 (0.04)	<0.001	0.56 (0.04)	<0.001
≧4,000	1.43 (0.08)	<0.001	1.43 (0.08)	<0.001	1.36 (0.10)	<0.001	1.35 (0.10)	<0.001
Having elder sibling(s)								
No	Reference		Reference		Reference		Reference	
Yes	0.01 (0.02)	0.49	0.01 (0.02)	0.48	0.05 (0.02)	0.006	0.05 (0.02)	0.006
Maternal age (1 year increase)	0.003 (0.002)	0.16	0.003 (0.002)	0.16	0.01 (0.002)	0.005	0.006 (0.002)	0.005
Maternal educational level								
Junior high school	Reference		Reference		Reference		Reference	
High school	−0.07 (0.04)	0.09	−0.07 (0.04)	0.08	−0.08 (0.04)	0.06	−0.08 (0.04)	0.06
Some college or vocational school	−0.07 (0.04)	0.09	−0.07 (0.04)	0.09	−0.12 (0.04)	0.006	−0.12 (0.04)	0.006
More than college	−0.04 (0.05)	0.40	−0.04 (0.05)	0.40	−0.11 (0.05)	0.02	−0.11 (0.05)	0.02
Maternal smoking status at 0.5 years old								
No	Reference		Reference		Reference		Reference	
Yes	0.12 (0.03)	<0.001	0.12 (0.03)	<0.001	0.06 (0.03)	0.02	0.06 (0.03)	0.02
Paternal educational level								
Junior high school	Reference		Reference		Reference		Reference	
High school or less	−0.03 (0.03)	0.46	−0.03 (0.03)	0.46	−0.04 (0.04)	0.21	−0.04 (0.04)	0.21
Some college or vocational school	−0.07 (0.04)	0.06	−0.07 (0.04)	0.06	−0.10 (0.04)	0.02	−0.10 (0.04)	0.02
College or more	−0.09 (0.04)	0.02	−0.09 (0.04)	0.02	−0.11 (0.04)	0.005	−0.11 (0.04)	0.005

TABLE 2. (continued).

	Boys				Girls			
	Adjusted model[a]		Adjusted + Interaction term[b]		Adjusted model[a]		Adjusted + Interaction term[b]	
	Coefficient (SE)	*P* value	Coefficient (SE)	*P* value	Coefficient (SE)	*P* value	Coefficient (SE)	*P* value
Paternal smoking status at 0.5 years old								
No	Reference		Reference		Reference		Reference	
Yes	0.03 (0.02)	0.11	0.03 (0.02)	0.11	0.08 (0.02)	<0.001	0.08 (0.02)	<0.001
Total annual household income at 6 months of age (million yen)								
<2.5	Reference		Reference		Reference		Reference	
2.5-<5	0.02 (0.03)	0.57	0.02 (0.03)	0.57	−0.006 (0.03)	0.85	−0.006 (0.03)	0.86
5-<7.5	0.02 (0.03)	0.55	0.02 (0.03)	0.55	−0.01 (0.03)	0.71	−0.01 (0.03)	0.72
7.5-<10	0.03 (0.04)	0.39	0.03 (0.04)	0.39	0.04 (0.04)	0.26	0.04 (0.04)	0.25
≥10	0.04 (0.04)	0.36	0.04 (0.04)	0.36	0.01 (0.04)	0.77	0.01 (0.04)	0.77
Intercept	16.0 (0.09)	<0.001	15.9 (0.10)	<0.001	15.5 (0.09)	<0.001	15.5 (0.10)	<0.001

[a]Adjusted for birth weight, having elder sibling(s), maternal age, maternal educational level, maternal smoking status at 0.5 years old, paternal educational level, paternal smoking status at 0.5 years old and total household income at 0.5 years old. For example, in boys between 1.5 and 8 years old, the main effect of exclusive breastfeeding was a lower BMI (−0.10) compared to exclusive formula-feeding.
[b]In addition to adjusted model, interaction terms between breastfeeding exclusiveness and each age of children were added. For example, between 1.5 and 8 years old, exclusively breastfed boys showed more BMI reduction (−0.23) compared to exclusively formula fed boys (statistically significant $P < 0.001$).

(Table 2). Mixed and exclusively breastfed boys also showed a slower increase of inclination in BMI (Figure 1A and B). Regarding interaction between feeding type and age, the mixed models showed that exclusively breastfed boys showed more BMI reduction, especially from 1.5 to 7 years old (−0.18, $P = 0.002$) and from 1.5 to 8 years old (−0.23, $P < 0.001$), in comparison with formula-fed boys.

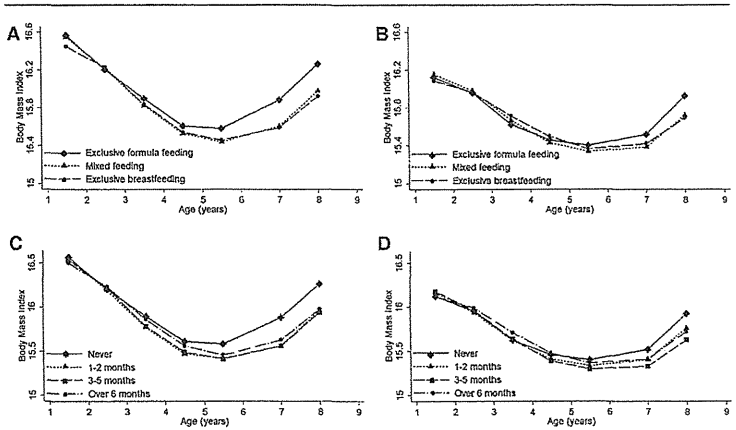

Figure 1 Trajectories of body mass index (BMI) stratified by breastfeeding exclusiveness (boys: A, girls: B) and breastfeeding duration (boys: C, girls: D).

TABLE 3 Mixed effects models to evaluate trajectories of body mass index (BMI) by breastfeeding duration among boys ($n = 21,425$) and girls ($n = 20,147$) at different ages

	Boys				Girls			
	Adjusted model[a]		Adjusted + Interaction term[b]		Adjusted model[a]		Adjusted + Interaction term[b]	
	Coefficient (SE)	*P* value	Coefficient (SE)	*P* value	Coefficient (SE)	*P* value	Coefficient (SE)	*P* value
Breastfeeding duration								
Never	Reference		Reference		Reference		Reference	
1-2 m	−0.13 (0.04)	0.001	0.01 (0.05)	0.82	−0.04 (0.04)	0.29	0.04 (0.06)	0.44
3-5 m	−0.12 (0.04)	0.003	−0.01 (0.05)	0.79	−0.05 (0.04)	0.23	0.08 (0.06)	0.16
Over 6 m	−0.07 (0.04)	0.07	−0.03 (0.05)	0.55	0.01 (0.04)	0.80	0.03 (0.05)	0.56
Age								
1.5 years old	Reference		Reference		Reference		Reference	
2.5 years old	−0.30 (0.01)	<0.001	−0.36 (0.05)	<0.001	−0.16 (0.01)	<0.001	−0.15 (0.05)	0.005
3.5 years old	−0.69 (0.01)	<0.001	−0.67 (0.05)	<0.001	−0.46 (0.01)	<0.001	−0.50 (0.05)	<0.001
4.5 years old	−0.99 (0.01)	<0.001	−0.96 (0.05)	<0.001	−0.69 (0.01)	<0.001	−0.66 (0.05)	<0.001
5.5 years old	−1.08 (0.01)	<0.001	−0.98 (0.05)	<0.001	−0.79 (0.01)	<0.001	−0.71 (0.05)	<0.001
7 years old	−0.91 (0.01)	<0.001	−0.68 (0.05)	<0.001	−0.74 (0.01)	<0.001	−0.60 (0.05)	<0.001
8 years old	−0.54 (0.01)	<0.001	−0.29 (0.05)	<0.001	−0.41 (0.01)	<0.001	−0.19 (0.05)	<0.001
Age*Breastfeeding duration								
2.5 years old* 1-2 m			−0.02 (0.06)	0.76			−0.07 (0.06)	0.24
3.5 years old* 1-2 m			−0.13 (0.06)	0.02			−0.04 (0.06)	0.48
4.5 years old* 1-2 m			−0.14 (0.06)	0.01			−0.09 (0.06)	0.11
5.5 years old* 1-2 m			−0.17 (0.06)	0.005			−0.11 (0.06)	0.06
7 years old* 1-2 m			−0.34 (0.06)	<0.001			−0.15 (0.06)	0.01
8 years old* 1-2 m			−0.31 (0.06)	<0.001			−0.20 (0.06)	0.001
2.5 years old* 3-5 m			0.05 (0.06)	0.38			−0.06 (0.06)	0.29
3.5 years old* 3-5 m			−0.08 (0.06)	0.14			−0.04 (0.06)	0.49
4.5 years old* 3-5 m			−0.09 (0.06)	0.14			−0.13 (0.06)	0.03
5.5 years old* 3-5 m			−0.13 (0.06)	0.02			−0.16 (0.06)	0.006
7 years old* 3-5 m			−0.29 (0.06)	<0.001			−0.25 (0.06)	<0.001
8 years old* 3-5 m			−0.29 (0.06)	<0.001			−0.35 (0.06)	<0.001
2.5 years old* over 6 m			0.09 (0.05)	0.10			0.03 (0.06)	0.63
3.5 years old* over 6 m			0.03 (0.05)	0.57			0.09 (0.05)	0.09
4.5 years old* over 6 m			0.02 (0.05)	0.75			0.02 (0.05)	0.73
5.5 years old* over 6 m			−0.06 (0.05)	0.24			−0.04 (0.06)	0.53
7 years old* over 6 m			−0.20 (0.06)	<0.001			−0.11 (0.06)	0.06
8 years old* over 6 m			−0.23 (0.05)	<0.001			−0.19 (0.06)	0.001
Birth weight (g)								
<2,500	Reference		Reference		Reference		Reference	
2,500-3,999	0.58 (0.04)	<0.001	0.58 (0.04)	<0.001	0.55 (0.04)	<0.001	0.56 (0.04)	<0.001
≧4,000	1.42 (0.08)	<0.001	1.42 (0.08)	<0.001	1.35 (0.10)	<0.001	1.35 (0.10)	<0.001
Having elder sibling(s)								
No	Reference		Reference		Reference		Reference	
Yes	0.01 (0.02)	0.45	0.01 (0.02)	0.44	0.05 (0.02)	0.007	0.05 (0.02)	0.007
Maternal age (1 year increase)	0.003 (0.002)	0.14	0.003 (0.002)	0.14	0.006 (0.002)	0.007	0.006 (0.002)	0.007
Maternal educational level								
Junior high school	Reference		Reference		Reference		Reference	
High school	−0.09 (0.04)	0.05	−0.09 (0.04)	0.04	−0.08 (0.04)	0.07	−0.08 (0.04)	0.07
Some college or vocational school	−0.09 (0.04)	0.04	−0.09 (0.04)	0.04	−0.12 (0.04)	0.005	−0.12 (0.04)	0.005
College or more	−0.06 (0.05)	0.21	−0.06 (0.05)	0.21	−0.12 (0.05)	0.02	−0.12 (0.05)	0.02

TABLE 3. (continued).

	Boys				Girls			
	Adjusted model[a]		Adjusted + Interaction term[b]		Adjusted model[a]		Adjusted + Interaction term[b]	
	Coefficient (SE)	*P* value	Coefficient (SE)	*P* value	Coefficient (SE)	*P* value	Coefficient (SE)	*P* value
Maternal smoking status at 0.5 years old								
No	Reference		Reference		Reference		Reference	
Yes	0.13 (0.03)	<0.001	0.13 (0.03)	<0.001	0.07 (0.03)	0.008	0.07 (0.03)	0.008
Paternal educational level								
Junior high school	Reference		Reference		Reference		Reference	
High school	−0.02 (0.03)	0.48	−0.02 (0.03)	0.49	−0.04 (0.04)	0.21	−0.04 (0.04)	0.22
Some college or vocational school	−0.07 (0.04)	0.09	−0.07 (0.04)	0.09	−0.10 (0.04)	0.02	−0.10 (0.04)	0.02
More than college	−0.08 (0.04)	0.02	−0.08 (0.04)	0.02	−0.11 (0.04)	0.004	−0.11 (0.04)	0.004
Paternal smoking status at 0.5 years old								
No	Reference		Reference		Reference		Reference	
Yes	0.03 (0.02)	0.08	0.03 (0.02)	0.08	0.08 (0.02)	<0.001	0.08 (0.02)	<0.001
Total annual household income at 6 months of age (million yen)								
<2.5	Reference		Reference		Reference		Reference	
2.5-<5	0.02 (0.03)	0.48	0.02 (0.03)	0.48	−0.01 (0.03)	0.74	−0.01 (0.03)	0.74
5-<7.5	0.02 (0.03)	0.48	0.02 (0.03)	0.49	−0.01 (0.03)	0.72	−0.01 (0.03)	0.72
7.5-<10	0.04 (0.04)	0.31	0.04 (0.04)	0.31	0.05 (0.04)	0.21	0.05 (0.04)	0.21
≥10	0.04 (0.04)	0.34	0.04 (0.04)	0.35	0.02 (0.04)	0.73	0.02 (0.04)	0.74
Intercept	16.0 (0.09)	<0.001	15.9 (0.10)	<0.001	15.5 (0.09)	<0.001	15.5 (0.10)	<0.001

m; month.
[a]Adjusted for birth weight, having elder sibling(s), maternal age, maternal educational level, maternal smoking status at 0.5 years old, paternal educational level, paternal smoking status at 0.5 years old and total household income at 0.5 years old. For example, for boys between 1.5 and 8 years old, the main effect of 3-5 months of exclusive breastfeeding a lower BMI (−0.12) compared to who were never breastfed.
[b]In addition to adjusted model, interaction terms between breastfeeding duration and each age of children were added. For example, between ages of 1.5 and 8 years old, boys who were breastfed over 6 months showed more BMI reduction (−0.23) compared to those who were never breastfed (statistically significant, $P < 0.001$).

A similar association was found for girls, although the main effect was not statistically significant.

When we replaced breastfeeding type with breastfeeding duration in the model, we obtained similarly strong evidence that boys and girls who were breastfed longer were less likely to become both overweight and obese (Figure 1C and D), and the trend was more noticeable in later childhood and among boys. That is, the main effect of breastfeeding duration was significant for 1–2 and 3–5 months, and marginally significant for over 6 months among boys; but not significant among girls (Table 3). Regarding interaction between breastfeeding duration and age, breastfeeding over 6 months showed more BMI reduction from 1.5 to 7 (−0.20, $P < 0.001$) and 8 years old (−0.23, $P < 0.001$), in comparison with BMI reduction among never breastfed; those at earlier time points were not statistically significant. Similar associations were generally found among girls, except reduction of BMI, for those breastfed for over 6 months between 1.5 to 7 years old compared to never breastfed (−0.11, $P = 0.06$), was marginal.

These findings were confirmed by our additional logistic models evaluating the differences in the odds of developing overweight or obesity at 5.5, 7, and 8 years by the exclusiveness of breastfeeding in infancy (Table 4). For example, compared with exclusively formula-fed boys, exclusively breastfed boys at 8 years of age had an adjusted OR of 0.70 (95% CI, 0.55-0.88) for overweight and 0.53 (95% CI, 0.34-0.82) for obesity. Similarly, at 8 years of age, exclusively breastfed girls had an adjusted OR of 0.68 (95% CI, 0.53-0.88) and 0.37 (95% CI, 0.23-0.60) for overweight and obesity, respectively.

Similar findings were obtained by the logistic models of overweight and obesity at 5.5, 7, and 8 years for breastfeeding duration (Table 5). For example, compared with boys who had never been breastfed, boys breastfed for 1–2, 3–5, and over 6 months had an adjusted OR of 0.86, 0.81, and 0.78 for overweight at the age of 8, respectively (adjusted *P* value for trend = 0.03). Adjusted ORs for obesity at the age of 8 were 0.66, 0.72, and 0.58, respectively, with the dose-response relationship being significant (adjusted *P* value for trend = 0.02). Compared with girls who had never been breastfed, girls breastfed for 1–2, 3–5, and over 6 months had an adjusted OR of 0.49, 0.36, and 0.43 for obesity at 8 years, respectively, with the dose-response relationship being significant (adjusted *P* value for trend = 0.004).

Sensitivity analysis excluding data from subjects with missing values demonstrated almost the same results, although several significant associations were attenuated and became marginally significant (Supporting Information Tables S1-S4).

TABLE 4 Crude and adjusted odds ratio of maternal breastfeeding exclusiveness for overweight and obesity at age of 5.5, 7, 8 stratified by sex

	Boys				Girls			
	Overweight		Obesity		Overweight		Obesity	
	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)
At 5.5 years old								
Exclusive formula feeding	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Mixed feeding	0.65 (0.52-0.82)	0.71 (0.56-0.89)	0.57 (0.37-0.86)	0.67 (0.44-1.02)	0.74 (0.59-0.92)	0.79 (0.64-0.99)	0.55 (0.35-0.84)	0.62 (0.40-0.97)
Exclusive breastfeeding	0.64 (0.50-0.82)	0.73 (0.57-0.94)	0.57 (0.36-0.90)	0.73 (0.45-1.17)	0.70 (0.55-0.89)	0.77 (0.61-0.99)	0.41 (0.25-0.68)	0.48 (0.29-0.81)
P for trend	0.02	0.16	0.12	0.51	0.03	0.14	0.002	0.01
At 7 years old								
Exclusive formula feeding	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Mixed feeding	0.73 (0.59-0.90)	0.77 (0.62-0.96)	0.63 (0.43-0.91)	0.71 (0.49-1.04)	0.70 (0.56-0.87)	0.75 (0.60-0.94)	0.47 (0.31-0.71)	0.54 (0.36-0.82)
Exclusive breastfeeding	0.64 (0.50-0.81)	0.70 (0.55-0.89)	0.47 (0.31-0.72)	0.56 (0.36-0.87)	0.68 (0.53-0.87)	0.75 (0.59-0.96)	0.41 (0.26-0.66)	0.50 (0.31-0.80)
P for trend	0.001	0.008	0.001	0.01	0.04	0.17	0.005	0.03
At 8 years old								
Exclusive formula feeding	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Mixed feeding	0.77 (0.63-0.95)	0.84 (0.68-1.03)	0.60 (0.42-0.87)	0.67 (0.46-0.97)	0.72 (0.58-0.90)	0.80 (0.64-1.00)	0.38 (0.26-0.56)	0.45 (0.30-0.67)
Exclusive breastfeeding	0.61 (0.48-0.76)	0.70 (0.55-0.88)	0.45 (0.29-0.69)	0.53 (0.34-0.82)	0.60 (0.47-0.77)	0.68 (0.53-0.88)	0.30 (0.19-0.47)	0.37 (0.23-0.60)
P for trend	<0.001	0.001	0.001	0.007	<0.001	0.002	<0.001	0.001

Adjusted for birth weight, having elder sibling(s), maternal age, maternal educational level, maternal smoking status at 0.5 years old, paternal educational level, maternal smoking status at 0.5 years old and total household income at 0.5 years old.
n in boys (girls): 16,393 (16,342) at 5.5 years of age, 15,546 (14,620) at 7 years of age and 15,979 (15,076) at 8 years of age.
Overweight *n* (%): boys 1,163 (7.1%), girls 1,432 (8.8%) at 5.5 years of age; boys 1,470 (9.5%), girls 1,869 (12.4%) at 7 years of age; boys 1,659 (10.4%), girls 1,967 (13.1) at 8 years of age.
Obesity *n* (%): boys 278 (1.7%), girls 249 (1.5%) at 5.5 years of age; boys 372 (2.4%), girls 255 (1.7%) at 7 years of age; boys 385 (2.4%), girls 243 (1.6%) at 8 years of age
Definitions of overweight and obesity were based on the International Obesity Task Force cut points of age-sex-specific BMI.
OR, odds ratio; CI, confidence interval.

TABLE 5 Crude and adjusted odds ratio of maternal breastfeeding duration for overweight and obesity at age of 5.5, 7, 8 stratified by sex

	Boys				Girls			
	Overweight		Obesity		Overweight		Obesity	
	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)
At 5.5 years old								
Never	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
1–2 m	0.66 (0.51-0.86)	0.68 (0.53-0.88)	0.56 (0.34-0.90)	0.60 (0.37-0.96)	0.77 (0.61-0.99)	0.79 (0.61-1.01)	0.60 (0.37-0.99)	0.63 (0.39-1.04)
3–5 m	0.63 (0.49-0.81)	0.68 (0.52-0.87)	0.67 (0.42-1.07)	0.78 (0.49-1.26)	0.74 (0.58-0.95)	0.79 (0.62-1.01)	0.48 (0.29-0.79)	0.55 (0.33-0.91)
Over 6 m	0.64 (0.51-0.81)	0.73 (0.58-0.92)	0.52 (0.34-0.80)	0.65 (0.42-1.01)	0.71 (0.57-0.89)	0.79 (0.63-0.99)	0.49 (0.31-0.76)	0.59 (0.37-0.92)
P for trend	0.01	0.32	0.02	0.30	0.01	0.23	0.008	0.10
At 7 years old								
Never	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
1–2 m	0.74 (0.58-0.94)	0.75 (0.59-0.95)	0.66 (0.43-1.01)	0.69 (0.45-1.06)	0.77 (0.60-0.98)	0.77 (0.60-0.99)	0.62 (0.39-0.99)	0.65 (0.41-1.04)
3–5 m	0.69 (0.55-0.88)	0.73 (0.57-0.93)	0.56 (0.36-0.86)	0.64 (0.41-0.99)	0.71 (0.55-0.90)	0.75 (0.59-0.96)	0.35 (0.21-0.58)	0.40 (0.24-0.67)
Over 6 m	0.70 (0.56-0.87)	0.76 (0.61-0.95)	0.56 (0.39-0.83)	0.68 (0.46-1.00)	0.66 (0.53-0.83)	0.73 (0.58-0.92)	0.43 (0.28-0.66)	0.52 (0.34-0.80)
P for trend	0.02	0.22	0.01	0.23	0.001	0.04	<0.001	0.01
At 8 years old								
Never	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
1–2 m	0.83 (0.66-1.04)	0.86 (0.68-1.08)	0.64 (0.42-0.98)	0.66 (0.44-1.01)	0.79 (0.61-1.01)	0.81 (0.63-1.04)	0.45 (0.29-0.71)	0.49 (0.31-0.77)
3–5 m	0.75 (0.60-0.95)	0.81 (0.65-1.02)	0.65 (0.43-0.99)	0.72 (0.47-1.09)	0.71 (0.55-0.91)	0.78 (0.61-1.00)	0.30 (0.19-0.49)	0.36 (0.22-0.59)
Over 6 m	0.69 (0.56-0.85)	0.78 (0.63-0.97)	0.50 (0.35-0.74)	0.58 (0.40-0.86)	0.65 (0.52-0.82)	0.75 (0.60-0.95)	0.34 (0.23-0.51)	0.43 (0.29-0.66)
P for trend	<0.001	0.03	0.001	0.02	<0.001	0.03	<0.001	0.004

Adjusted for birth weight, having elder sibling(s), maternal age, maternal educational level, maternal smoking status at 0.5 years old, paternal educational level, paternal smoking status at 0.5 years old and total household income at 0.5 years old.
n in boys (girls): 16,03 [15,342] at 5.5 years of age, 15,646 (14,820) at 7 years of age and 15,979 (15,076) at 8 years of age.
Overweight n (%): boys 1,144 (7.1%), girls 1,418 (9.3%) at 5.5 years of age; boys 1,453 (9.4%), girls 1,355 (9.4%) at 7 years of age; boys 1,642 (10.4%), girls 1,350 (9.0) at 8 years of age.
Obesity n (%): boys 271 (1.7%), girls 244 (1.6%) at 5.5 years of age; boys 384 (2.4%), girls 250 (1.7%) at 7 years of age; boys 359 (2.3%), girls 238 (1.6%) at 8 years of age.
Definitions of overweight and obesity were based on the International Obesity Task Force cut points of age-sex-specific BMI.
OR, odds ratio; CI, confidence interval.

Discussion

In this longitudinal study that employed a nationally representative sample of Japanese children, we found that breastfed boys and girls were less likely to develop obesity or overweight in late childhood than were those who had never been breastfed. We also found that children with exclusive or longer duration of breastfeeding were less likely to develop overweight or obesity. Importantly, the BMI differences between the children with different breastfeeding statuses were statistically significant only in late childhood—at the ages of 7 and 8. Moreover, our data suggest that these effects of breastfeeding are stronger among boys than girls.

Our study supported the hypothesis that breastfeeding has a latent protective effect on childhood BMI (15,16). The latent effects of breastfeeding may explain the inconsistency in previous results on the association between BMI and breastfeeding (13,23,24). In previous studies, the children's ages ranged predominantly from 3 to 6 years (7,24-26) or the children were over 9 years old (6,12). In our study, a significant slower increase of BMI with age was observed in both boys and girls in late childhood, that is, after 7 years in boys and at 8 years in girls, who were breastfed compared with those who were formula-fed. Furthermore, breastfeeding was shown to have a significant protective effect on overweight and obesity with a dose-response relationship, and this effect was strongest at 8 years of age for both boys and girls. These results support the hypothesis that breastfeeding has a latent protective effect against childhood overweight and obesity (15,16). In a longitudinal study with 1,037 children followed until the age of 26 years, Poulton and Williams demonstrated that the protective effect of breastfeeding on childhood overweight was relatively weak up to age of 7 years and then strengthened in late childhood (9–11 years) (16). Their results, together with ours, suggest that studies investigating the effect of breastfeeding at early childhood (i.e., below the age of 7) might be unable to show a significant slower increase of BMI with age or a protective effect against overweight and obesity because data were collected too early.

The contradictory results from previous studies that showed no significant association between breastfeeding and childhood overweight and obesity in American and European samples (11-14) may be due to the difference in prevalence of breastfeeding in Japan and in western countries. The percentage of breastfeeding behavior, that is, exclusive and partial breastfeeding in Japan (78% for boys and 77% for girls) were higher than in the USA (54%) (24) and in the UK (66%) (27). More specifically, in a recent randomized controlled trial reporting no preventive effect on overweight and obesity at age of 6.5 and 11.5 years old, the percentage of any form of breastfeeding was relatively lower, even among intervention group. Only 43% of participants breastfed for six months or more (11,12). Potential methodological issues, such as high rates of missing values in breastfeeding information (32%) (13) and drop out (57.9%) at the age of outcome measurement (14), may have also influenced the null association in those studies.

Several underlying mechanisms for the relationship between breastfeeding and childhood obesity have been proposed (28). One of them is behavioral factors, such as infants' capabilities of self-regulation of milk intake. Li et al. found that bottle-fed infants in early infancy were more likely to empty the bottle in late infancy than were those who were fed directly at the breast, regardless of whether the contents of the bottle were breast or formula milk (29). Another mechanism was bioactive factors in breast milk. Breastfeeding decreases appetite associated peptide and secretion of ghrelin, which may reduce babies' appetite and result in reduced risk of obesity (30). Higher protein intake in early childhood has also been proposed to promote secretion of insulin and IGF-1, which were associated with an early adiposity rebound (31). Formula-fed children have been reported to have a higher protein intake than breastfed children (32), which may increase the risk of obesity in late childhood. Regardless of the actual mechanism, it is still unclear why breastfeeding has a latent protective effect on overweight and obesity in late childhood.

We found a stronger association between breastfeeding and BMI among boys than among girls. This finding is in line with a previous study that showed greater benefits of longer breastfeeding duration for boys than for girls in reducing body fats and BMI from 0.5 to 7 years (21). This may be due to girls' intrinsically high insulin resistance. Girls at the age of 5 have been found to have higher levels of triglycerides and lower concentrations of HDL cholesterol than boys of the same age (33), findings that indicate that metabolic disturbances are more advanced in girls than in boys. An animal study showed that baboons who were overfed by formula during infancy were more likely to have a higher fat score at 5 years of age, but this tendency was found only in females not males (34). These metabolic vulnerabilities in females might attenuate the effect of breastfeeding and result in non-significance in trajectories of BMI in girls and delayed effect of breastfeeding on BMI.

The strengths of our study include repeated measures of anthropometric data, the use of a large nationally representative sample of Japanese children, the assessment of breastfeeding status in a prospective manner, and high follow-up rates (73–89%, higher than those of other cohort studies) (6,25). However, this study also had several limitations. First, anthropometric data were based on parents' report. The validity of parent-reported height and weight in children varies across countries. A German study reported that parental reports of their children's BMI were underestimated and sensitivity and specificity for overweight ranged from 66.7% to 67.1% and from 90.1 to 91.2%, respectively, for boys and girls (35). However, a Japanese study suggests that parent-reported BMI is more precise; the correlations between parent-reported and measured BMI ranged between 0.86 and 0.97, and sensitivity and specificity for the presence of obesity ranged from 83.3% to 93.3% and 96.3% to 98.9%, respectively (36). In our study, the BMI data were almost equivalent to the Japanese national BMI reference data in 2000, which comprised of nationally representative cross-sectional sample of children aged from 0 to 17 years with objective measurement (37). Moreover, the use of parent-reported height and weight data may introduce non-differential misclassification in overweight and obesity, which will bias the results toward the null value (38). Nevertheless, our results showed that breastfeeding had a significant protective effect on development of overweight and obesity in late childhood. Second, we did not control for parents' BMI, which may lead to residual confounding. Maternal obesity is significantly associated with breastfeeding discontinuation, at least among white (39) and Hispanic (40), but not black women (40). Reliable data on the effects of maternal BMI on breastfeeding among Asian populations are lacking.

Given the findings of our study, further research should evaluate the preventive latent effects of breastfeeding for childhood obesity,

using standardized protocol for measuring height and weight, in other Asian populations as well as in other parts of the world. Important covariates such as maternal BMI, maternal weight gain during pregnancy, children's dietary intake and physical activities should be adjusted. Potential mechanisms suggested, for example, the roles of self-regulation, appetite associated peptide and secretion of ghrelin, and IGF-1, warrant further study. Importantly, our study demonstrated that not only exclusive, long-term breastfeeding but also mixed breastfeeding and breastfeeding for less than 6 months also had a protective effect against childhood overweight and obesity. This finding may have important public health implications—even if discontinued or mixed with formula feeding for various reasons, breastfeeding still has a protective effect on BMI trajectories and overweight and obesity. Thus, breastfeeding should be recommended even if mixed with formula feeding or for a shorter duration. O

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Associations of Childhood Socioeconomic Status and Adulthood Height With Functional Limitations Among Japanese Older People: Results From the JAGES 2010 Project

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Background. We examined the associations between childhood socioeconomic status and adulthood height with functional limitations in old age.

Methods. Data were obtained from the baseline survey of the Japan Gerontological Evaluation Study 2010, a population-based cohort of people aged ≥65 years enrolled from 27 municipalities across Japan (N = 15,499). People aged 65–69, 70–74, 75–79, and ≥80 years experienced the end of World War II when they were aged 0–4, 5–9, 10–14, and ≥15 years, respectively. Subjective socioeconomic status during childhood and current height were obtained by self-report through questionnaire in 2010. Higher-level functional capacity was assessed using a validated questionnaire scale. Poisson regression with robust variance estimator was employed to determine the association between childhood subjective socioeconomic status, height, and functional limitations.

Results. Lower childhood subjective socioeconomic status was consistently associated with higher prevalence rate ratio of limitations in higher-level functional capacity, regardless of age cohort. Height was associated with functional limitation only among the group aged 70–74 years: taller (≥170 cm for men and ≥160 cm for women) people were 16% less likely to report functional limitation in comparison with shorter (<155 cm for men and <145 cm for women) individuals in the fully adjusted model (prevalence rate ratio: 0.84, 95% confidence interval: 0.74–0.96).

Conclusions. Low childhood subjective socioeconomic status had a robust association with functional limitation regardless of age cohort. In addition, those who lived through World War II before they reached puberty and attained shorter height were more likely to report functional limitations in old age.

Key Words: Disability—Life-course approach—Subjective socioeconomic status—Height—Childhood environment.

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DISABILITY is a long-term process that is associated with socioeconomic status (SES), health behaviors (eg, smoking or physical inactivity), and disease status (eg, stroke) (1). Social inequalities in health behaviors and disease status lead to corresponding social inequalities in disability status and functional limitations (2). Most studies have focused on risk factors for disability beginning in midlife (3–5), but increasingly studies have adopted a life-course perspective to examine the associations between childhood environment, adulthood SES, health behaviors (6), disability, and activities of daily living (ADL) (7,8).

Few studies have investigated the impact of childhood environment on limitations in higher-level functional capacity (7), such as those social activities or activities that require higher cognitive function (eg, reading a newspaper, visiting a friend's house), which are critical to the concept of "successful" aging (9). For example, the results of the Whitehall II study in the United Kingdom (10) showed that childhood SES was associated with cognitive function among midlife adults, suggesting that there is a sensitive period during childhood development during which adversity can result in limitations of higher-level functional capabilities later in life (11). Notably, the Whitehall results indicated that childhood adversity can result in deleterious effects on health in adulthood even if the individual escapes adverse socioeconomic conditions later in life—which is referred to as the latent effects model. Koyano and colleagues developed a scale to assess limitations in higher-level functional capacity among older people based on Lawton's model of competence (12), which was designed to cover instrumental self-maintenance, intellectual activities, and social roles (13). An investigation of the childhood determinants of limitations in higher-level functional capacity is critical for the development of a strategy to promote healthy and active aging (14).

Most previous studies on the life-course approach have investigated the impact of childhood SES by using paternal occupation as an indicator (6,15–19), while some studies have adopted other proxies, such as perceptions of wealth during childhood (16), housing conditions (20), or number of siblings (21), to measure early childhood social environment. Recent studies have demonstrated the utility of subjective socioeconomic status (SSS) as a predictor of health (22), although an association between childhood SSS and disability has not been reported to our knowledge. An additional proxy for childhood adversity is adulthood height, which can be thought of as a marker of cumulative social and environmental exposures during early childhood (23). Around 20% of variation in height is due to environmental variation (23), which is mainly made up of childhood nutrition, disease status, educational attainment and lower socioeconomic position (24). Previous reviews have indicated a robust link between short stature and a range of diseases (25). To the best of our knowledge, no study has investigated the associations between childhood SSS and height with limitations in higher-level functional capacity among older people.

The Japan Gerontological Evaluation Study Project is a cohort study that evaluated both childhood environment and higher-level functional capacity among community-dwelling people aged ≥65 years in Japan. Baseline surveys were administered in 2010–2011 to individuals who were free of disability as defined by the national long-term care insurance system.

Some of the participants lived through World War II, which lasted from 1937 to 1945, while they were in early childhood. People aged 65–69, 70–74, 75–79, and ≥80 years experienced the end of World War II when they were aged 0–4, 5–9, 10–14, and ≥15 years, respectively. The period during and immediately after World War II (1937–1945) in Japan was associated with food shortages, rationing, and severe restrictions in the nutritional environment (26,27). Thus, this cohort provides a unique opportunity to investigate the impact of height (as a proxy of early childhood nutritional deprivation) on subsequent limitations in higher-level functional capacity.

Methods

Study Population

The goal of the Japan Gerontological Evaluation Study 2010 Project was to evaluate the health status and social determinants of nondisabled people aged ≥65 years sampled from 27 municipalities in 10 of the 47 prefectures in Japan. The municipalities were selected throughout the major islands of Japan (Hokkaido, Honshu, Kyushu, and Okinawa), with the exception of Shikoku. Since the primary objective of the cohort is to examine the predictors of disability onset, older people who were eligible to receive public long-term care insurance benefits were excluded (ie, older people with disability registered in municipality were excluded) from the sample. In 15 municipalities, we sampled the entire population of residents older than 65 years (complete enumeration), while in the remaining 12 municipalities we mailed the surveys to a simple random sample based on the official residential registers obtained from municipal authorities.

A total of 117,494 residents aged ≥65 years at the time of the baseline survey (which took place from August 10, 2010 to May 9, 2011) were targeted for the baseline questionnaire. Of the eligible participants, 78,769 people responded to the survey (response rate: 67.0%, which is quite high for a community-based survey of this type, where response rates of 20% is the norm in many western countries). Of the returned surveys, 4,425 were rejected because of missing data (valid response rate: 63.3%). One-quarter of the sample in 25 municipalities (N = 18,194) was asked about childhood environment. We further limited the sample to respondents who gave nonmissing responses on sex and responded ≥65 years of age (N = 17,723). To focus on the association between childhood environment and limitations in higher-level functional capacity, although initially sample with disability registered in municipality were excluded, the sample was further limited to those who reported no limitations in ADL, defined as those who can walk, take a bath, and do toilet without assistance (N = 16,870). The excluded sample with ADL limitations showed similar childhood SSS with included sample (p = .37), although the height of the excluded sample was shorter in general (p < .01). Finally, since the study's main outcome measure is higher-level functional capacity, those who did not respond fully to the Tokyo Metropolitan Institute of Gerontology Index of Competence were excluded; this reduced the size of the analysis sample to 15,499.

Assessment of Limitations in Higher-Level Functional Capacity

Limitations in higher-level functional capacity was assessed using the Tokyo Metropolitan Institute of Gerontology Index of Competence (12), which was derived from Lawton's model of competence, comprised of 13 items (see Supplementary Appendix), designed to cover instrumental self-maintenance (5 items), intellectual activities (4 items), and social roles (4 items) for older people (13). For example, the respondents were asked, "Can you use public transportation (bus or train) by yourself?" with response

items of "yes" or "no." If respondents marked "no" for any item, the respondent was classified as having some limitation in higher-level functional capacity, while respondents who marked "yes" for all items were classified as being without limitation in higher-level functional capacity. This scale is widely used in Japan to assess limitations in higher-level functional capacity among older people (28–30).

Childhood SSS and Adulthood Height

Childhood SSS was assessed retrospectively by the following question on the self-administered questionnaire: "How do you rate your social status when you were aged 15 years in comparison with standards at that time?" Responses were rated on a five-point Likert scale with the following anchors: high, middle-high, middle, middle-low, and low. Retrospectively, recalled SSS has been used in a previous study and showed similar association with health status in comparison with objective SES in childhood, although only among men (31). The participants' current height was also reported in the self-administered questionnaire. Previous studies confirmed a high correlation between self-reported and measured height among Japanese (32) and older people in Australia (33). Individuals reporting height above 3 *SDs* from the mean height (as retrieved from the 2010 Japanese National Health and Nutrition Survey (34)) were excluded because considered as potential outliers, yielding 1,617 invalid reports (10.4%). Further, height was categorized into five groups in 5-cm intervals for each sex: for men: <155, 155–159.9, 160–164.9, 165–169.9, and ≥170 cm; and for women: <145, 145–149.9, 150–154.9, 155–159.9, and ≥160 cm.

Adult SES, Health Behaviors, Disease Status, and Other Covariates

Potential mediators of the association between childhood adversity and old age functional limitations—such as adult SES, health behaviors, and disease status—were also assessed by self-administered questionnaire. Indicators of adult SES included years of schooling (<6, 6–9, 10–12, or ≥13 years) and annual household income in the year before the survey (<1.5, 1.5–2.9, 3.0–4.9, or ≥5 million yen, 1 million yen is equivalent to 10,000 dollars). Health behaviors included drinking (current, quit, or never), smoking (current, quit ≤4 years ago, quit ≥5 years ago, or never), vegetable and/or fruit intake during the past month (two servings daily or more, once daily, 4–6 times weekly, 2–3 times weekly, once weekly, less than once weekly, or never), and average walking time per day (<30, 30–59, 60–89, or 90+ min). The respondents were also asked whether they were currently under medical treatment for the following diseases with yes/no responses: cancer, heart disease, stroke, hypertension, diabetes mellitus, obesity, hyperlipidemia, osteoporosis, joint disease/neuralgia, respiratory disease, gastrointestinal disease, liver disease, psychiatric disease, visual impairment, hearing impairment, impaired excretion, sleep disorder, and other. Sex, marital status (married, widowed, divorced, never married, or other), and living status (whether or not the respondent was living alone) were also asked via questionnaire. Further, municipality dummy codes were added to adjust for municipality fixed effects.

Analysis

Poisson regression with robust variance estimator was used to examine the associations between childhood SSS and height with limitations in higher-level functional capacity, stratified by age group. We employed Poisson regression analysis with robust variance estimator because of the relatively high prevalence of limitation of higher-level functional capacity (>10%), which would result in the divergence of odds ratios from the risk ratio (35,36). Model 1 was adjusted for age and sex, model 2 additionally adjusted for adult SES, model 3 additionally adjusted for health behaviors, model 4 additionally adjusted for disease status, and model 5 (the final model) additionally adjusted for marital and living status. All analyses were performed using STATA MP version 12.

Results

The overall and age-stratified characteristics of the study sample are shown in Supplementary Table 1. Of the respondents in the total sample, 72%, 22%, and 11% were married, widowed, and living alone, respectively. Regarding childhood SSS, 44% considered that their childhood SES was low compared with the rest of society; this did not vary by age group. The distribution of participants in the five height categories was as follows: 11% (in the shortest group), 22%, 30%, 19%, and 7% (in the tallest group); 10% of respondents were missing information on height. Around half of participants completed less than 10 years of education. A further 45.2% earned less than 3 million yen in annual income (1 million yen is equivalent to 10,000 dollar). One third were current drinkers, while 10% were current smokers. The major comorbid conditions reported by participants were hypertension (39.8%), visual impairment (14.0%), diabetes mellitus (12.9%), heart disease (11.9%), joint disease or neuralgia (11.5%), and hyperlipidemia (9.3%). In terms of limitations in higher-level functional capacity, 57% of the total sample reported some disability (as did 49%, 54%, 60%, and 71% of the sampled groups aged 65–69, 70–74, 75–79, and ≥80 years, respectively).

Table 1 shows the prevalence rate ratios (PR) of limitations in higher-level functional capacity according to childhood SSS and height, stratified by age group, using Poisson regression. Overall, low childhood SSS showed a positive association with limitations in higher-level functional capacity in all age groups. For example, older people aged

Table 1. Prevalence Rate Ratio of Childhood SES and Adulthood Height for Limitation of Higher-Level Functional Capacity by Poisson Regression Analysis

			Model 1 (adjusted age, sex)		Model 2 (model 1 + adult SES)		Model 3 (model 2 + health behavior)		Model 4 (model 3 + disease)		Model 5 (model 4 + marital. living alone)	
			PR	95% CI	PR	95% CI	PR	95% CI	PR	95% CI	OR	95% CI
65–69 y	SES in childhood	High or middle-high	ref		ref		ref		ref		ref	
		Middle	1.20	1.06–1.36	1.14	1.01–1.29	1.15	1.02–1.30	1.16	1.02–1.30	1.16	1.03–1.31
		Middle-low or low	1.39	1.23–1.57	1.26	1.11–1.42	1.27	1.13–1.43	1.28	1.13–1.44	1.28	1.14–1.44
	Adulthood height category	Short	ref		ref		ref		ref		ref	
		Middle-short	1.02	0.88–1.18	1.05	0.91–1.21	1.03	0.89–1.18	1.02	0.88–1.18	1.02	0.89–1.18
		Middle	0.95	0.82–1.09	0.99	0.86–1.14	0.97	0.85–1.12	0.97	0.85–1.12	0.97	0.85–1.12
		Middle-tall	0.90	0.78–1.04	0.97	0.84–1.11	0.96	0.83–1.10	0.95	0.82–1.09	0.95	0.82–1.09
		Tall	0.97	0.83–1.13	1.04	0.89–1.21	1.03	0.88–1.20	1.03	0.88–1.20	1.03	0.89–1.20
70–74 y	SES in childhood	High or middle-high	ref		ref		ref		ref		ref	
		Middle	1.10	0.99–1.23	1.06	0.95–1.17	1.05	0.94–1.16	1.05	0.95–1.17	1.06	0.95–1.17
		Middle-low or low	1.30	1.17–1.44	1.19	1.07–1.31	1.17	1.06–1.29	1.17	1.06–1.29	1.17	1.06–1.30
	Adulthood height category	Short	ref		ref		ref		ref		ref	
		Middle-short	0.91	0.83–1.01	0.94	0.85–1.04	0.95	0.86–1.05	0.94	0.85–1.04	0.94	0.85–1.05
		Middle	0.86	0.78–0.94	0.90	0.82–0.99	0.89	0.81–0.98	0.89	0.81–0.98	0.89	0.81–0.98
		Middle-tall	0.86	0.78–0.95	0.92	0.83–1.02	0.92	0.83–1.01	0.91	0.82–1.01	0.91	0.83–1.01
		Tall	0.78	0.69–0.89	0.85	0.74–0.97	0.84	0.74–0.96	0.84	0.74–0.95	0.84	0.74–0.96
75–79 y	SES in childhood	High or middle-high	ref		ref		ref		ref		ref	
		Middle	1.11	1.00–1.24	1.05	0.95–1.18	1.06	0.95–1.17	1.05	0.95–1.17	1.05	0.95–1.17
		Middle-low or low	1.31	1.18–1.46	1.21	1.09–1.34	1.20	1.08–1.33	1.20	1.08–1.33	1.20	1.08–1.33
	Adulthood height category	Short	ref		ref		ref		ref		ref	
		Middle-short	0.99	0.90–1.08	1.02	0.93–1.11	1.01	0.92–1.10	1.02	0.93–1.11	1.02	0.93–1.11
		Middle	0.92	0.84–1.01	0.96	0.88–1.05	0.95	0.87–1.04	0.95	0.87–1.04	0.96	0.88–1.05
		Middle-tall	0.92	0.83–1.02	0.98	0.88–1.08	0.97	0.87–1.07	0.97	0.88–1.08	0.98	0.88–1.08
		Tall	0.99	0.85–1.14	1.06	0.92–1.22	1.04	0.90–1.20	1.05	0.91–1.21	1.05	0.92–1.21
80+ y	SES in childhood	High or middle-high	ref		ref		ref		ref		ref	
		Middle	1.07	1.00–1.17	1.04	0.96–1.12	1.03	0.96–1.11	1.03	0.96–1.11	1.03	0.96–1.11
		Middle-low or low	1.18	1.10–1.27	1.12	1.04–1.21	1.11	1.03–1.19	1.10	1.02–1.18	1.10	1.02–1.19
	Adulthood height category	Short	ref		ref		ref		ref		ref	
		Middle-short	0.95	0.89–1.01	0.95	0.90–1.02	0.96	0.90–1.02	0.96	0.90–1.03	0.97	0.91–1.03
		Middle	0.95	0.89–1.02	0.96	0.89–1.03	0.96	0.89–1.02	0.96	0.90–1.03	0.96	0.90–1.03
		Middle-tall	0.98	0.89–1.07	0.99	0.90–1.08	0.98	0.89–1.07	0.99	0.91–1.08	0.99	0.91–1.09
		Tall	1.06	0.93–1.20	1.07	0.94–1.21	1.07	0.94–1.21	1.07	0.94–1.21	1.07	0.94–1.21

Notes: Short, men: <155 cm, women: <145 cm; Middle-short, men: 155–159.9 cm, women: 145–149.9 cm; Middle, men: 160–164.9 cm, women: 150–154.9 cm; Middle-tall, men: 165–169.9 cm, women: 155–159.9 cm; Tall, men: 170+ cm, women: 160+ cm. CI = confidence interval; OR = odds ratio; PR = prevalence rate ratio; SES = socioeconomic status. Values in bold are significant at the $p = .05$ level.

65–69 years who considered their childhood SES as low or middle-low were 1.39 times (95% confidence interval [CI]: 1.23–1.57) more likely to report limitations in higher-level functional capacity in comparison with similarly aged people with high or middle-high childhood SES, after adjustment for age and sex. Similar PRs were observed for other age groups: for older people aged 70–74, 75–79, and ≥80 years, the PRs of limitations in higher-level functional capacity among those with low as opposed to high childhood SSS were 1.30 (95% CI: 1.17–1.44), 1.31 (95% CI: 1.18–1.46), and 1.18 (95% CI: 1.10–1.27), respectively. The significant associations remained in all age groups even after correction for mediators (adult SES, health behaviors, disease status, marital status, and living status), although the point estimates of PR were attenuated by covariance adjustment.

In contrast to childhood SSS, adulthood height was significantly inversely associated with limitations in higher-level functional capacity only among the group aged 70–74 years, that is, among those who experienced the end of World War II when they were aged 5–9 years. Model 1 indicates that in comparison with shorter older people, the PRs of limitations in higher-level functional capacity across ascending height groups were 0.91 (95% CI: 0.83–1.01), 0.86 (95% CI: 0.78–0.94), 0.86 (95% CI: 0.78–0.95), and 0.78 (95% CI: 0.69–0.89), respectively. The "dose-response" relationship was statistically significant according to the test for linear trend (p for trend < .001). This association persisted even after adjustment for mediators. Further, the p for linear trend between height and limitations in higher-level functional capacity remained significant in model 5 (p for trend = .008, data not shown). An association between height and functional limitations was not found in the younger age groups.

The impact of childhood SSS and adulthood height on specific type of functional limitations (ie, instrumental self-maintenance, intellectual activities, and social role limitations) was further investigated (see Supplementary Appendix). Then, we found that low childhood SSS was significantly positively associated with limitations in intellectual activities and social role limitations (see Supplementary Table 2). By contrast, limitations in instrumental self-maintenance activities were not associated with childhood SSS. A significant inverse association was observed between height and the intellectual activities subcategory of limitations in higher-level functional capacity for all age groups. Among older people aged 70–75 years, for example, the tallest group was 28% less likely to report limitations in intellectual activities compared with the shortest group (PR: 0.72, 95% CI: 0.58–0.90). The remaining subcategories (ie, instrumental self-maintenance and social role limitations) were not associated with height, except social role limitations among people aged 70–74 years.

Discussion

Using data from a large population-based study, we showed that low childhood SSS was significantly associated with limitations in higher-level functional capacity among older people without ADL limitations, especially in the domains of intellectual activities and social roles. These findings were consistent across all studied age groups (ie, 65–69, 70–74, 75–79, and ≥80 years). Furthermore, adulthood height (considered a proxy of childhood nutritional and social environment) was inversely associated with limitations in higher-level functional capacity among older people aged 70–74 years, who experienced the end of World War II when they were aged 5–9 years. The fact that these associations persisted after adjustment for SES attained in adulthood suggests the long-lasting influence of childhood adversity on functional limitations in old age.

The following pathways can possibly explain how low childhood SES and height exert long-term influences on higher-level functional activity limitations in old age: First, low childhood SES may deleteriously affect the development of health maintenance behaviors across the life course. For example, those raised in low SES circumstances may lack role models in terms of intellectual activities or social roles—or what is referred to as the accumulation of "cultural capital." For example, parents in high SES households are more likely to read newspapers and participate in a variety of social roles (37–39). This may explain why low childhood SSS was not associated with self-maintenance instrumental ADL in this study, that is, even those raised in low SES circumstances acquire habits such as the use of public transportation. Second, low childhood SES may trigger a chain of risk that includes low adulthood SES, poor health behaviors, and disease status, which are all associated with limitation in higher-level functional capacities—the so-called "pathways model" in the life-course literature. In our study, adding adult SES, health behaviors, and disease status to the statistical model attenuated the point estimates of PR for limitations in higher-level functional capacity; this suggests that low adult SES, poor health behaviors (such as inactivity), and having a disease (such as coronary heart disease) partially mediated the association between low childhood SES and the outcome.

Our findings are consistent with those of previous studies on childhood SES and disability. Using data from the U.S. Health and Retirement Study, Bowen and González reported that low childhood SES (assessed by parental education and occupation) was associated with ADL, instrumental ADL, late-life disabilities as well as social and behavioral health risks in adult life (7). Furthermore, among midlife populations, childhood SES has been directly linked with functional limitations (ie, grip strength, reaching, walking, and stair climbing) in the 1946 British National Birth Cohort Study (8) and indirectly associated with cognitive function in the UK Whitehall II study (10). Our study adds to this literature by showing that low childhood SSS was directly associated with higher levels of functional (especially, intellectual and social role) limitations.

To the best of our knowledge, this is the first study that has shown an association between height and limitations in higher-level functional capacity. Previous studies reported that short height was associated with mortality or morbidity from stroke and coronary heart disease (40,41), dementia (42), and cognitive function (43,44). Moreover, a recent study showed that height was associated with intelligence and brain gray matter volume (45). Further, the current study was conducted in a non-western setting, suggesting the generalizability of the impact of childhood environment on functional limitation in older age.

The impact of poor childhood nutritional environment on limitations in higher-level functional capacity seems to implicate the presence of a critical period in early childhood, assuming that the period during and immediately after World War II (1937–1945) was associated with the most severe restrictions in nutritional environment (26,27). An important caveat is that we lacked data on the location where participants spent their childhood, although nutrition and clean water likely varied by location. The results are interesting, as those exposed to the War conditions at ages 0–4 years showed no impact on higher functional ability; the reasons for this result are unknown. The 65- to 69-year-old cohort might have had a better environment after World War II, while people aged 70–74 years might have suffered from a poor nutritional environment even when they were aged 0–4 years during and immediately after World War II. Our findings suggest that the prepubertal period is critical for physical and cognitive development, as those who experienced World War II after the prepubertal period (ie, those aged 75–79 and ≥80 years) showed no association between height and functional limitations. The importance of the prepubertal period was also reported in a previous study, although the measured outcome was not height; that study reported that the age of achieving pubertal milestones (assessed as first nocturnal emission, voice breaking, and pubarche) was associated with cognitive functioning among older men (46).

Our study has several limitations. First, childhood SSS was assessed retrospectively because of the study's cross-sectional design; thus, the data are participant to recall bias, and current health status might have affected the assessment of childhood SSS. However, a previous study confirmed the validity of retrospective assessed of childhood SSS using sibling's recall of measures of childhood socioeconomic position (47). Second, in conjunction with the first point, childhood SES was assessed subjectively in this study, although previous studies assessed this variable in terms of parental occupation or education (7,8,10). However, we considered that SSS is a useful indicator that taps aspects of social status beyond objective measures such as educational attainment or occupation. Third, we used only relative childhood SSS, but not other aspects of childhood adversity such as parental death, divorce, or child maltreatment (48). Fourth, adulthood height was self-reported, not measured objectively; this could introduce measurement error. However, we used height as not a continuous but as a categorical variable, which minimizes misclassification. Fifth, our response rate to the survey was 67%, and it is likely that those who had activity limitations as well as those from low childhood SSS backgrounds were less likely to respond to the questionnaire; suggesting that our reported results might underestimate the true underlying associations. Sixth, the AGES cohort excluded persons with ADL limitations from the baseline study sample, which may have led to an underestimation of the impact of height on functional limitations.

In summary, our findings implicate the "long arm" of childhood socioeconomic circumstances on functional capacity at older ages. Policies that mitigate childhood adversity may yield health dividends at a distant point in the future. Conversely, policies to address the prevention of old age disability need to target not just those in midlife, but points that are further "upstream" in the life course.

Supplementary Material

Supplementary material can be found at: http://biomedgerontology.oxfordjournals.org/

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Conflict of Interest

None declared.

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Impact of caste on the neurodevelopment of young children from birth to 36 months of age: a birth cohort study in Chitwan Valley, Nepal

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Abstract

Background: Caste, a proxy of socioeconomic position, can influence the neurodevelopment of children through several pathways, including exposure to toxic elements. Studies from developing countries where caste is represented by prevailing caste groups and people are highly exposed to toxic elements can provide useful insights into the mechanisms of neurodevelopmental inequities among children. This study aims to investigate the impact of caste on the neurodevelopment of children from birth to 36 months of age in Chitwan Valley, Nepal, where people are exposed to high levels of arsenic (As) and lead (Pb).

Methods: Participants (N = 94) were mother-infant pairs from the Chitwan district in Nepal. The neurodevelopment of the infants was assessed using the Brazelton Neonatal Behavioral Assessment Scale, Third Edition, (NBAS III) at birth and the Bayley Scales of Infant Development, Second Edition, (BSID II) at ages 6, 24, and 36 months. Caste was categorized based on surname, which, in Nepal generally refers to one of four caste groups. We also measured the concentrations of As and Pb in cord blood.

Results: Caste was positively associated with the state regulation cluster score of the NBAS III at birth after adjustment for covariates (p for trend < 0.01). Adding cord blood As levels attenuated the association (p for trend = 0.12). With regard to neurodevelopment at six months of age, the third-ranked caste group scored higher than the first-ranked caste group on the Mental Development Index (MDI) of the BSID II (coefficient = 3.7; 95% confidence interval (CI) = 1.3 to 6.0). This difference remained significant after adjustment for cord blood As levels and other covariates was made (coefficient = 3.9; 95% CI = 1.2 to 6.7). The remaining clusters of the NBAS III and BSID II at 6, 24, and 36 months were not significantly associated with caste group.

Conclusions: Caste was positively associated with the state regulation cluster score of NBAS III at birth. This association was partially mediated by cord blood As levels. However, the negative impact of caste on neurodevelopment disappeared as the children grew. Furthermore, an inverse association between caste and MDI at six months of age was observed. Additional studies are needed to elucidate the mechanism of how caste affects neurodevelopment.

Keywords: Nepal, Caste system, Socioeconomic position, Child development, Toxic elements, Essential elements

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Background

Exposure to socioeconomic disadvantage during pregnancy and early childhood impairs neurodevelopment in children [1,2]. Despite evidence indicating that the association between socioeconomic position (SEP) and the neurodevelopment of newborns and young children [3-9], the results of epidemiological studies on the association of SEP with later neurodevelopment have been inconsistent [6,7,10].

For example, in the Port Pirie prospective cohort study, Tong et al. [7] reported a 0.8–2.0 unit increment in children's cognitive scores per ten-unit increment in their SEP scores, while in a Bolivian cohort, Ruiz-Castell et al. [10] could not detect an association between SEP and cognitive development. Such discrepancies may have been caused by differential representation of actual SEP by the assessment indicators used. In the Bolivian cohort, most of the participating families did not have any members with permanent jobs (rather, they held temporary, short-term jobs); thus, parents' occupation (which was used as a proxy of SEP) likely did not reflect actual social or economic level. However, although SEP was evaluated by a similar indicator (i.e., parents' occupation) in the Port Pirie cohort, the fact that they held professional (permanent) occupations may have reflected their actual social or economic level. Other studies have considered family income, education, and occupation as proxies of SEP [6,11-13]. However, the use of these proxies might not exactly represent SEP as such, because each proxy measures a different aspect of SEP [14]. Considering these disadvantages of SEP measurement, caste group might be a good indicator of SEP. To the best of our knowledge, no previous studies have evaluated the effect of caste group on neurodevelopment in young children.

Caste refers to a person's status within the structure of society. In Nepal, the caste system still forms an important pillar of the social hierarchy [15], even though it was officially abolished by law in 1964 [16]. The Hindu caste structure segregates people into four caste groups on the bases of ritual purity and occupation, namely *Brahmin*, *Chetri*, *Vaishya*, and *Shudra*. The *Brahmins*—who taught, interpreted religious customs and rules, and administered the Hindu religion—were at the top of the hierarchy. They were followed by the *Chetri*, who were considered the rulers and warriors of society. Next in the hierarchy were the *Vaishya*, who were farmers and merchants. At the lowest level were the *Shudra*, who were laborers made to serve those belonging to the upper three castes [17].

We hypothesized that caste group is associated with neurodevelopment in young children through exposure to toxic elements during pregnancy. Toxic elements, such as lead (Pb) or arsenic (As), are harmful to neurodevelopment because they can induce oxidative stress and the production of free radicals, resulting in neuronal apoptosis [18,19]. We targeted Chitwan Valley in lowland Nepal because this district is exposed to high levels of As via high-level As contamination [20]. In addition, Pb exposure is high in this district because the region is situated at the junction between two main highways from Kathmandu and East-West Highway; this location serves as a major artery for a number of vehicles that emit Pb into the environment via leaded gasoline [21]. Further, this district is well recognized as a central immigration target among many caste groups from different parts of the country [22]. Thus, it was hypothesized that the association between neurodevelopment and caste group via exposure to toxic elements would be more visible in the Chitwan district versus others in Nepal. The objectives of the present study were to investigate the impact of caste on neurodevelopment scores from birth to three years of age, and to investigate whether it is driven by exposure to toxic elements during pregnancy in the Chitwan District.

Methods

Study sample

The eligibility criteria to be met for participation in the present study were as follows: living in the Chitwan Valley for at least two years, full term pregnancy (i.e., more than 37 weeks of gestation) at a specified hospital visit, aged 18–40 years, *per vaginam* delivery, singleton birth, and no reports of diabetes, hypertension or pre-eclampsia. Two hundred pregnant mothers were approached from September to October 2008 in the Bharatpur General Hospital of the Chitwan district. Among them, 119 were eligible to participate in the study. Eligible mothers were informed of the background and objectives of the study, what they would experience during the study process, the potential benefits they might experience and potential (although unexpected) risks. One hundred women (84%) signed a letter of informed consent and participated. The study protocol was approved by the Ethical Committee of the Graduate School of Medicine at the University of Tokyo (approval no. 2244) and that of the Bharatpur General Hospital, Chitwan, Nepal.

Neurodevelopmental indicators

The third edition of the Brazelton Neonatal Behavioral Assessment Scale (NBAS III) [23] was used to assess neurodevelopment at birth. The NBAS III has frequently been used in the field of neurotoxicology [24,25]. Details regarding NBAS III assessments and research findings from this cohort have been published previously [26]. NBAS III clusters were composed of 7 dimensions: habituation, orientation, motor system, state organization, state regulation, autonomic stability, and abnormal reflex.

The second edition of the Bayley Scales of Infant Development (BSID II) [27] was used to assess neurodevelopmental status at ages 6, 24 and 36 months. The BSID II scale has also frequently been used in the field of

neurotoxicology [28,29]. The BSID II provides three neurodevelopmental clusters: Mental Development Index (MDI), Psychomotor Development Index (PDI), and Behavioral Rating Scale (BRS). The MDI reflects an infant's level of cognitive function, language, and personal and social development. The PDI reflects gross and fine motor function, and the BRS is a record of the examiner's impression of the infant's neurobehavioral integrity.

The BSID II test was conducted in the infants' homes and administered within four weeks of the target age (i.e., at age 6, 24 or 36 months ± one month). The infant's age in number of days at the time of testing was also recorded. Single rater (RPP) conducted both the NBAS III and BSID II assessment.

Caste groups

During the interview process, the complete name, detailed home address, and mobile or home phone number of the parents was collected to enable the collection of prospective follow-up data. There is no single widely accepted definition or classification of each caste group [30]. Thus, we classified participants into the four ancient caste groups according to occupational specialization (i.e., *Brahmin* [priest], *Chetri* [warrior], *Vaishya* [trader and farmer], and *Shudra* [laborer]) [31]. These groupings are widely accepted despite the formal abolition of the caste system. In the present study, the classification was based on the surname of the father of the cohort baby (see Table 1 for details). However, in cases of confusing surnames, phone conversations were held with parents to ascertain their caste groups. The rank of the caste group was placed in the following order: *Brahmin, Chetri, Vaishya, and Shudra* were ranked first, second, third, and fourth respectively.

Measurements of cord blood toxic elements levels

To assess the levels of toxic elements, cord blood was collected from the placenta by midwives following common aseptic procedures. Cord blood (10 mL) was collected into a trace-metal–free cryovial that contained ethylene diamine tetra-acetic acid (EDTA) as an anticoagulant. Cord blood samples were stored in a standard freezer (-20°C) for less than one month, then kept frozen with dry ice during transport to a laboratory in Tokyo where they were stored in a deep freezer (-78°C) until analyzed. Detailed methods regarding the measurement of cord blood As and Pb levels in this cohort have been published previously [26].

Table 1 Categorization of caste groups according to surname

Caste name	Surname or Family name
Brahmin	*Kharel, Adhikari, Subedi, Kandel, Chapagain, Gaire, Dhakal, Neupane, Sharma*, Gautam, Sapkota, Rijal, Dawadi, Neure, Kattel, Khanal, Parajuli, Wosti, Pathak, Puri, Nepal, Poudel, Aryal, Lamichhane, Bhattarai, Prasai, Ghimire*, Shinkhada,*
Chetri	*Thapa, Chhetri, Kuwar, Khadka, Khatri, KC, Thakuri, Burlakoti, Yadav*
Vaishya	*Chaudhari, Shrestha, Mahato, Manandhar, Rauniyar, Lama, Tamang, Aale, Gurung, Thapa*
Shudra	*Pariyar, BK, Sunar, Kumal, Giri*, Sharma*, Baraili, Nagarkoti, Rana, Darai*

*The same surname is currently being used by *Shudra* for social assimilation. However, they were categorized into four caste groups based on home and phone consultations.

Covariates

The height and weight of mothers were recorded before delivery. Body weight was measured to the nearest 0.1 kg using a portable digital scale (Model BF-046 WH; Tanita, Tokyo, Japan). Height was measured to the nearest 0.1 cm. Body mass index (BMI) was calculated by dividing weight (kg) by height squared (m^2). The birth weights of the newborns were obtained from hospital records. Height and weight were also taken at 6, 24, and 36 months of age using the same devices and methods.

The following information was collected during hospital face-to-face interviews via a structured questionnaire: mother's age, mother's parity, baby's gender, gestational age, time and date of delivery, mother's level of education, annual family income, mother's smoking status during pregnancy, and mother's status of alcohol intake during pregnancy. A single rater (RPP) visited the home of each mother-infant pair approximately 6 and 36 months after delivery and evaluated the postnatal home environment on the Home Observation for Measurement of Environment scale (HOME) [32].

Statistical analyses

The distribution of all variables were examined for normality. Cord blood levels of toxic elements and annual family income were log transformed. Associations between caste group and demographics, birth outcomes, and prenatal and postnatal environmental variables were analyzed by linear trend tests.

Using a bivariate model, the individual associations between caste group and each NBAS III cluster score were analyzed. Multivariate analyses were conducted and adjusted for mother's age [33], parity [29], family income [34], mother's level of education [29,35], mother's BMI before giving birth [36], gestational age [36] and infant's age at the time of the NBAS III assessment (Model 1). Further, As levels were adjusted (Model 2). For ages 6, 24, and 36 months, multiple regression models of each BSID II cluster, MDI, PDI, and BRS were adjusted for maternal age, maternal education, log-transformed income, parity, maternal BMI, birth weight, concurrent age at BSID assessment, infant weight, and HOME score (Model 1) and log As levels was further adjusted (Model 2). The 6-month-old HOME score was adjusted to create the model for 24-months-old since the 6-month score can represent the home environment for up to three years. Trend tests for neurodevelopment indicators were also performed by caste group. Statistical significance was determined with a criterion level set at $p < 0.05$. All analyses were performed with a statistical software package (Stata version 11.0).

Results

Table 2 summarizes the characteristics of mother-infant pairs at birth and at 6, 24, and 36 months after birth. The maternal, household, and newborn characteristics of this cohort have been published previously [26]. The mothers' level of education showed a linear trend in terms of caste (i.e., more education among higher-ranked caste, $p < 0.001$). Infants' ages during the six-month BSID II assessment also varied by caste rank ($p = 0.02$). Evaluation using the BSID II began in areas distant from the Chitwan Valley, where predominantly lower-caste parents reside. Thus, babies' ages at BSID II assessment were lower among lower-caste groups. The HOME scores were consistently higher among high-ranked caste groups than low-ranked caste groups at ages 6 and 36 months ($p < 0.001$).

Table 3 summarizes the distribution of cord blood Pb and As levels, and birth outcomes according to caste group at birth and 6, 24, and 36 months after birth. Higher cord blood levels of As were found among lower-ranked caste groups ($p < 0.01$), but Pb was not significantly associated with caste ($p = 0.59$). Birth weight and body weight at ages 6, 24, and 36 months did not differ by caste group. Among the NBAS III clusters, the newborns' regulation of state cluster score (as evaluated by the NBAS III) was more elevated in higher-caste groups ($p < 0.01$). The remaining clusters of the NBAS III were not associated with caste group. Scores on the BSID II indices (i.e., MDI, PDI, and BRS) did not differ by caste group at ages 6, 24, or 36 months.

Table 4 shows the coefficients of NBAS III clusters at birth by caste group with reference to *Brahmin*, the first-ranked caste group. In Model 1—which was adjusted for maternal age and education, log-transformed income, maternal BMI, age at NBAS III assessment, parity, and birth weight—the state regulation cluster score for *Vaishya* (i.e., the third-ranked caste group) was lower than the score for *Brahmin* (coefficient = −3.6; 95% CI = −5.8 to −1.3). While attenuated, the association remained significant in Model 2 when including log As as a covariate, (coefficient = −2.8; 95% CI = −5.3 to −0.3). Although the trend was significant in Model 1, it became insignificant in Model 2, suggesting that cord blood As levels mediated the association between caste group and state regulation score at birth. Interestingly, significantly higher scores in the state organization cluster were found among the third-ranked caste group in Model 1, however, the corresponding

Table 2 Characteristics of participants in a birth cohort study: at birth, 6, 24 and 36 months after birth

	Caste groups, Mean (SD) or N (%)				*P* for trend
	Brahmin	*Chetri*	*Vaishya*	*Shudra*	
	(N = 37, 39.4%)	(N = 13, 13.8%)	(N = 26, 27.7%)	(N = 18, 19.2%)	
Mothers characteristics at birth (n = 94)					
Age (years)	23.4 (3.1)	22.4 (2.5)	23.1 (4.4)	22.3 (4.5)	0.41
Primipara n (%)	26 (27.7)	11 (11.7)	13 (13.8)	12 (12.8)	0.31
Education level (median, years)	**12**	**10**	**8**	**8**	**<0.001**
BMI (kg/m^2)	23.3 (2.5)	22.9 (2.3)	22.7 (3.8)	24.1 (2.9)	0.6
Newborn babies characteristics (n = 94)					
Gestational age (weeks)	39.1 (1.4)	39.5 (1.7)	39.1 (1.3)	38.8 (0.9)	0.61
Sex of baby n (% male)	19 (51.4)	7 (54.0)	11 (42.3)	8 (44.4)	0.48
Age of neurodevelopmental assessment					
NBAS III at birth (in hours) (n = 94)	17.2 (4.0)	17.1 (2.9)	17.7 (3.0)	17.6 (2.5)	0.56
BSID II assessment at 6 months (in days) (n = 94)	**195.3 (13.2)**	**199.2 (12.7)**	**188.7 (12.3)**	**188.9 (12.6)**	**0.02**
BSID II assessment at 24 months (in months) (n = 89)	25.9 (0.4)	25.9 (0.4)	25.7 (0.4)	25.9 (0.4)	0.36
BSID II assessment at 36 months (in months) (n = 83)	36.9 (0.4)	36.9 (0.3)	36.7 (0.4)	36.9 (0.4)	0.37
Household characteristics					
Annual family income (USD)	2891 (3256)	1944 (1697)	2798 (3434)	1771 (1744)	0.06
Total HOME Scale score at 6 months (n = 94)	**31.8 (5.4)**	**30.3 (4.0)**	**26.8 (4.7)**	**26.5 (4.3)**	**<0.001**
Total HOME Scale score at 36 months (n = 83)	**41.2 (6.0)**	**40.0 (6.0)**	**36.5 (6.8)**	**33.9 (7.6)**	**<0.001**

Bold signifies $p < 0.05$.

Table 3 Distribution of birth outcome variables by caste groups in a birth cohort study: at birth, 6, 24 and 36 months after birth

	Caste groups, Mean (SD) or Median				*P* for trend
	Brahmin (N = 37)	*Chetri* (N = 13)	*Vaishya* (N = 26)	*Shudra* (N = 18)	
In utero exposure of toxic elements (n = 94), mean					
Arsenic (μg/L)§	**1.3 (1.4)**	**1.3 (0.3)**	**1.7 (0.7)**	**1.5 (0.5)**	**<0.01**
Lead (μg/L)§	30.5 (40.3)	31.4 (27.7)	36.7 (39.6)	26.4 (17.5)	0.59
Anthropometric characteristics, mean					
Birth weight (kg) (n = 94)	3.0 (0.5)	3.0 (0.4)	3.1 (0.4)	3.1 (0.5)	0.16
Body weight (kg) at 6 months after birth (n = 94)	7.3 (1.1)	7.3 (0.8)	7.3 (0.7)	7.3 (0.8)	0.93
Body weight (kg) at 24 months after birth (n = 89)	11.5 (1.6)	11.0 (1.3)	10.9 (1.2)	10.8 (1.0)	0.09
Body weight (kg) at 36 months after birth (n = 83)	12.9 (1.7)	12.5 (1.1)	12.4 (1.4)	12.6 (1.3)	0.30
NBAS III cluster score at birth (n = 94), median					
Habituation	27	27	28	26.5	0.47
Orientation	45	37	44	38	0.30
Motor system	26	24	25.5	26	0.21
State organization	11	14	15.5	9.5	0.58
State regulation	**28**	**28**	**25**	**26**	**<0.01**
Autonomic stability	13	13	13	13	0.26
Abnormal reflex	7	7	5	5	0.23
BSID II cluster score at 6 months after birth (n = 94), median					
MDI	104	104	107	104	0.07
PDI	103	100	101.5	104	0.80
BRS	122	127	124	121	0.39
BSID II cluster score at 24 months after birth (n = 89), median					
MDI	94	94	94	92	0.49
PDI	100	107	104.5	100	0.75
BRS	106	114	109.5	104	0.43
BSID II cluster score at 36 months after birth (n = 83), median					
MDI	95	93	97	90	0.19
PDI	116	116	119	116	0.60
BRS	106	104	102	104	0.17

§Log transformed values were tested.
Bold signifies $p < 0.05$.
NBAS: Brazelton neonatal behavioral assessment scale, BSID: Bayley scale of infant development, MDI: mental development index, PDI: psychomotor development index, BRS: behavioral rating scale.

association was not significant in Model 2. The remaining NBAS III cluster scores were not associated with caste group.

Table 5 shows the coefficients of the BSID II index scores at 6, 24 and 36 months after birth by caste group, again, with reference to *Brahmin*, the first-ranked caste group. In the crude model, *Vaishya* (the third-ranked caste group) showed higher MDI scores at six months of age (coefficient = 3.7; 95% CI = 1.3 to 6.0) than *Brahmin*. This association remained significant after adjustment for covariates (Model 1, coefficient = 4.0; 95% CI = 1.4 to 6.7) and covariates plus log-transformed As levels (Model 2, coefficient = 3.9; 95% CI = 1.2 to 6.7). However, the trend in MDI scores by caste at six months of age was not significant ($p = 0.15$ for Model 1 and $p = 0.19$ for Model 2). The remaining BSID II cluster scores were not associated with caste group at ages 6, 24, and 36 months.

Discussion

Caste was positively associated with one cluster of neurodevelopmental indicators at birth, namely state regulation as measured by the NBAS III. It was not, however, associated with BSID II scores at ages 6, 24, or 36 months, excluding MDI at 6 months. The positive association

Table 4 Coefficient and 95% confidence interval of social status or caste group with NBAS III clusters at birth using multivariate regression model (n = 94)

		Brahmin (N = 37)	*Chetri* (N = 13)	*Vaishya* (N = 26)	*Shudra* (N = 18)	p for trend	Constant
Habituation	Crude	Ref	0.4 (-1.8 to 2.5)	1.6 (-0.1 to 3.3)	-0.1 (-2.0 to 1.9)	0.47	26.4
	Model 1	Ref	0.5 (-1.9 to 2.8)	1.9 (-0.1 to 3.9)	-0.0 (-2.4 to 2.3)	0.51	27.4
	Model 2	Ref	0.4 (-1.9 to 2.8)	1.8 (-0.3 to 3.8)	-0.1 (-2.5 to 2.3)	0.62	27.2
Orientation	Crude	Ref	-5.7 (-12.4 to 1.0)	0.5 (-4.8 to 5.8)	-4.9 (-10.9 to 1.1)	0.30	42.1
	Model 1	Ref	-5.5 (-12.6 to 1.6)	-0.2 (-6.3 to 5.9)	-6.3 (-13.5 to 0.9)	0.23	27.4
	Model 2	Ref	-5.4 (-12.5 to 1.7)	0.3 (-6.0 to 6.7)	-6.0 (-13.3 to 1.3)	0.27	27.7
Motor system	Crude	Ref	0.7 (-2.6 to 1.1)	0.2 (-1.3 to 1.6)	1.1 (-0.5 to 2.8)	0.21	24.5
	Model 1	Ref	-0.5 (-2.5 to 1.4)	0.3 (-1.4 to 2.0)	1.4 (-0.6 to 3.4)	0.20	26.6
	Model 2	Ref	-0.5 (-2.4 to 1.5)	0.8 (-0.9 to 2.5)	1.7 (-0.3 to 3.7)	0.09	27.2
State organization	Crude	Ref	0.7 (-2.6 to 4.0)	1.9 (-0.7 to 4.5)	-2.1 (-5.0 to 0.8)	0.59	13.5
	Model 1	Ref	1.7 (-1.7 to 5.2)	**3.1 (0.1 to 6.0)**	-0.4 (-3.9 to 3.1)	0.62	6.7
	Model 2	Ref	1.6 (-1.7 to 5.0)	2.2 (-0.7 to 5.2)	-0.9 (-4.4 to 2.5)	0.98	5.6
State regulation	Crude	Ref	-1.9 (-4.7 to 0.9)	**-3.6 (-5.8 to -1.3)**	-2.5 (-5.0 to 0.0)	**<0.01**	28.9
	Model 1	Ref	-1.1 (-3.9 to 1.8)	**-3.5 (-5.9 to -1.8)**	-1.9 (-4.7 to 1.0)	0.05	15.6
	Model 2	Ref	-0.9 (-3.7 to 1.8)	**-2.8 (-5.3 to -0.3)**	-1.4 -4.3 to 1.4)	0.12	16.5
Autonomic stability	Crude	Ref	-0.1 (-1.1 to 0.9)	-0.7 (-1.5 to 0.1)	-0.2 (-1.1 to 0.7)	0.26	13.2
	Model 1	Ref	0.2 (-0.9 to 1.2)	-0.4 (-1.3 to 0.5)	0.2 (-0.9 to 1.3)	0.91	9.5
	Model 2	Ref	0.1 (-0.9 to 1.2)	-0.6 (-1.5 to 0.3)	0.1 (-1.0 to 1.1)	0.71	9.3
Abnormal reflex	Crude	Ref	-0.3 -2.2 to 1.7)	-1.5 (-3.0 to 0.1)	-0.5 (-2.2 to 1.3)	0.23	6.9
	Model 1	Ref	-0.2 (-2.3 to 2.0)	-1.1 (-2.9 to 0.8)	-0.0 (-2.2 to 2.1)	0.65	5.9
	Model 2	Ref	-0.2 -2.3 to 1.9)	-1.4 (-3.3 to 0.5)	-0.2 (-2.4 to 2.0)	0.51	5.6

Bold signifies $p < 0.05$.
Model 1 Adjusted for age of mother, maternal education, log income, maternal BMI, age at NBAS III assessment, parity, and birth weight.
Model 2 Adjusted for Model 1 plus Log As.

between caste group and state regulation at birth was partially mediated by cord blood As levels. Interestingly, the third-ranked caste group showed significantly higher MDI scores than the highest-ranked caste group.

To the best of our knowledge, this is the first study that has evaluated the effects of caste on neurodevelopment in younger children. In 1964, King Mahendra abolished caste system laws, declaring that as a nation Nepal opposed this form of population categorization. However, it is interesting that nearly 50 years after this abolition, the caste groups still show prominent association with neurodevelopment at birth. Thus, caste-related health disparities might still be prevalent in Nepal.

Similar to earlier studies [3-5,7,8,37-39], newborns in lower caste groups showed less optimal neurodevelopment at birth. This trend was partially mediated by cord blood As levels, suggesting that *in utero* exposure to As could drive the occurrence of lower-state regulation scores among lower-caste groups. The present study also showed that cord blood As levels were harmful to NBAS III state regulation cluster scores among the sample as a whole [26]. We also found that the *Vaishya* caste group showed higher cord blood levels of As than the *Brahmin* caste group. Since people from the *Vaishya* caste group are traditionally engaged in agricultural and outdoor activities, they may be more likely to be exposed to As.

The BSID II cluster scores did not differ across the caste groups at ages 6, 24, or 36 months. As suggested by Henn and colleagues, attenuation of this effect during the postnatal period may be one reason for this [40]. For example, urinary excretion of most of the As burden from the infant's body may have occurred since decreased urinary As concentrations were also reported during the first four months after birth (80 μg/L during the first two days of life to <30 μg/L at four months of age) [41]. Hence, the harm induced by cord blood As levels on the neurodevelopment of infants might not persist until six months of age. Furthermore, the neuroplasticity of the immature brain may contribute to the attenuated effect of cord blood As over time [42].

Interestingly, infants from the *Vaishya* caste group achieved higher scores than those from the highest caste (*Brahmin*) on the MDI index of the BSID II scale at six months of age. Since those categorized as *Vaishya* members

Table 5 Coefficients of caste group on MDI, PDI and BRS scores of BSID II at 6, 24, and 36 months using multivariate regression model

			Brahmin (N = 37)	*Chetri* (N = 13)	*Vaishya* (N = 26)	*Shudra* (N = 18)	p for trend	Constant
6 months	MDI	Crude	Ref	1.4 (-1.6 to 4.3)	**3.7 (1.3 to 6.0)**	1.0 (-1.6 to 3.7)	0.07	103.1
(n = 94)		Model 1	Ref	2.1 (-0.9 to 5.1)	**4.0 (1.4 to 6.7)**	1.0 (-2.1 to 4.1)	0.15	118.4
		Model 2	Ref	2.1 (-0.9 to 5.1)	**3.9 (1.2 to 6.7)**	1.0 (-2.1 to 4.1)	0.19	118.5
	PDI	Crude	Ref	-0.5 (-6.6 to 5.5)	-0.9 (-5.7 to 4.0)	-0.4 (-5.8 to 5.0)	0.80	102.2
		Model 1	Ref	1.6 (-4.6 to 7.9)	1.1 (-4.4 to 6.6)	2.2 (-4.3 to 8.7)	0.52	123.0
		Model 2	Ref	1.6 (-4.6 to 7.9)	1.0 (-4.7 to 6.8)	2.2 (-4.4 to 8.8)	0.53	123.0
	BRS	Crude	Ref	6.2 (-3.4 to 15.9)	-0.1 (-7.8 to 7.6)	-4.0 (-12.6 to 4.6)	0.39	119.9
		Model 1	Ref	6.9 (-2.9 to 16.7)	4.5 (-4.1 to 13.2)	-0.2 (-10.3 to 10.0)	0.82	76.7
		Model 2	Ref	6.8 (-2.8 to 16.5)	2.9 (-5.9 to 11.7)	-1.1 (-11.3 to 9.0)	0.95	77.6
24 months	MDI	Crude	Ref	2.1 (-6.1 to 10.2)	-2.1 (-8.8 to 4.5)	-1.8 (-9.2 to 5.7)	0.49	91.6
(n = 89)		Model 1	Ref	4.6 (-2.9 to 12.2)	5.1 (-1.8 to 11.9)	4.4 (-3.7 to 12.4)	0.19	0.73
		Model 2	Ref	4.8 (-2.7 to 12.4)	6.3 (-0.7 to 13.3)	5.0 (-3.1 to 13.1)	0.13	-3.7
	PDI	Crude	Ref	4.0 (-5.5 to 13.6)	-2.5 (-10.3 to 5.3)	0.2 (-8.5 to 8.9)	0.75	103.3
		Model 1	Ref	6.4 (-3.0 to 15.7)	3.1 (-5.3 to 11.5)	4.2 (-5.8 to 14.1)	0.42	-184.5
		Model 2	Ref	6.3 (-3.0 to 15.7)	3.0 (-5.7 to 11.7)	4.1 (-5.9 to 14.2)	0.43	-184.4
	BRS	Crude	Ref	-0.5 (-11.5 to 10.5)	-0.6 (-9.6 to 8.4)	-4.7 (-14.8 to 5.3)	0.43	106.9
		Model 1	Ref	-0.3 (-11.7 to 11.1)	1.2 (-9.1 to 11.5)	-6.1 (-18.2 to 6.1)	0.49	-57.2
		Model 2	Ref	-0.4 (-11.8 to 11.0)	0.2 (-10.5 to 10.8)	-6.7 (-18.9 to 5.6)	0.39	-52.3
36 months	MDI	Crude	Ref	-1.4 (-7.9 to 5.2)	1.4 (-3.9 to 6.7)	-5.8 (-11.6 to 0.0)	0.20	97.4
(n = 83)		Model 1	Ref	-0.8 (-6.4 to 4.7)	3.0 (-1.8 to 7.9)	-1.9 (-8.0 to 4.1)	0.91	533.4
		Model 2	Ref	-0.8 (-6.4 to 4.5)	2.7 (-2.3 to 7.7)	-2.1 (-8.2 to 4.1)	0.98	538.5
	PDI	Crude	Ref	-4.3 (-10.5 to 1.8)	-0.6 (-5.6 to 4.4)	-2.0 (-7.5 to 3.5)	0.60	115.7
		Model 1	Ref	-3.6 (-9.0 to 1.9)	-0.5 (-5.2 to 4.3)	-1.4 (-7.3 to 4.6)	0.74	438.5
		Model 2	Ref	-3.5 (-8.9 to 1.8)	-1.5 (-6.3 to 3.3)	-1.8 (-7.6 to 4.0)	0.51	449.4
	BRS	Crude	Ref	-7.1 (-22.1 to 7.9)	-7.6 (-19.8 to 4.5)	-8.1 (-21.4 to 5.3)	0.17	105.7
		Model 1	Ref	-7.0 (-22.1 to 8.0)	-5.7 (-18.8 to 7.4)	-12.5 (-28.9 to 3.9)	0.15	43.0
		Model 2	Ref	-7.0 (-22.1 to 8.2)	-6.7 (-20.3 to 6.8)	-12.9 (-29.4 to 3.6)	0.12	54.0

Bold signifies $p < 0.05$.
MDI: mental development index, PDI: psychomotor development index, BRS: behavioral rating scale.
Model 1 of 6 months adjusted for baseline characteristics (maternal age, maternal education, log income, parity, maternal BMI, birth weight), age at BSID assessment on 6 months, weight of infants at 6 months, and HOME score at 6 months. For Model 1 of 24 months, baseline characteristics plus age at BSID assessment on 24 months, weight of infants at 24 months, and HOME score at 6 months were adjusted. For Model 1 of 36 months, baseline characteristics plus age at BSID assessment on 36 months, weight of infants at 36 months, and HOME score at 36 months were adjusted. Model 2 of all months adjusted Model 1 plus log As.

are merchants and agricultural workers, their infants may benefit from an environmentally enriched setting due to community visits to their houses and shops. Such an atmosphere might induce a level of neural stimulation etiologically relevant to neurodevelopment and learning, ultimately evident as higher MDI scores at six months of age. Alternatively, the higher MDI scores at six months of age among *Vaishya* members might be due to chance since we made 10 comparisons (7 from NBAS III and 3 from BSID II) that revealed a negative association between cord blood As levels and the NBAS III state regulation cluster. This negative association may be plausible because it was measured close to the time of birth.

The current study has some limitations, which should be considered. First, the small sample size and hospital-based sampling technique limit the generalizability of the findings. As such, associations alternative to those presented here may have been missed due to this lack of statistical power. Second, the classification of caste groups was based on family names. Although we can categorize caste precisely for *Brahmin* and *Chetri*, similar surnames and controversial classifications between *Vaishya* and *Shudra* might have caused occasional misclassification of caste groups. Third, postnatal As and Pb exposure was not measured, including levels in breast milk, drinking water, or other foods digested during the study period.

Fourth, we did not assess breastfeeding status, although previous studies in Nepal reported that ever-breastfed rate was more than 99% regardless of SEP [43,44]. Fifth, additional confounds, such as history of asphyxia at birth, iodine status, and significant illness in early infancy, were not measured. Sixth, the Nepali translated version of the BSID II was not standardized in Nepal; thus, the findings in this study may not be generalizable to this specific region. Overall, this study has a number of strengths. The sample is the first longitudinal birth cohort from Nepal about which considerable information was collected regarding cord blood levels of toxic elements and potential confounds. Moreover, the NBAS III and BSID II were administered by a single investigator within the participants' homes, increasing inter-rater reliability and diminishing underperformance effects by infants attributable to being assessed in an unfamiliar environment.

Collectively, these findings indicate that health education and awareness should be developed and implemented by local governmental health institutions among lower-ranked caste groups, especially among *Vaishya* members, in order to educate them with regard to the detrimental effects of As exposure on neurodevelopment.

Conclusions

Using a birth cohort study in Chitwan Valley, Nepal, revealed that caste was positively associated with NBAS III state regulation scores at birth, possibly mediated by cord blood As levels. Contrarily, BSID II scores at ages 6, 24, and 36 months were not associated with caste group. Finally, an inverse association between caste and MDI at six months was also observed. Further studies are needed to replicate the associations documented herein between caste and neurodevelopment at birth and their mediation by cord blood As levels. Most importantly, health policy recommendations should include measures to reduce exposure to As in Chitwan Valley, Nepal, especially among lower-ranked caste groups.

Abbreviations

SEP: Socioeconomic position; Pb: Lead; As: Arsenic; EDTA: Ethylene diamine tetra-acetic acid; BMI: Body mass index; NBAS III: Neonatal behavioral assessment scale, third edition; BSID-II: Bayley scales of Infant development, second edition; MDI: Mental development index; PDI: Psychomotor development index; BRS: Behavioral rating scale; HOME: Home observation for measurement of environment.

Competing interests

We hereby disclose that the authors have no conflicts of interest, financial or otherwise.

Authors' contributions

RPP collected, analyzed, and interpreted the data and wrote the first draft; TF conceived study hypothesis, interpreted data, and finalized the manuscript; and MU and CW critically revised the manuscript. All authors read and approved the final manuscript.

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Original article

Breastfeeding and risk of atopic dermatitis up to the age 42 months: a birth cohort study in Japan

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ABSTRACT

Purpose: The purpose of this study was to investigate the association between breastfeeding and atopic dermatitis (AD) up to the age 42 months.
Methods: Data from a nationally representative population-based birth cohort study in Japan were used (N = 38,757). Feeding pattern and breastfeeding duration were investigated via questionnaires when infants were aged 6 months. Physician-diagnosed AD during the previous 1 year was ascertained via questionnaires when the children were aged 18, 30, and 42 months. The associations between feeding patterns or breastfeeding duration and physician-diagnosed AD from the age 6 to 42 months, categorized by AD status (no history of AD, episodic AD, and persistent AD), were analyzed using ordered logistic regression adjusted for covariates.
Results: Breastfeeding was positively associated with AD, with dose-response association (P for trend < .001). Exclusively breastfed infants were 1.26 times more likely to have AD (95% confidence interval, 1.12–1.41) than infants fed formula alone. Furthermore, children with a longer breastfeeding duration were also significantly more likely to have AD (P for trend < .001).
Conclusions: Breastfeeding is associated with an increased risk of AD up to the age 42 months. Further study is needed to elucidate the mechanism underlying the association between breastfeeding and AD.

Introduction

Atopic dermatitis (AD) is one of the most common chronic skin disorders among infants and young children, which is characterized by itchy skin with eczematous changes [1]. The association between breastfeeding and AD has been studied for more than 70 years [2], but the results have been controversial. Although some epidemiology studies including meta-analysis [3] showed that breastfeeding had a protective effect on AD [4–6], other studies suggested that breastfeeding increased the risk of AD [7–9] or that there was no relationship [10–12]. These differences may stem from differences in study design, the definitions of exposure and outcome, sample size, or adjustment for confounders [13–15]. Kramer [14] proposed 12 criteria to assess study designs addressing the relationship between breastfeeding and atopic disease. Those criteria included nonreliance on prolonged maternal recall, strict diagnostic criteria, severity of outcome, assessment of effect in children at high risk, and adequate statistical power. No studies have completely fulfilled these standards thus far [16]. Furthermore, the location of the study may be relevant. Studies in Finland, Denmark, New Zealand, or Japan—countries in which people eat relatively large quantities of fish—showed a positive association between breastfeeding and AD using a prospective study design [8–10,17], suggesting that the contents of the breast milk may be associated with the risk of AD.

The Longitudinal Survey of Babies in the 21st century is a nationwide large birth cohort study implemented by the Ministry of Health, Labour, and Welfare in Japan. It investigated feeding patterns and breastfeeding duration for infants at the age 6 months, and physician-diagnosed AD during the previous 1 year was queried for children at the age 18, 30, and 42 months. Using the data, the association between breastfeeding and AD can be investigated by adopting a prospective design with sufficient statistical power. The purpose of the present study was, therefore, to investigate the association between breastfeeding and the duration of breastfeeding on the development of AD in young children from the age 6 to 42 months in Japan.

Author contribution: Dr J.I. analyzed the data and wrote the first draft. Dr T.F. conceived the study design, acquired data, and finalized the manuscript.
Conflict of interest statement: The authors have no conflicts of interest to disclose.
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Methods

Study sample

The data used for this study were taken from the Longitudinal Survey of Babies in the 21st century conducted by the Japanese Ministry of Health, Labour, and Welfare from 2001 to 2004. The study sample included all infants born in Japan during the periods of January 10–17, 2001, and July 10–17, 2001 using the birth record list (N = 53,575). Questionnaires were mailed to all subjects when the infants were aged 6 months. The subjects were considered to have agreed to participate in the study if they returned the questionnaire to the Ministry. The total number of respondents was 47,015 (response rate, 87.8%). The second and the third questionnaires were mailed in 2002 and 2003 to all subjects who participated in the first survey when the children were aged 18 and 30 months, during which 43,925 and 42,812 subjects responded, respectively (response rates, 93.4% and 91.1%, respectively, of those responding to the first survey). The fourth questionnaires were mailed in 2004 to all subjects who participated in the second or the third survey (N = 45,072) when the children were aged 42 months and 41,559 subjects responded (92.2% of those responding to the second or third survey). Because this study focused on breastfeeding and AD up to the age 42 months, subjects without record of breastfeeding status (n = 308) and those who did not answer the question about AD in every survey (n = 1720) were excluded. We further excluded multiple births (n = 832). Therefore, the final sample size for this study was 38,757 (Fig. 1). Because the study was based on an anonymous public use data set with no identifiable information on the survey questionnaire, this study has been exempted from ethical review.

Feeding pattern and breastfeeding duration

Information regarding feeding pattern and breastfeeding duration was obtained in the first survey. Participants were asked about the duration of breastfeeding and formula feeding for the past 6 months. If the mother answered that she had not given any formula, she was included in the category of "exclusive breastfeeding." If she answered that she had given only colostrum or had not given any breast milk, she was included in the category of "formula only." Finally, if the mother answered that she had given both breast milk and formula, she was included in the category of "partial breastfeeding." Thus, we categorized the feeding pattern during the first 6 months of life as "formula only," "partial breastfeeding," or "exclusive breastfeeding." All infants were also categorized into four groups according to the duration of breastfeeding: never, 1–2, 3–5, or 6+ months.

Atopic dermatitis

Information regarding doctor-diagnosed AD was obtained in the second, third, and fourth survey using the following question: "Has your child seen a doctor for AD or eczema treatment in the last

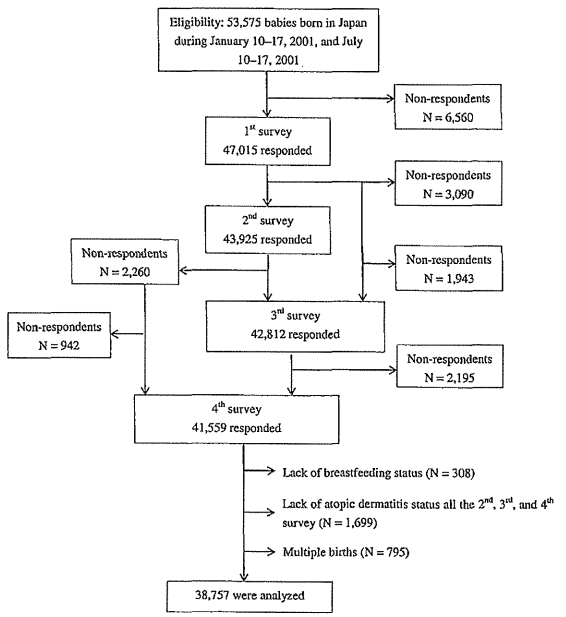

Fig. 1. Flow chart of study participants.