Impaired glucose tolerance among adolescents with low birth history: the Tanjungsari cohort study in Indonesia

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ABSTRACT

Background and Objectives: Diabetes prevalence has been increasing overtime in Indonesia along with its complications and morbidities. Diabetes prevention program is still a challenge. Previous study concluded poor intrauterine nutritional status, low birth weight (LBW), and nutrition status early in life were risk factors for impaired glucose tolerance (IGT) or type 2 diabetes mellitus in adulthood. This study aimed to evaluate the association between both LBW and intrauterine growth restriction (IUGR) with IGT in adolescents. **Methods and Study Design:** Total of 536 subjects from Tanjungsari Cohort Study were included in this study. Subjects were in their early adolescence age (12-14 years). Anthropometric data were collected and IGT was determined by using 2-hour postprandial plasma glucose level, then it was assessed based on their birth weight and intrauterine nutritional status. **Results:** Subjects with LBW history were shorter, had lower body weight and body mass index (p<0.05, respectively). The proportion of IGT is significantly higher among subject with LBW (RR 1.692 [1.079–2.653]). There was no difference on proportion of IGT among subjects with IUGR compared with subjects who were not IUGR or born preterm (p=0.286). Multiple regression analysis showed the effect of LBW remain independent after adjusted with sex and socioeconomic variables (RR 1.650 [1.054–2.584]). **Conclusions:** Significant association was found between LBW and IGT in comparison to those who were born with normal birth weight. Hence, diabetes should be prevented as early as possible, even since in the pregnancy.

Key Words: adolescents aged 12-14, birth weight, body mass index, insulin resistance, impaired glucose tolerance

INTRODUCTION

The prevalence of diabetes has increased over time in Indonesia (from 6.9% in 2011 to 8.5% in 2018).[1] Chronic complication of diabetes increases morbidity and mortality. These microvascular and macrovascular complications reduced patient's quality of life and eventually increased health costs.[2] Most chronic diseases are associated with several risk factors such as adult lifestyles including smoking, diet, and exercise.[3-5] Intrauterine environment was a risk factor in early life which are now considered as a developmental origin of chronic disease in adulthood.[6-8]

Globally, low birth weight (LBW) is still a major problem, moreover, 96.5% of them were born in developing countries; with overall prevalence of LBW of 15.9% (range 9.0 to 35.1%).[9,10] Indonesia Basic Health Research 2018 showed the national prevalence of LBW

was 6.2%.[1] However, other studies in Indonesian population showed higher prevalence of LBW which was 12.2 %,[9] and in South Kalimantan, Indonesia was 20.2%.[11] There was an inversed relationship between birth weight and insulin resistance (diabetes or impaired glucose tolerance (IGT)) in adult life. Preterm birth or IUGR is the most common cause of LBW.[6-8,12] Reduced intrauterine growth is strongly linked to impaired glucose tolerance.[8] Fetal programming and adaptation occur during intrauterine growth restriction (IUGR) such as increased insulin and peripheral glucose sensitivity, decreased β-cell mass and insulin secretion, and increased glucose production. If these persist into postnatal life, they will increase risk of developing obesity and eventually insulin resistance.[13]

Psycho-socioeconomic conditions, maternal age, malnutrition and poverty affect birth weight.[10] Previous study concluded both poor intrauterine nutritional status and LBW were risk factors for IGT or frank type 2 diabetes mellitus in adulthood.[12] Early socioeconomic factor disadvantage was also predicted as unequal life-course trajectories that ultimately influence health and increased the odds of prediabetes and diabetes in later life indirectly.[14]

One of the objectives of Tanjungsari Cohort Study (TCS) was to evaluate the association between birth weight and intrauterine nutritional status with IGT.

MATERIALS AND METHODS

Tanjungsari Cohort Study (TCS) 1988-1989

The TCS was conducted in conjunction with Department of Internal Medicine, Cerebrovascular Disease Working Group, Research Unit of Faculty of Medicine Universitas Padjadjaran/ Dr. Hasan Sadikin Hospital Bandung and Frontier for Health Foundation. The study protocol was reviewed and approved by the Ethics Committee of the Faculty of Medicine of University of Indonesia on February, 13th 2003 (No.: 690/PT02.H4.FK/N/2003). The study was initiated in 1987 and included all pregnant women in Tanjungsari districts, Sumedang, West Java, who gave their consent to participate. All infants who were born in the period from 1 January 1988 to 31 March 1990 were included in the study. The infants were excluded if they were aborted, still-birth, or twin, resulted in total of 3.350 infants. The data collected included gestational age, birth weight, and birth length.

In October 2002-February 2003, we conducted cross-sectional survey to evaluate their anthropometric measurement and oral glucose tolerance test (OGTT). From 2618 subjects aged 12-14 years old, we randomly selected them from each stratified categories based on their pre and post natal growth status. Further information regarding our data collecting system was explained in our previous studies.[15, 16]

Anthropometric measurements

At birth, all newborns were weighed by using spring scale (Kern and Sohn GmBH, Germany) with a maximum load of 7 kg and recorded to the nearest 0.1 kg. Their length was measured using elastic tape, recorded to nearest 1 cm.

When they reached adolescence age, we conducted their anthropometric measurement. These adolescents were weighed wearing minimal clothing using standardized procedures,[17] and calibrated equipment by trained research assistants. Weight was measured using electronic scale (Seca 770, Seca GmbH & Co. KG., Hamburg, Germany) and recorded to the nearest 0.1 kg. Height was measured using microtoise to the nearest 0.1 cm. Z-scores for BMI-for-age (BAZ) was calculated using the WHO 2008 growth reference data.[18]

Inclusion criteria

Sampling and inclusion of subject

Following a nested cohort design, study subjects were selected according to their birth weight and length as demonstrated in our previous study.[16] Sample size for this study was obtained by using the calculation for unpaired analytical cohort study. The confidence interval (CI) was 95% and the power test was 80%. From previous study, the P1 and P2 were 0.3 and 0.17 respectively.[8]

From the calculation using a formula below, we required a minimum of 104 subjects for each group with predictor (LBW) and without predictor (not LBW).

$n1 = n2 = (Z_{1-\alpha/2} \sqrt{2pq} + Z_{1-\beta} \sqrt{(p_1q_1+p_2q_2)^2}) / (p_1 - p_2)^2$

Study equation for minimum sample size needed

Intrauterine growth restriction was determined based on cross-tabulation of birth weight and birth length without employing the gestational age; newborns were considered as non-IUGR if their birth weight were ≥2700 g and birth length were ≥48 cm. Otherwise, they were considered as IUGR or probably preterm, according to our classification as explained previously in our study.[15] At term, cutoff birth weight for IUGR is 2,500 g.[16] While LBW was determined to all babies with birth weight under 2,500 grams.[10] Preterm birth was assessed to all babies who were born before 37th weeks of pregnancy.[10] Socioeconomic status in this study was assessed by household' access to drinking water source and latrine availability.[19] Impaired fasting glucose (IFG) was determined if fasting plasma glucose was 100-125 mg/dL. Fasting plasma glucose was obtained from subject's blood samples collected after a minimum 8-h overnight fast. Two-hour postprandial plasma glucose level was collected at 120 min after

a standard (75 g) oral glucose load. If two-hour postprandial plasma glucose 140-199 mg/dL after taking OGTT, subject was defined as IGT.[20]

Exclusion criteria

We excluded the study subjects who did not come or did not give their consent for the test or had moved outside Tanjungsari area or those with missing data.

Statistical analysis

Data in numeric scale were described in mean or median (min-max). We evaluated the characteristics of independent variables between groups and descriptive data in percentage. The data were tested for normality using Kolmogorov-Smirnov test.

We evaluated the association between age, sex, pregnancy risk, maternal education background, socioeconomic status, fasting plasma glucose category (IFG vs no IFG), two-hour post prandial (2h-PP) plasma glucose level category (IGT vs no IGT) in low and normal birth weight subjects using the chi-square test or an alternative to Fisher-exact test. The association between height, weight, WHO BMI for age Z score, fasting plasma glucose and 2h-PP plasma glucose level in low and normal birth weight subjects were evaluated by using Mann Whitney U test. While, the association between WHO BMI Categories and maternal age group in low and normal birth weight subjects were evaluated by Kruskall Wallis test.

We evaluated the association between age, sex, pregnancy risk, maternal education background, socioeconomic status, in IUGR vs not IUGR vs preterm subjects using the chi-square test or an alternative to Fisher-exact test. While, the association between weight, height, BMI, WHO BMI Categories and maternal age group, two-hour post prandial (2h-PP) plasma glucose level category (IGT vs no IGT) in IUGR vs not IUGR vs preterm subjects were evaluated by Kruskall Wallis test.

Binomial logistic regression was used to predict the risk ratio (RR) parameter. According to bivariate analysis, variables with p value <0.25 were included in multivariate analysis. All statistical calculation was done using IBM® SPSS® Statistic software (SPSS, Inc, Chicago, Illinois) under the license of Universitas Padjadjaran. p value <0.05 was considered statistically significant

RESULTS

After validation of data, 779 adolescents were invited to join this study (Figure 1). Some of these adolescents did not come for the test or did not give consent or had moved outside

Tanjungsari area. Furthermore, about 5% of subjects vomited after ingesting glucose solution during the OGTT and had to be excluded from the study. Eventually, only 536 subjects were willing to participate in and fulfilled research categories. We found 67 out of 536 (12.5%) subjects had IGT.

Table 1 demonstrated baseline characteristics, maternal background, and socioeconomic status of study subjects, including statistical tests of the differences between the LBW (<2500 g) and normal birth weight (≥2500 g) group. There were no significant age differences among the groups (p=0.109). Adolescents with LBW had lower median body weight (35.6 kg vs 37.2 kg; p= 0.001), lower height (144.8 cm vs 147.0 cm; p= 0.000) and lower body mass index (BMI) (16.7 kg/m^2 vs 17.0 kg/m^2; p= 0.027) than those who were born with normal birth weight (NBW). Maternal age (p=0.180), education (p=0.391), and family socioeconomic status (drinking water type [p=0.752]; latrine [p=0.966]) were not associated with LBW. There was a significant increased risk of having IGT for those who were born with LBW (RR 1.692 [1.079 – 2.653]).

Adolescents with IUGR had lower median body weight (35.5 kg vs 38.1 kg vs 36.2 kg; p=0.001), lower height (145.1 cm vs 148.1 vs 146.1 cm; p= 0.001) , and lower BMI (16.7 kg.m^2 vs 17.1 kg/m^2 vs 17.0 kg/m^2; p= 0.212) than those who were not IUGR or born preterm (Table 2). There were significant age and sex differences between the groups (p=0.007 and p=0.040, respectively). However, maternal age (p=0.754), education (p=0.350), and family socioeconomic status (drinking water type [p=0.103]; latrine [p=0.068]) were not associated with IUGR. We found the no difference on proportion of IGT among subjects with IUGR compared with subjects who were not IUGR or born preterm (33 vs 13 vs 21; p=0.286).

In addition, we also evaluated the association of LBW with IGT using multivariate analysis (Table 3). Sex and drinking water sources were added as possible confounding variables. Eventually, after multivariable adjustment for these confounding factors, the risk of having IGT for those who were born with LBW was not differed (adjusted RR 1.650 [1.054 – 2.584]).

DISCUSSION

During early adolescence stage, we found that those who were born with LBW had higher risk of having IGT. Impaired prenatal development that we found as LBW or IUGR seems to influence subject's plasma glucose level and their risks of having insulin resistance.

Low birth weight as a risk factor of impaired glucose tolerance

Fetal programming hypothesis suggests that intrauterine undernourishment causing glucose conserving adaptation which reduces glucose consumption by periphery in favor of brain; the condition could lead to permanent metabolic shift towards insulin resistance.[6,7] Our study showed that there was a significant association between LBW and IGT. Previous study in China which demonstrated infant with birth weight less than 2500 g was associated with impaired glucose regulation in later life (mean age 60.99 years ±8.26).[12] Jornayvaz et al also demonstrated in women aged about 50 years old, those who were born with LBW was significantly associated with a higher likelihood of developing diabetes and insulin resistance.[21]

Previous study showed small for gestational age (SGA) also had a tendency of hyperinsulinemia and insulin resistance showed by HOMA-IR, although they were not associated.[22] Chronic hyperinsulinemia was found to cause metabolic derangement and eventually causing insulin resistance both in adipose and muscle tissues.[23] These correlate with other studies stated LBW was a risk factor of insulin resistance in later life.[7,21,24] Children who were born with LBW had higher fasting plasma glucose levels compared to those who were born with normal birth weight.[21,25]

Furthermore, our study is important because the subjects were still at the age of 12 to 14 years old. This unveiled the fact that IGT could present at such young age for those who were born with LBW, even when there was no obesity.

Low birth weight, BMI and insulin resistance

We found that BMI was not associated with their 2-h postprandial plasma glucose level. The result was in contrary to previous studies and theories. Previous study showed low BMI and weight at birth trigger type 2 diabetes mellitus (T2DM) in later life. Low-fat deposition leading to thinness at birth and during infancy results in fat acquisition during childhood, which promotes the risk of developing T2DM.26 Chinese adolescents with T2DM or prediabetes have significantly had higher BMI. These adolescents were also less physically active in comparison to those without T2DM or prediabetes.[27] Similarly, an observational study of obese children and adolescents with normal glucose tolerance showed more than 10% of them were converted to IGT. Both obesity and entry to adolescents' puberty stage were risk factors for developing IGT.[28]

Glucose intolerance and its pathophysiology

Impaired development of the pancreas could be found in those who were born with LBW. Furthermore, the thrifty phenotype hypothesis demonstrated that nutrition deficiencies during fetal and neonatal periods might cause hypoplasia of the pancreatic cells and trigger hyposecretion of insulin by pancreatic beta cells. This alteration of the pancreatic cells and function were irreversible. As they grow into adulthood, insulin requirements will increase and diabetes mellitus will develop eventually.[29,30]

Although not all individual with LBW will develop T2DM in their later life, this study showed that they had more risks of having diabetes in younger age than those with normal birth weight. However, there was another factor that may affect the development of insulin resistance, such as genetics. According to this study and in accordance with Barker's hypothesis, good prenatal care, such as carefully monitor intrauterine growth and nutritional status, also BMI observation throughout pregnancy and adolescents might give us a promising way to prevent insulin resistance.

Strength and Limitation of the study

The TCS is one of few cohort in developing countries that involved large amount of subjects with standardized anthropometric data. Hence, in this cohort study we could evaluate the causative relationship between LBW, IUGR and IGT. However, there were several limitations of the study: a) This study did not include other factors which could influence results such as smoking habit, sex maturity rating, dietary intake of study subjects; b) We determined subjects' socioeconomic status by using only their drinking water sources and latrine availability; c) We determined IUGR using their birth weight and birth length instead of applying their gestational age or more sophisticated measuring tools like the fetal ultrasonography. Previous report have shown that gestational age was not reliable in this cohort, and ultrasonography was not available.[15]

Conclusion

In this study we could conclude that LBW was an important risk factor for IGT in adolescence. Hence, we suggest diabetes prevention program focusing on improving maternal and newborn baby nutritional and health status should be implemented during pregnancy and in childhood period.

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CONFLICT OF INTEREST AND FUNDING DISCLOSURE

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Table 1. Association between subject characteristics and birth weight

	Birth Weight (n=536)		*p* value
	<2500 grams (n=226)	≥2500 grams (n=310)	
Age (years) n (%)			
12 (n=80)	26 (32.5)	54 (67.5)	0.109†
13 (n=295)	134 (45.4)	161 (54.6)	
14 (n=161)	66 (41.0)	95 (59.0)	
Sex, n (%)**			0.018†
Men (n=255)	94 (36.9)	161 (63.1)	
Women (n=281)	132 (47.0)	149 (53.0)	
Height (cm)*	144.8 (125.5-161.0)	147.0 (127.5-170.0)	0.000‡
Weight (kg)*	35.6 (22.0-56.9)	37.2 (20.3-63.8)	0.001‡
BMI kg/m^2**	16.7 (11.3-25.5)	17.0 (10.4-23.2)	0.027‡
WHO criteria (BMI for age, Z scores)**	-1.0 (-4.0 – 1.71)	-0.9 (-4.0 – 1.54)	0.037‡
Categories *			0.002 §
Severe thinness	19 (65.5)	10 (34.5)	
Thinness	33 (52.4)	30 (47.6)	
Normal	171 (39.3)	264 (60.7)	
Overweight	3 (33.3)	6 (66.7)	
Obese	0 (0)	0 (0)	
Maternal age			
< 20 years old	70 (45.2)	85 (54.8)	0.180§
20-35 years old	146 (42.1)	201 (57.9)	
> 35 years old	10 (29.4)	24 (70.6)	
Pregnancy risk			0.955†
High risk pregnancy	80 (42.3)	109 (57.7)	
Normal pregnancy	146 (42.1)	201 (57.9)	
Maternal educational background			0.391†
None	60 (37.7)	99 (62.3)	
Elementary school graduates	153 (44.2)	193 (55.8)	
Junior high school graduates	13 (41.9)	18 (58.1)	
Socioeconomic status:			
Drinking water type:			0.752†
Improved (bored, protected well, tap water, electric pump)	83 (41.3)	118 (58.7)	
Unimproved (fountain, headwater, river, unprotected well)	143 (42.7)	192 (57.3)	
Latrine:			0.966†
Improved (water seal, pit latrine)	108 (43.5)	140 (56.5)	
Unimproved (open pit, river, pond, gully, anywhere)	118 (41)	170 (59.0)	
Fasting Plasma Glucose (mg/dL)	87.0 (65.0-109.0)	86.0 (54.0-104.0)	0.164‡
<100 mg/dL, n (%)	215 (42.0)	297 (58.0)	0.710†
100-125 mg/dL, n (%)	11 (45.8)	13 (54.2)	
Two-hour Post Prandial Plasma Glucose Level (OGTT)	113.0 (70.0-187.0)	114.0 (51.0-232.0)	0.348‡
No IGT (<140 mg/dL), n (%)**	189 (83.6)	280 (90.3)	0.021†
IGT (140-199 mg/dL), n (%)**	37 (16.4)	30 (9.7)	

IFG: impaired fasting glucose; IGT: impaired glucose tolerance.
Data are median (min-max) or number (%).
†Chi-square test.
‡Mann-whitney U test; §Kruskall-wallis test.
*p<0.01, **p<0.05.

Table 2. Association between basic characteristics in subject's with or without IUGR or preterm

	Not IUGR (n=145)	IUGR (n=250)	Preterm (n=141)	*p* value
Age (years) n (%)*				0.007†
12 (n=81)	29 (36.3)	40 (50.0)	11 (13.8)	
13 (n=303)	74 (25.1)	146 (49.5)	75 (25.4)	
14 (n=165)	42 (26.1)	64 (39.8)	55 (34.3)	
Sex, n (%) **				0.040†
Men (n=255)	82 (32.2)	110 (43.1)	63 (24.7)	
Women (n=281)	63 (22.4)	140 (49.8)	78 (27.8)	
Height (cm)*	148.1 (131.9-170.0)	145.1 (126.1-169.9)	146.1 (125.5-163.5)	0.001‡
Weight (kg)*	38.1 (24.3-55.4)	35.5 (20.3-63.8)	36.2 (22.9-57.4)	0.001‡
BMI kg/m^2	17.13 (11.3-23.2)	16.72 (10.4-25.5)	16.96 (11.3-23.8)	0.212‡
WHO criteria (BMI for age, Z scores)	-0.8 (-4.0 – 1.5)	-1.0 (-4.0 – 1.7)	-0.9 (-4.0 – 1.3)	0.100‡
Categories**				0.003‡
Severe thinness	2 (6.9)	18 (62.1)	9 (31)	
Thinness	11 (17.5)	35 (55.6)	17 (27)	
Normal	128 (29.4)	195 (44.8)	112 (25.7)	
Overweight	4 (44.4)	2 (22)	3 (33.3)	
Obese	0 (0)	0 (0)	0 (0)	
Maternal age				0.754‡
< 20 years old	40 (25.8)	71 (45.8)	44 (28.4)	
20-35 years old	97 (28.0)	161 (46.4)	89 (25.6)	
> 35 years old	8 (23.5)	18 (52.9)	8 (23.5)	
Pregnancy risk				0.791†
High risk pregnancy	48 (25.4)	89 (47.1)	52 (27.5)	
Normal pregnancy	97 (28.0)	161 (46.4)	89 (25.6)	
Maternal educational background				0.350†
None	36 (22.6)	85 (53.5)	38 (23.9)	
Elementary school graduates	100 (28.9)	152 (43.9)	94 (27.2)	
Junior high school graduates	9 (29.0)	13 (42.0)	9 (29.0)	
Socioeconomic status				
Drinking water type:				0.103‡
Improved (bored, protected well, tap water, electric pump)	65 (32.3)	87 (43.3)	49 (24.4)	
Unimproved (fountain, headwater, river, unprotected well)	80 (23.9)	163 (48.7)	92 (27.5)	
Latrine:				0.068†
Improved (water seal, pit latrine)	68 (27.4)	116 (46.8)	64 (25.8)	
Unimproved (open pit, river, pond, gully, anywhere)	77 (26.7)	134 (46.5)	77 (26.7)	
Fasting plasma glucose (mg/dL)	86.0 (70.0-104.0)	86.0 (54.0-107.0)	88.00 (67.0-109.0)	0.053‡
Normal (<100 mg/dL, n (%))	139 (27.1)	241 (47.1)	132 (25.8)	0.431‡
IFG (100-125 mg/dL, n (%))	6 (25.0)	9 (37.5)	9 (37.5)	
Two-hour post prandial plasma glucose level (OGTT) (mg/dL)	114.0 (51.0-205.0)	113.00 (69.0-232.0)	115.00 (71.0-177.0)	0.611‡
No IGT (<140 mg/dL), n (%)	132 (90.6)	217 (86.8)	120 (85.1)	0.286‡
IGT (140-199 mg/dL), n (%)	13 (9.4)	33 (13.2)	21 (14.9)	

IFG: impaired fasting glucose; IGT: impaired glucose tolerance.
Data are median (min-max) or number (%).
†Chi square; ‡Kruskall Wallis test.
*p<0.01, **p<0.05;.

Table 3. Role of body weight, sex, and drinking water source on impaired glucose tolerance

	Crude RR (95% CI)	Adjusted RR (95% CI)
Birth weight (<2500 g)	1.692 (1.079 – 2.653)**	1.650 (1.054 – 2.584)**
Sex (Women)	1.431 (0.902 – 2.270)	1.361 (0.859 – 2.155)
Drinking water sources (unimproved/ fountain, headwater, river, unprotected well)	1.410 (0.861 – 2.309)	1.449 (0.886 – 2.371)

RR: risk ratio.
Dependent variable: impaired glucose tolerance (IGT).
** $p<0.05$.

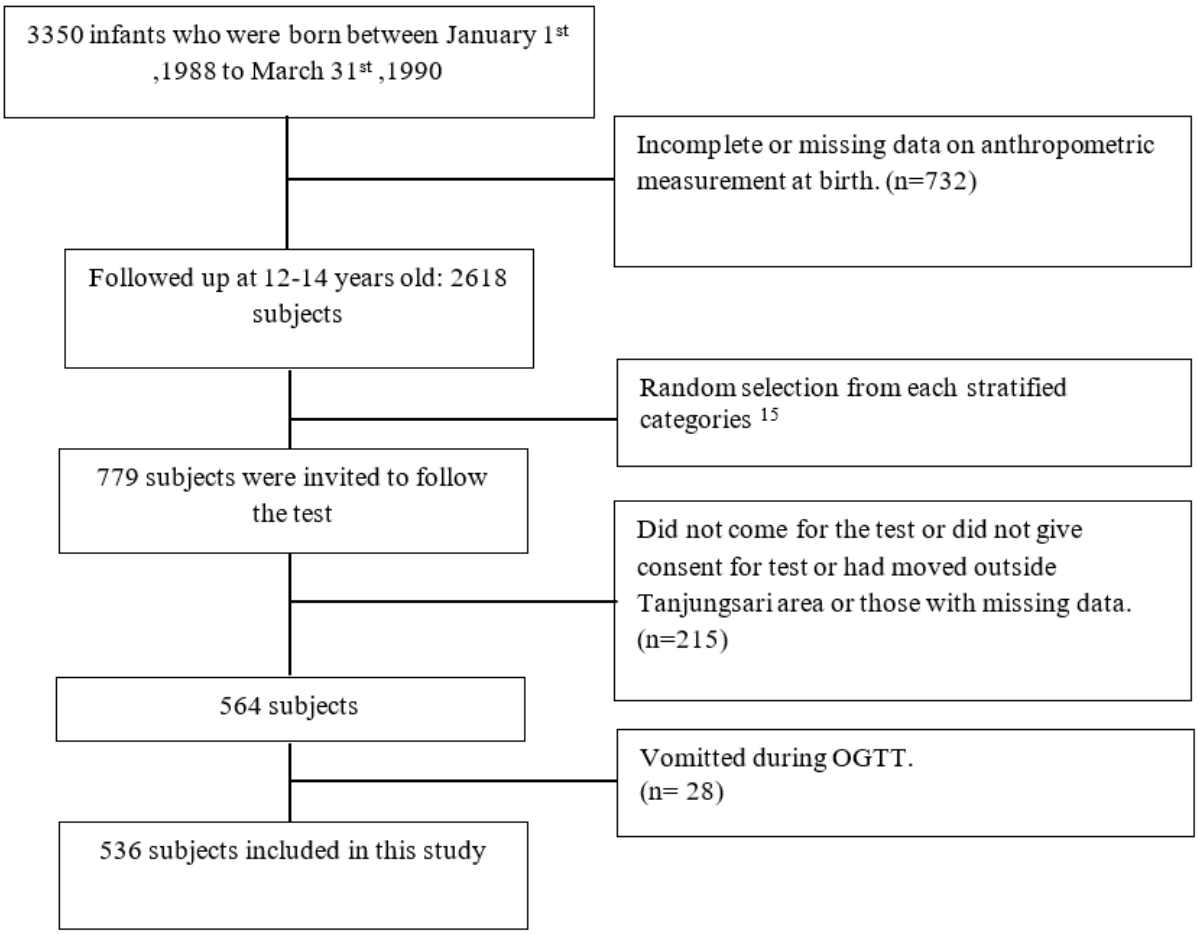

Figure 1. Inclusion and exclusion of subjects in the cohort.