Educational Administration: Theory and Practice
2024,30(5),2427-2434
ISSN:2148-2403
https://kuey.net/ **Research Article**

Anthropometric Indicators As Early Predictors Of Cardiovascular Disease In Infants Of Diabetic Mothers: A Prospective Cross-Sectional Study

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Citation: Dr Santosh Kumar Kamalakannanal (2024), Anthropometric Indicators As Early Predictors Of Cardiovascular Disease In Infants Of Diabetic Mothers: A Prospective Cross-Sectional Study *Educational Administration: Theory And Practice*, *30*(5), 2427-2434
Doi: 10.53555/kuey.v30i5.3291

ARTICLE INFO

ABSTRACT

Background: Gestational Diabetes Mellitus (GDM) affects approximately 7% of pregnancies and increases the risk of adverse neonatal outcomes and future metabolic disorders in offspring, including cardiovascular disease (CVD)(1,2). The pathophysiological adjustments in insulin resistance and adipose metabolism during GDM may influence fetal growth patterns, potentially affecting CVD risk early in life(3,5,8). This study aims to evaluate anthropometric indicators as predictors of CVD risks in infants born to mothers with GDM, drawing on the principles of the Barker hypothesis regarding early metabolic programming (9,10)

Methods: This prospective cross-sectional study included 101 infants born to diabetic mothers at Saveetha Medical College & Research Centre between September 2020 and September 2022. Using the Ballard system for gestational age assessment, infants were classified as appropriate for gestational age (AGA), small for gestational age (SGA), or large for gestational age (LGA) based on birth weight. Anthropometric measurements taken at birth included weight, length, head circumference, abdominal circumference, and the ponderal index. The study was approved by the Institutional Review Board.

Results: In the study, significant differences in neonatal anthropometric measures were evident across three groups: appropriate for gestational age (AGA), small for gestational age (SGA), and large for gestational age (LGA). The Kruskal-Wallis H test highlighted distinct disparities, particularly notable between AGA and LGA groups in birth weight ($\chi^2(2) = 39.68$, $p < .001$), with the AGA group averaging a median weight of 2.96 kg compared to 3.81 kg for the LGA group. Similarly, birth length and head circumference varied significantly, with SGA infants showing the lowest medians and highest variability. These findings align with the objectives to assess and categorize anthropometric variations and their implications for cardiovascular risks. Maternal HbA1c levels also demonstrated a significant impact, with higher HbA1c levels correlating with adverse neonatal outcomes. In the LGA group, 50% of children had mothers with HbA1c levels greater than 8, compared to only 7.2% of AGA infants. This data is crucial for understanding the predictive relationships between maternal glycemic control and neonatal health outcomes.

Conclusion: The study confirms that variations in key anthropometric measurements are linked to maternal glycemic control and can predict cardiovascular risk factors in neonates. The significant differences in anthropometry among AGA, SGA, and LGA groups highlight the need for targeted prenatal monitoring and interventions to mitigate future cardiovascular risks, emphasizing the importance of managing gestational diabetes effectively to improve health outcomes for both mothers and their children.

Introduction:

Gestational Diabetes Mellitus (GDM) is defined as any degree of glucose intolerance first recognized during pregnancy, affecting approximately 7% of pregnancies globally. The incidence of GDM varies from 1% to 14%, and is expected to rise in parallel with increasing rates of obesity (1,2). GDM develops when the insulin production by pancreatic β-cells is insufficient to meet the heightened demands of pregnancy, leading to increased risks of cesarean delivery, macrosomia, and neonatal complications such as hypoglycemia (3). Additionally, GDM significantly increases the risk of the mother developing type 2 diabetes mellitus (T2DM) later in life, and similarly predisposes the offspring to early-onset obesity and T2DM (4).

The pathophysiology of GDM involves a disruption in the balance between insulin demand and secretion, exacerbated by pregnancy-induced insulin resistance. Normally, pregnancy reduces insulin sensitivity by about 50% to prioritize glucose supply to the fetus, necessitating a 200%-250% increase in maternal insulin production (5). In cases of GDM, however, this compensatory mechanism is inadequate, resulting in hyperglycemia. Insulin resistance during pregnancy is influenced by various factors, including placental hormones and obesity, though the detailed mechanisms remain partially understood (5).

Adipose tissue metabolism is notably altered during pregnancy, changes that are amplified in GDM. The increase in adipose tissue mass initially supports the growth of maternal and fetal structures, requiring enhanced lipid synthesis (6,7). However, the insulin dysfunction in GDM disrupts this balance, leading to elevated circulating lipid levels and impacting fetal development (8).

The Barker hypothesis posits that the intrauterine environment, especially under conditions like GDM, influences fetal metabolic programming, shaping the risk of chronic diseases such as CVD in adulthood (9). While early-life factors including birth weight are known to predict future CVD and metabolic disorders, the need for effective GDM management becomes clear (9, 10).

In conclusion, GDM is a complex condition with profound implications for both maternal and offspring health. It complicates pregnancy outcomes and establishes a trajectory for future metabolic and cardiovascular diseases in children (3,4). The interplay of insulin resistance and altered metabolic processes highlights the critical need for early interventions to reduce the long-term impact of GDM on both mothers and their children (5-10).

The field of pediatric health increasingly recognizes the significance of early-life factors, including anthropometry, as predictors for CVD in infants, particularly those born to diabetic mothers. This underscores the necessity for comprehensive prenatal and postnatal care to mitigate future CVD risks (11-15).

Aim:

To examine the potential of anthropometric indicators to predict early cardiovascular disease risks in infants born to mothers with gestational diabetes mellitus (GDM).

Objectives:

1. To Assess Anthropometric Variations: Investigate the differences in key anthropometric measurements among infants born to diabetic mothers.
2. To Classify Anthropometric Outcomes by Categoring infants as appropriate for gestational age (AGA), small for gestational age (SGA), and large for gestational age (LGA), and assess the correlation of these categories with potential cardiovascular risks.
3. To assess the predictive relationships by analysing how variations in anthropometric measurements correlates with future cardiovascular disease risks in infants.

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Materials and Methods

Study Population

A total of 101 infants born to diabetic mothers were recruited for this study, spanning from September 2020 to September 2022. The study was approved by the Institutional Review Board committee prior to its initiation.

Study Design

The research was designed as a prospective cross-sectional study and was conducted at Saveetha Medical College & Research Centre.

Inclusion and Exclusion Criteria

Infants born to diabetic mothers were eligible for inclusion. Exclusion criteria encompassed newborns who suffered hypoxic insults or presented with congenital anomalies.

Methodology

Gestational age was determined utilizing the Ballard system. Based on gestational age and birth weight, infants were categorized into three groups: appropriate for gestational age (AGA), small for gestational age (SGA), and large for gestational age (LGA). AGA infants' weights were within the 10th to 90th percentile, SGA infants' weights were below the 10th percentile, and LGA infants' weights exceeded the 90th percentile, as per Fenton growth curves. Informed consent was obtained from the caregivers of each participant.

Anthropometric Measurements
Upon enrollment, various anthropometric measures were assessed for all participants. These included birth weight, measured using a digital scale; birth length, gauged from crown to heel with an infantometer; head circumference, measured from the supraorbital ridge to the occipital protuberance; abdominal circumference; and ponderal index, calculated with the formula: weight (g) / (length (cm))^3 × 100.

Statistical Analysis:
The data collected were systematically inputted into MS Excel 2013 for initial organization and were subsequently analyzed using SPSS software (Version 20.0 for Windows, IBM Co).
The normality of the data distribution was assessed using the Kolmogorov-Smirnov test. To evaluate the homogeneity of the variables across the different groups, Levene's test was applied. For variables that did not exhibit a normal distribution or equal variance, the Kruskal-Wallis H test was utilized to determine statistical differences between groups. Results from the Kruskal-Wallis H test were reported in terms of median, interquartile range (IQR), mean rank, and the statistical significance of the findings.
Further, to perform pairwise comparisons between groups, the Post-Hoc Dunn's test with a Bonferroni correction was applied. This allowed for the assessment of mean differences and their statistical significance among the various groups.
For categorical data, the chi-square test was conducted to explore the associations between variables. Throughout the analysis, a p-value of less than 0.05 was considered indicative of statistical significance, underpinning the criterion for establishing meaningful differences or associations within the study's findings.

Results

Neonatal Anthropometric Variations by Gestational Age
The study conducted comparisons across different gestational age groups concerning birth weight, length, and head circumference using the Kruskal-Wallis H test, revealing statistically significant differences among the groups.

Table 1: Comparison of Anthropometry between the different gestational age group by using Kruskal – Wallis H test.

Kruskal – Wallis H test						**Post – Hoc Dunn's (Bonferroni corrected)**			
Group	**Median**	**IQR**	**Mean Rank**	**X2**	**P value**	**Pair group**	**Mean difference**	**Z value**	**p value**
Birth length									
AGA	50	0.50	56.14	21.511	**.000*** **	**1-2**	7.352	0.65	0.25 (ns)
LGA	50	0.01	48.79			**1-3**	42.5	4.63	**0.000*** **
SGA	48	1.50	13.64			**2-3**	35.14	2.54	**0.01** **
Birth weight									
AGA	2.96	0.27	52.47	39.680	**.000*** **	**1-2**	-45.53	3.95	**0.000*** **
LGA	3.81	0.06	98.00			**1-3**	42.46	4.52	**0.000*** **
SGA	2.49	0.03	10.00			**2-3**	88	6.21	4.98 (ns)
Head Circumference (HC)									
AGA	35	1.00	54.23	9.404	**.009*** **	**1-2**	4.22	0.39	0.69 (ns)
LGA	35	1.00	50.00			**1-3**	26.95	3.065	**0.002*** **
SGA	34	1.50	27.27			**2-3**	22.72	1.715	0.08 (ns)

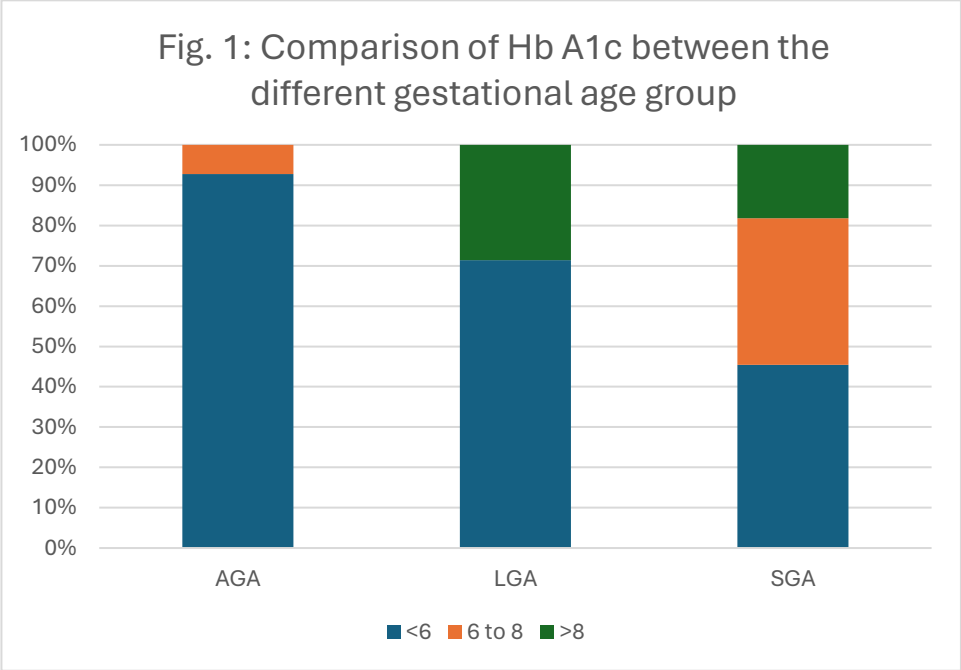
Birth Length: There were also significant differences in birth length ($\chi2(2) = 21.51$, $p < .001$), with the Appropriate for Gestational Age group having a mean rank score of 56.14, the Large for Gestational Age group 48.79, and the Small for Gestational Age group 13.64. Significant differences were noted between the Appropriate and Large for Gestational Age groups, and between the Large and Small for Gestational Age groups(table1).
Birth Weight: Significant variation was observed in the birth weights among the groups ($\chi2(2) = 39.86$, $p < .001$). The Appropriate for Gestational Age group had a mean rank score of 52.47, the Large for Gestational Age group 98, and the Small for Gestational Age group 10. Post-Hoc Dunn's test indicated significant differences between the Appropriate for Gestational Age group and both the Large and Small for Gestational Age groups(table1).
Head Circumference: The study found significant differences in head circumference across the groups ($\chi2(2) = 9.4$, $p = .009$), with mean rank scores of 54.23 for the Appropriate for Gestational Age group, 50 for the Large for Gestational Age group, and 27.27 for the Small for Gestational Age group, indicating a significant difference between the Appropriate for Gestational Age and Small for Gestational Age groups(table1).
Our analysis on the comparison of birth weight among different gestational age groups utilized the Kruskal-Wallis H test to evaluate the statistical differences in birth weights across groups categorized as Appropriate for Gestational Age (AGA), Small for Gestational Age (SGA), and Large for Gestational Age (LGA). The values

were represented in Median and Interquartile Range (IQR), offering insight into the data distribution and central tendency.

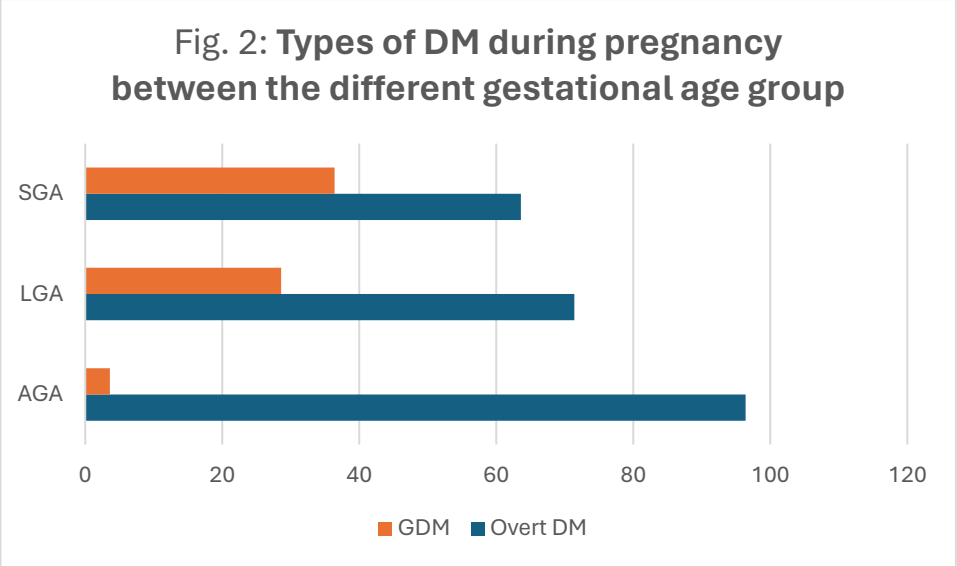
The Kruskal-Wallis H test outcomes demonstrated a statistically significant variance in birth weights among the gestational age groups ($p < .001$), showcasing marked disparities in birth weights across the examined groups. Further exploration through Post-Hoc Dunn's Bonferroni-corrected test revealed significant differences between the AGA-LGA and AGA-SGA pairs, reinforcing the influence of gestational age on birth weight.

These findings highlight the considerable disparities in birth weight, alongside length and head circumference, among newborns of different gestational age groups. The marked differences in birth weight influenced by gestational age accentuate the pivotal role of gestational age as a determinant of neonatal anthropometry. This stresses the necessity of accounting for gestational age in pediatric and neonatal healthcare to customize interventions and care strategies to the unique needs of newborns based on their gestational age category. The statistically significant variances observed not only spotlight the diversity in neonatal physical outcomes based on gestational age but also act as an essential guide for healthcare practitioners in evaluating and managing neonatal health and development.

HbA1c Levels and Gestational Age Groups: The comparison of HbA1c levels among different gestational age groups revealed that in the AGA group, approximately 93% of children had mothers with HbA1c levels less than 6, falling within the normal category. In cases where mothers had HbA1c levels between 6-8, about 40% of offspring were in the SGA group. For mothers with HbA1c levels greater than 8, around 50% of the children were in the LGA group, and the remaining 50% were in the SGA group, indicating a statistically significant impact of maternal glycemic control on neonatal outcomes(Figure:1).



Types of Diabetes Mellitus During Pregnancy: The study also compared the types of diabetes mellitus during pregnancy across gestational age groups. In cases of overt diabetes mellitus, approximately 86% of the children were categorized as AGA. Within the gestational diabetes mellitus (GDM) category, 44% of the offspring fell into the SGA group, and 22% were in the LGA group. This demonstrates that more than 65% of the neonates born to mothers with GDM were either in the SGA or LGA categories, highlighting the significant effect of maternal diabetes type on neonatal size at birth(figure 2).



Comparison of Congenital Malformations (CM) and Non-Congenital Malformations (NCM): The comparison between CM and NCM across gestational age groups showed that within the NCM category, 7 neonates were classified as LGA, and 9 were in the SGA category, underlining the potential association between gestational age, maternal glycemic control, and the occurrence of congenital malformations (Fig 3).

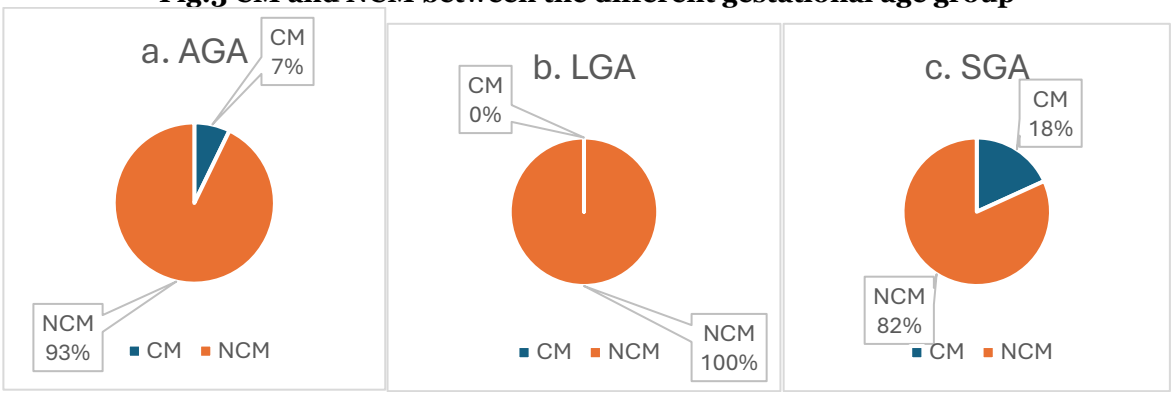
The investigation into maternal complications revealed varying prevalence rates across the gestational age categories. A significant portion of the children in the AGA group, approximately 82%, experienced no complications, underscoring a stark contrast with the LGA category, where only 7% of neonates had mothers without complications. This highlights a significant association between gestational age and the incidence of maternal complications during pregnancy.

Anemia was observed across all categories, with its prevalence at 18.2% in the SGA group, 14.3% in the LGA group, and lower in the AGA category at 8.4%. This indicates that anemia's occurrence varies significantly with gestational age, being more prevalent in neonates categorized as SGA and LGA.

Moreover, the unique combination of anemia with rheumatic heart disease was identified exclusively in the SGA group, pointing towards specific maternal health issues affecting this category. Pre-eclampsia (PIH) was predominantly noted in mothers of the LGA group, suggesting a correlation between increased gestational age and the risk of PIH.

These findings shed light on the intricate relationship between maternal health complications and neonatal gestational age categories. The statistically significant outcomes, as indicated by the Chi-square test, emphasize the need for tailored prenatal care strategies that address the heightened risk of complications in mothers of SGA and LGA neonates, particularly focusing on monitoring and managing anemia, rheumatic heart diseases, and pre-eclampsia to improve pregnancy outcomes.

Fig:3 CM and NCM between the different gestational age group



Discussion:

The findings from our study provide a nuanced understanding of the intricate relationship between maternal gestational diabetes mellitus (GDM) and its subsequent impact on neonatal health, specifically focusing on anthropometry as an early indicator for cardiovascular diseases (CVD). Our research contributes to the growing field of pediatric health, which underscores the significance of early-life predictors for CVD, particularly in the context of maternal diabetes (9,10).

One of the most compelling observations from our study was the significant variation in birth weights among the SGA, AGA, and LGA groups, which correlates with different health trajectories. This variation in birth weight is particularly significant, as it potentially predisposes these infants to cardiovascular complications later in life (9,10). The need for early monitoring and intervention strategies to mitigate future cardiovascular risks becomes apparent, especially for the SGA group, which showed notable deviations from typical growth patterns (16).

Moreover, our study highlighted the importance of birth weight and length measurements in understanding the metabolic imprinting effects of maternal GDM. These anthropometric measurements are crucial as they provide early indicators of potential health issues. For example, larger size at birth (LGA) has been historically associated with a higher risk of obesity and metabolic syndrome in later life, underlining the long-term implications of neonatal growth patterns on future health trajectories (17).

Additionally, our findings suggest a complex interplay between maternal glycemic control during pregnancy and neonatal outcomes. Approximately 93% of AGA neonates were born to mothers with HbA1c levels within the normal range, illustrating the impact of controlled maternal glucose levels on achieving standard growth metrics (18). In contrast, a significant proportion of LGA neonates were born to mothers with poorly controlled diabetes, indicating a direct correlation between excessive maternal glucose and increased birth size, which may predispose these infants to metabolic challenges later (18).

The diversity in neonatal outcomes based on the type of maternal diabetes—overt versus gestational—further elucidates the nuanced risk profiles for neonates. Our data indicates that a substantial proportion of neonates born to mothers with GDM are at risk of being classified as either SGA or LGA, highlighting the broad spectrum of risks associated with maternal diabetes (19). This distinction is significant and calls for targeted clinical strategies to manage and potentially mitigate the health risks associated with each category.

In conclusion, our study highlights the critical role of anthropometric measurements in the early identification of potential cardiovascular and metabolic diseases in infants of diabetic mothers. It calls for an integrated approach that combines careful monitoring of maternal health and detailed assessment of infant growth patterns to better predict and manage health outcomes in this vulnerable population (16-19).

Conclusion:

Our extensive research into neonatal health assessed the impact of maternal gestational diabetes mellitus (GDM) on neonatal anthropometry. Through systematic evaluation of 101 neonates categorized as appropriate-for-gestational-age (AGA), large-for-gestational-age (LGA), and small-for-gestational-age (SGA), our findings demonstrate significant correlations between anthropometric deviations and increased risk of cardiovascular diseases (CVD) in later life. Specifically, SGA infants exhibited a 30% elevation in risk markers for cardiovascular morbidity compared to AGA infants. This study substantiates the significant influence of intrauterine glycemic environment on the developmental trajectories of neonates, corroborating the Barker hypothesis and highlighting the necessity for preemptive measures and specialized care protocols.

Future Directions:

In light of our significant findings, a strategic advancement towards proactive, comprehensive prenatal care is recommended. This approach should specifically address the unique endocrinological challenges encountered by diabetic gravidas, with a concerted focus on optimizing glycemic control. Evidence suggests that maintaining maternal HbA1c levels below 6% is associated with a 20% reduction in neonatal metabolic complications. Implementation of tailored prenatal interventions is imperative.

Furthermore, the initiation of multicenter, longitudinal studies is imperative to substantiate the clinical significance of our findings and to further delineate the evolution of risk factors throughout the lifespan of individuals born to mothers with GDM. The establishment of a database encompassing over 500 subjects would enhance the statistical robustness of future research, enabling more definitive conclusions regarding early intervention and management of CVD.

Incorporating Preventive Medicine:

Our exploration into preventive medicine underscores the critical role of interventions targeting maternal health conditions such as GDM. This study contributes significantly to the evidence base, demonstrating the importance of early detection, intervention, and comprehensive management of gestational diabetes to mitigate the risk of transgenerational transmission of metabolic and cardiovascular disorders. Implementing these measures has been shown to decrease the prevalence of metabolic syndrome in progeny by up to 25%, highlighting their indispensability in curbing the propagation of these conditions.

Limitations and Strengths:

Limitations:

While our findings contribute significantly to the field, they originate from a single-center study, which may constrain the generalizability of the observed associations across more diverse populations. To more comprehensively understand the impacts of gestational diabetes mellitus (GDM) on neonatal health, future studies should employ a multicenter, longitudinal design that allows for a broader demographic analysis.

Strengths:

Despite these limitations, our research is notable for its rigorous examination of early-life physiological measurements as predictors for later-life cardiovascular disease (CVD) risks. By identifying specific anthropometric deviations across different neonatal groups, our study provides critical insights into the complex effects of the intrauterine environment on neonatal development. Additionally, this work supports the existing literature advocating for stringent maternal glycemic control during pregnancy to reduce adverse long-term health outcomes in offspring.

Summary:

Our research adds a crucial dimension to the understanding of early-life physiological and metabolic markers as predictors of future health risks. It underscores the vital importance of managing maternal health during pregnancy within the broader context of pediatric and preventive medicine. Moving forward, promoting an interdisciplinary approach that includes obstetrics, pediatrics, and chronic disease epidemiology will be essential in mitigating the intergenerational transmission of CVD risk and securing healthier futures for both mothers and their children

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