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Size for Gestational Age Affects the Risk for Type 1 Diabetes in Children and Adolescents: A Swedish National Case - Control Study

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Main question (s) posed by the study and study design

The study's major goal is to determine how a baby's size for gestational age impacts the likelihood to acquire type 1 diabetes later in childhood.

This review examined past, conflicting literature that looked into the relationship between birth weight and the onset of childhood diabetes. All of which, unlike this sizable, countrywide study, appeared to ignore additional confounders, that would have increased the possibility of errors.

It is a case - control study with the following features:

- There are two participant groups picked. One set (the cases) will include the condition of interest whereas the other will not (the controls).
- The goal was to make the controls as comparable as possible to their corresponding cases.
- The next step is to ascertain whether anyone in each group has ever been exposed to the alleged risk factor. Personal interviews, the use of pre - existing records, and laboratory tests could all be used to do this.
- Since they concentrate on exposure from the past, case - control studies are also known as retrospective studies.
- The relationship between exposure to the identified risk factor and the outcome in question is then deduced using logic. " modified from; Medical Statistics from Scratch: An Introduction for Health Professionals, edited by David Bowers, John Wiley & Sons, Incorporated, 2014. P111a

Despite being frequently suitable for rare diseases, the case - control approach has some limitations:

- Although populations that often use particular facilities are frequently used to choosing cases, this could mean that these cases are not necessarily representative of the greater community that suffers the same condition.
- It can be challenging to select appropriate control volunteers who do not have the disease under investigation and the issue of recollection bias, which depends on humans, is another drawback.
- "extracted from Medical Statistics from Scratch: An Introduction for Health Professionals, edited by David Bowers, John Wiley & Sons, Incorporated, 2014. P115b"

Participants and measures:

The study population includes children (0–18 years old) who had a type 1 diabetes diagnosis between January 2000 and October 2012 and who were registered in the Swedish Medical Birth Register (MBR), which compiles data from antenatal, obstetric, and neonatal medical files, as well as SWEDIABKIDS (the Swedish pediatric diabetes quality register).

Four controls (n = 37, 504) who were registered in MBR, were matched with every diabetes child.

There were 9376 diabetic cases in all that were recruited.

The necessary sample size, however, is a different issue. "It's intimately tied up with the notion of 'power' and error, as well as the nature of the study. According to Medical Statistics from Scratch: An Introduction for Health Professionals, edited by David Bowers, John Wiley & Sons, Incorporated, 2014. P133c

The matching criteria taken into account were: the gender, place, year, and day of birth while the maternal characteristics were adjusted.

The study excluded children who weren't singletons.

It mentioned no blinding in any way.

Swedish definition for small and large for gestational ages (SGA, LGA) is birth weights that were less than and more than two standard deviations from the gestational weight mean, respectively. Children considered to be gestationally appropriate were neither SGA nor LGA (AGA). When values for gestational age or birth weight were unavailable (n = 0.3%), the study used AGA as a default. These definitions are absolutely trustworthy because they were taken directly from the nationally recognized standards for Sweden.

Children were separated into four groups for the study according to gestational age at delivery: very preterm, moderately preterm, term, and post term.

The measures used to identify the outcome and exposure variables are credible and relevant for study participants.

The study examined the presumed premise that a child's birth weight influences the likelihood that type 1 diabetes will be diagnosed in the future.

Due to potential wrong entry or missing maternal or neonatal data at delivery, collection records could not be totally accurate. It had little impact on the study, since it's randomly distributed among case and control groups.

Presentation of results

The correlation between type 1 diabetes onset in childhood and size for gestational age, among other exposure factors, was originally assessed using Pearson's $\chi 2$ test. In order to account for the influence of variable confounders in the study, logistic regression models were used afterward.

The following summarizes the findings from the study's results section and (Table 3):

- 93.8% of the children in the case and control groups were appropriate for gestational age.
- It was determined that macrosomia is a statistically significant risk factor for type 1 DM later in childhood when only considering term newborns.
- This study's unique finding was that the proportion of newborns with BW <2.5 kg who go on to acquire DM type 1 later in life increased proportionally with age at diagnosis, rising from 2% between (0 - 4) years to an upscale of 4% (15 - 18) years.
- An Odd Ratio (OR) of >1 (1.15) and a narrow 95% Confidence Interval range (all >1) show that LGA would statistically substantially raise DM type 1 later in childhood.

In contrast, an OR <1 indicates that SGA is a statistically significant factor to diminish this disease.

This was applied to both crude and adjusted OR and can be taken into consideration clinically.

- Among preterm infants, the moderate preterm group (32–36) has a higher adjusted OR of >1 for developing diabetes in childhood.
- With an OR >3, maternal diabetes is thought to be a major contributor to children's DM, however, older moms can also play a minor role.
- With an OR of 0.86, maternal smoking is expected to have a reciprocal impact on the development of type 1 diabetes.
- Overall, the statistical analysis revealed that children with type 1 diabetes were substantially more likely to be born with LGA and significantly less likely to be born with SGA than control children both before and after correcting for potential variables.

Regarding the study's critical appraisal:

Positive points:

1) Study was clearly written and easy to follow including its tables and figures.
2) Sample size was very large suggesting good power for the study but, no clear sample size and power calculation was given.
3) Baseline characteristics were described in detail for the variables included in the study.
4) The study has included all known confounders and excluded the gain in weight which seems to have no effect on other important associations such as these of LGA and SGA

Limitations

1) According to the results section, there was a significant interaction between maternal age and size for gestational age, with older women more frequently giving birth to LGA babies. Although this contact is crucial, little focus was placed on it. For instance, as a reader/clinician, I would want to know what "more often" means in terms of quantity; more often is a general statement that may or may not have clinical significance.
2) The study didn't adjust for ethnicity. Although the majority of the cohort is Swedish, this may be justified, the matter was not made clear. Ethnicity may interact with LGA and SGA, and if so, this may have an impact on the outcomes.
3) As the authors have clearly pointed out, the finding that smoking is protective is difficult to interpret. This, however, brought up more concerns about how the matching was handled.

Study discussion and conclusions:

Overall, in my opinion, thestudy's findings were logical and convincing.

The report's strengths and limitations were fully stated by the authors.

For instance, the article's high sample size and careful consideration of a variety of confounding variables made it statistically significant.

The author openly discussed some missing data, the potential for misclassification due to incorrectly entered data, and some confounder true or false interactions that could significantly impact the study's findings and their application in clinical situations.

The paper recommends additional research to confirm or rule out these potential impacts.

References

[1] David, B. Medical Statistics from Scratch: An Introduction for Health Professionals, Third Edition Published 2014 by John Wiley & Sons, Ltd. .
[2] Lindell, N.1, 2 & Bladh, M.1, 2 & Carlsson, A.3 & Josefsson, A.1, 2 &Aakesson, K.2, 4 & Samuelsson, U.2. Size for gestational age affects the risk for type 1 diabetes in children and adolescents: a Swedish national case - control study, (from Diabetology article) Received: 31 August 2020 /Accepted: 11 November 2020/ Published online: 5 February 2021

Abbreviations:
LGA: Large for gestational age
SGA: small for gestational age
AGA: Appropriate for gestational age
OR: Odds Ratio
MBR: Medical Birth Register
SWEDIABKIDS: the Swedish pediatric diabetes quality register
DM: Diabetes Mellitus, referred to type 1 in this study

Appendix
2X2 tables created for the assignment purpose to roughly measure the OR of the size for gestational age:

LGA

**	Diabetic (cases)	Non - DM (controls)	Total
LGA	434 (A)	1, 299 (B)	1, 733 (A+B)
SGA+AGA	183+8, 661 (C)	962+34, 789 (D)	44, 595 (C+D)
Total	9, 278 (A+C)	37, 050 (B+D)	46, 328 (A+B+C+D)

Odds of being born LGA if child became diabetic = A / C = 434 / 8, 844 = 0.05
Odds of being born LGA if child didn't become diabetic = B / D = 1, 299 / 35, 751 =0.04
Odds ratio = AXD / BXC = 1.35 (>>1)
LGA increases risk of DM significantly

SGA:

**	Cases: Diabetic	Controls: non - DM	Total
SGA	183 (A)	962 (B)	1, 145 (A+B)
LGA + AGA	434+8, 661 (C)	1, 299+34, 789 (D)	45, 183 (C+D)
Total	9, 278 (A+C)	37, 050 (B+D)	46, 328 (A+B+C+D)

Odds of being born SGA if child became diabetic = A / C = 183 / 9, 095 = 0.02
Odds of being born SGA if child didn't become diabetic = B / D = 962 / 36, 088 = 0.03
Odds ratio = AXD / BXC = 0.75 (<<1)
SGA reduces risk of DM significantly

AGA:

**	Cases: Diabetic	Controls: non - DM	Total
AGA	8, 661 (A)	34, 789 (B)	43, 450 (A+B)
SGA + LGA	183+434 (C)	962+1, 299 (D)	2, 878 (C+D)
Total	9, 278 (A+C)	37, 050 (B+D)	46, 328 (A+B+C+D)

Odds of being born AGA if child became diabetic = A / C = 8, 661 / 617 = 14.04
Odds of being born AGA if child didn't become diabetic = B / D = 34, 789 / 2, 261 = 15.39
Odds Ratio = AXD / BXC = 0.91 (around 1)
AGA doesn't hugely impact the development of DM later in childhood

Table 3 (copied from the original study), which is referenced in the result section to summarize the study findings.

Table 3: Logistic regression model with ORs for developing type 1 diabetes

From: Size for gestational age affects the risk for type 1 diabetes in children and adolescents: a Swedish national case–control study

Characteristic	All cases		
	Crude OR (95% CI)	Adjusted OR (95% CI) a	Adjusted OR (95% CI) b
Size for age			
AGA	Reference	Reference	Reference
SGA	0.76 (0.65, 0.90)	0.80 (0.66, 0.98)	0.76 (0.63, 0.92)
LGA	1.34 (1.20, 1.50)	1.15 (1.01, 1.31)	1.16 (1.02, 1.32)
Gestational age			
Very preterm (<32 weeks)	0.69 (0.50, 0.95)	0.70 (0.46, 1.07)	0.69 (0.47, 1.02)
Moderately preterm (32–36 weeks)	1.11 (1.01, 1.23)	1.10 (0.97, 1.24)	1.06 (0.94, 1.19)
Term (37–42 weeks)	Reference	Reference	Reference
Post term (>42 weeks)	0.87 (0.63, 1.20)	0.91 (0.62, 1.34)	0.92 (0.62, 1.35)
Maternal diabetes			
No	Reference	Reference	NA
Yes, any kind	3.51 (2.98, 4.14)	3.34 (2.77, 4.03)	NA
Maternal BMI			
Underweight (<18.5 kg/m2)	0.86 (0.74, 1.01)	0.90 (0.77, 1.05)	NA
Normal weight (18.5–24.9 kg/m2)	Reference	Reference	NA

Overweight (25.0–29.9 kg/m2)	1.09 (1.02, 1.16)	1.07 (1.00, 1.14)	NA
Obese (≥30 kg/m2)	1.26 (1.15, 1.38)	1.22 (1.11, 1.34)	NA
Maternal diabetes and BMI			
No maternal diabetes and BMI <25 kg/m2	Reference	NA	Reference
No maternal diabetes and BMI ≥25 kg/m2	1.12 (1.06, 1.19)	NA	1.12 (1.06, 1.18)
Maternal diabetes and BMI <25 kg/m2	3.79 (2.91, 4.94)	NA	3.64 (2.79, 4.74)
Maternal diabetes and BMI ≥25 kg/m2	3.60 (2.79, 4.65)	NA	3.52 (2.71, 4.55)
Maternal smoking during pregnancy			
No	Reference	Reference	Reference
Yes	0.84 (0.79, 0.90)	0.86 (0.80, 0.92)	0.86 (0.80, 0.92)
Maternal age			
13–29 years	Reference	Reference	Reference
>29 years	1.05 (1.00, 1.10)	1.04 (0.98, 1.10)	1.04 (0.99, 1.10)

1) Adjusted OR includes size for gestational age, gestational age, maternal diabetes, maternal BMI, maternal smoking habits and maternal age
2) Adjusted OR includes size for gestational age, gestational age, the combination variable of maternal diabetes and BMI, maternal smoking habits and maternal age
3) NA, not applicable