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Chikungunya during Pregnancy and Childhood Obesity: A Nationwide Population-based Longitudinal Study using Linked Registry Data in Brazil

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Additional Declarations:
There is **NO** Competing Interest.

This study used secondary, de-identified data from linked Brazilian administrative health registries within the CIDACS Birth Cohort. As the data were anonymized and collected for routine public health/administrative purposes, the requirement for individual participant/legal guardian consent was waived by the approving research ethics committee.

Title:

Chikungunya during Pregnancy and Childhood Obesity: A Nationwide Population-based Longitudinal Study using Linked Registry Data in Brazil

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Abstract (250/250 words):

Background: Childhood obesity affects one in five children globally, with metabolic risks beginning to accumulate before birth. However, the potential impact of infections during pregnancy on offspring obesity remains under-investigated. This study aimed to investigate the association between in-utero Chikungunya exposure and childhood obesity in the first five years of life.

Methods: We conducted a registry-based cohort study using data from the CIDACS Birth Cohort, Brazil. We included singleton live births from 2015–2018 to women aged 15–49 years who were followed from birth until age five. In-utero CHIK exposure was ascertained through maternal records in the notifiable disease surveillance system. The primary outcome was weight-for-length or body mass index z-score, with obesity defined as z-score ≥+3. Associations were assessed using age-specific cross-sectional analyses and linear mixed-effects (LMM) models.

Findings: 2,266 Chikungunya-exposed and 3,134,229 non-exposed children were included. Chikungunya exposure was associated with higher z-scores across all age groups, reaching 54% higher odds for obesity in the second year of life (OR 1·54, 95% CI 1·29–1·83). LMM revealed persistently higher z-scores in exposed children throughout follow-up with largest difference in z-score at first year (0·28; 95% CI: 0·18–0·38), and fifth year (0·24; 95% CI: 0·13–0·34).

Conclusions: In-utero CHIK exposure was associated with increased childhood obesity risk, suggesting that the burden of arboviral disease may extend to long-term metabolic outcomes. If causal association is confirmed in future studies, in utero exposure to

Chikungunya could represent a potentially modifiable early-life risk factor for childhood obesity.

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Key-words: Obesity, infection during pregnancy, chikungunya

Introduction (328 words)

Childhood obesity affects nearly one in five children worldwide, with 35 million children under five being overweight.[1] Evidence suggests that metabolic risk begins to accumulate before birth, with in-utero exposures, such as maternal obesity, hyperglycaemia, and smoking, associated with increased obesity risk in offspring.[2] Low-grade systemic inflammation during pregnancy has been proposed as one of the pathways linking these intrauterine exposures to later obesity potentially through mechanisms including epigenetic regulation and alteration of neural development.[2–4]

The effects of in-utero exposure to infectious diseases on offspring obesity remain poorly understood, despite biological plausibility that infection induced maternal inflammation may mediate this association.[3] Previous studies across a range of pathogens — including bacterial infections,[5,6] COVID-19,[7] seasonal influenza,[8] syphilis [9], Zika virus [10,11], malaria [12,13], and HIV [14–16] have yielded inconsistent findings, with some reporting increased adiposity or accelerated postnatal weight gain in exposed offspring and others finding no significant effect. It remains unclear whether the observed associations are pathogen-specific or reflect shared inflammatory mechanisms, and evidence for mosquito-borne arboviruses other than Zika remains scarce.

Chikungunya (CHIK) is a mosquito-borne virus that has emerged, causing large outbreaks with over 600,000 cases reported worldwide in 2024.[17] Although CHIK was considered a self-limiting infection, recent evidence indicates eight-fold increase in mortality risk among infected individuals mainly due to exacerbation of preexisting conditions such as type-2 Diabetes Mellitus (DM).[18] Also, CHIK exposure during

pregnancy is shown to affect the offspring, with studies showing an elevated risk of adverse birth outcomes.[19,20] Long-term effects of in-utero CHIK exposure have also been reported, with a recent study from our team reporting increased all-cause hospitalization during infancy,[21] and the cohort from La Réunion reporting that 60% of children exposed to in-utero CHIK had learning difficulty at age 10.[22] However, no studies to date has evaluated the metabolic and obesogenic effect of CHIK during pregnancy.

Considering that CHIK during pregnancy can induce chronic systemic inflammation and exacerbate pre-existing conditions, we hypothesized that prenatal exposure to CHIK could be associated with an increased risk of obesity in early childhood. This study aimed to investigate the association between in-utero CHIK exposure and obesity during the first five years of life.

Methods (1602)

This project is part of the Study of Early-Life Exposures During Developmental Stages (SEEDS). It has been approved by the Research Ethics Committee (CEP) of the Gonçalo Moniz Research Centre (CAAE: 71054923·8.0000·0040).[23]

Study design

This is a registry-based cohort study using routinely collected data from Brazil. Individuals were followed from birth until the last available anthropometric measurement up to five years of age or until December 31, 2021, whichever occurred first.

Data source

Data for the CIDACS Birth Cohort was obtained from linking Live Birth Information System (Sistema de Informações Sobre Nascidos Vivos, SINASC) and Unified Registry for Social Programs (Cadastro Único para Programas Sociais, CADU), and represent the poorest half of the Brazilian live births.[23] The exposure was obtained from the Information System for Notifiable Diseases (SINAN), for which clinicians who diagnosed a suspected Arbovirus case are obliged to report. The outcome was obtained from the Food and Nutrition Surveillance System (SISVAN), which covers the child growth monitoring data for 45% of public health service users.[24] Details on the databases and the linkage process are explained in Supplementary Methods 1.

Study population

Eligible children were singletons live-born between January 1, 2015, and December 31, 2018, at ≥20 weeks of gestation with a birth weight ≥500g, to women aged 15 to 49 years and with at least one valid anthropometric measurement recorded in SISVAN. We excluded births with missing information on gestational age at birth or gestational age ≥42 weeks, births weight >6000g; documented in utero exposure to ZIK or DEN; and records with inconsistent CHIK infection data (details given in the exposure section).

Exposures

Exposed cases were defined as births to mothers with a confirmed CHIK notification in SINAN, with symptom onset occurring between the estimated date of conception and up to two days after delivery. The date of conception was calculated by subtracting gestational age at birth (in weeks) from the date of birth recorded in SINASC.

Individuals with a CHIK registry that the epidemiological surveillance concluded as inconclusive or ruled out, or that epidemiological surveillance was not recorded, were excluded from the study population. For individuals with more than one confirmed CHIK notification during the same pregnancy, the interval between the first and last registries was calculated. Multiple records within 30 days were considered the same infection episode, and the earliest record was used for analysis. If the interval exceeded 30 days, the individual was excluded due to uncertainty regarding the validity and timing of the infection, for CHIK infection confers lifelong immunity. Individuals with a symptom onset prior to January 2015 were excluded, for uncertainty of CHIK diagnosis accuracy before its outbreak in 2015.

Outcome

Our primary outcome was childhood obesity until age five. Standardized anthropometric indicators were calculated according to the World Health Organization (WHO) Child Growth Standards, 2006.[25] We defined obesity Z-score as a composite outcome that used weight-for-length z-scores (WLZ) for children below 24 months, and body mass index–for-age z-scores (BAZ) for children 24 months or older. The obesity Z-scores were analysed as both a continuous score and as a binary outcome, with obesity defined as Z-score≥+3.[25] Age at each visit was calculated by subtracting the date of anthropometric measurement in SISVAN from the date of birth in SINASC. Measurements obtained up to 2 days after the 5th birthday were included as a measure pertaining to the fifth year. For children born preterm (<37 weeks) and assessed before 24 months of age, corrected age was applied in accordance with WHO guidelines.[25]

SISVAN records were excluded for any of the following reasons: a date of birth inconsistent with that recorded in SINASC (0·37% of the records); the measurement date preceding the recorded birth date; or a negative corrected age at assessment (applicable only to children born preterm and <24 months). In addition, records with biologically implausible anthropometric values (Z-scores <–5 or >+5 for WLZ and BAZ; <–6 or >+6 for length-for-age; and <–6 or >+5 for weight-for-age) were excluded according to WHO standards.[25]

To minimize missing data and enhance the precision of multiple imputations, we defined one-year age intervals between measurements and selected one measurement per annualized age (age in months 0-11, 12-23, 24-35, 36-47, and 48-60). When multiple records existed for the age range, the measurement nearest to 6, 18, 30, 42, and 54 months were used (Supplementary Table 1 and 2).

Covariates

From a Directed Acyclic Graph (Supplementary Figure 1), we identified the following as confounders: Maternal education (none, 1-3, 4-7, 8-11, and 12 or more years), self-reported maternal race/skin colour as defined by the Brazilian Institute of Geography and Statistics (White, Black, Parda, Indigenous, and Asian descendants),[26] maternal age (15-19, 20-34, and 35-49 years old), region (North, Northeast, Southeast, Centre-east, and South) and urbanicity (urban or rural) of residence, and the month and the year of conception. The adequacy of the number of antenatal care visits (ANC), as a proxy for healthcare access, was calculated based on Ministry of Health recommendation for each gestational age (adequate for gestational age, one visit fewer than recommended, and fewer by two or more visits).[27]

In the analyses, the education level categories of none and 1-3 years, and the non-White race categories, were collapsed into a single category to avoid data sparsity. We hypothesized household income to be a confounder, and gestational complications (diabetes and obesity) to be effect modifiers, but the data was not available.

Statistical analysis

Missing data

We examined the distribution of anthropometric data in SISVAN to assess potential bias arising from missing not at random (MNAR)[28] (Supplementary Table 3). Recognizing that analytical strategies under MNAR may yield biased estimates, we triangulated our findings using two complementary approaches explained below (cross-sectional and LMM) with distinct assumptions and sources of bias. Also, we performed the two analyses using both complete case analyses (CCA) and multiple imputation by chained equations (MICE) to handle missing observations, with the results using MICE reported as the main analyses.

For the MICE imputation, we imputed missing annualized Z-scores based on baseline covariates and Z-scores observed in other age ranges. Imputation was performed separately for the exposed and unexposed groups (m=5, maxit=5).[29] Model convergence was assessed visually across iterations, and the distributions of observed and imputed Z-scores were compared to ensure plausibility. Imputed Z-scores beyond a child's last observed visit were excluded. Estimates and standard errors from the imputed datasets were combined using Rubin's rules, which account for both within- and between-

imputation variability to generate overall point estimates and standard errors.[28] Further details on the handling of missing data are provided in Supplementary Method 2.

In addition, using the MICE dataset, we further assessed the robustness of our findings by checking whether the results remain consistent under MNAR assumption.[30] Fixed constants (δ=±0·05, ±0·20, ±0·50, ±1·0) were added to all imputed Z-scores to simulate scenarios in which children without measurements were systematically more or less obese than those with measurements. We then re-calculated the LMM model under these assumptions.

Descriptive statistics

Basic demographic characteristics and the number of anthropometric measurements were presented for the exposed and non-exposed groups, and standardized mean differences (SMD) were calculated.

Cross-sectional models

We conducted age-specific cross-sectional analyses to estimate, at each annualized age, the association between in-utero CHIK exposure and (i) odds of obesity, or (ii) mean difference in z-scores. Measurements for each age range were treated as independent cross-sectional datasets, and a logistic regression with obesity as the outcome (i) and a linear regression with Z-score as the outcome (ii) were fitted, with the covariates as defined above. To account for potential correlation of outcomes within regions, robust sandwich variance estimators clustered at the region level were used to estimate standard errors.

Linear mixed effects models (longitudinal models)

To model obesity Z-score trajectories over time, we fit linear mixed-effects models (LMMs), specifying random intercepts for each child and including annualized age at visit as a 5-level factor. We also plotted predicted Z-score trajectories by exposure status using this model, conditioning on the most frequent covariate pattern (non-white, 20-34 years old mother with 8-11 years of education, in an urban area with adequate antenatal care visits, and conception in June 2015).

Sensitivity analyses

Sensitivity analyses were conducted to assess the robustness of our findings, listed in Supplementary Methods 3.

For both LMM and cross-sectional approaches, we performed: (i) CCA restricted to individuals with complete baseline information and anthropometric measurements at all five annualized intervals; and (ii) analysis including individuals with complete baseline information who had at least one anthropometric measurement, without requiring complete follow-up. For the cross-sectional analyses only, we conducted: (iii) analysis using imputed baseline covariates while restricting outcome measures to observed annualized Z-scores. For the LMM analysis only, we further performed: (iv) CCA including all individuals with complete baseline covariates and using all available Z-scores rather than annualized values, fitted with a linear mixed-effects model (lmer) which allows irregular measurement spacing.

We also conducted (v) sex-stratified LMM analyses using the MICE dataset, based on previous animal studies showing that the effect of in-utero inflammation may differ by sex.[31] Here, sex assigned at birth by a clinician, recorded in SINASC, was used. Further, to assess potential bias by the regional difference in CHIK exposure, we ran LMM analyses (vi) excluding non-exposed individuals from municipalities with no CHIK cases, and (vii) stratified by urbanicity of residence.

All analyses are reported based on the RECORD statement (Supplementary Table 4). Analyses were performed in R (versions 4·2.1 and 4·4.1) using the packages mice, miceadds, mitml, lme4, lmtest, geepack, and splines.

Role of the funding source

The study's funders had no role in the design, data collection, data analysis, data interpretation, or writing of the report.

Results (586)

Study population and baseline characteristics

Between 2015 and 2018, there were a total of 5,795,263 live births in the CIDACS Birth Cohort. Of these births, 3,462,371 (59·7%) had at least one valid anthropometric measurement. Children with available anthropometric record, compared with those in the CIDACS birth cohort without such records, were more likely to have younger, non-White mothers with lower educational attainment and residing in rural areas (Supplementary Table 5). After applying the exclusion criteria, the study population comprised 2,266 CHIK-

exposed (1,066 laboratory confirmed) and 3,134,229 non-exposed individuals (Figure 1), Overall, 7·44% (N=233,600) had anthropometric measurements at all annualized intervals (Supplementary Table 6). Characteristics of the exposed and the unexposed children are summarized in Table 1. Compared with unexposed infants, exposed infants were more likely to have Black/Parda mothers (70·5% versus 81·3%, SMD=0·52), have adequate number of ANC (84·3% versus 76·8%, SMD=0·19), and live in an urban area (76·8% versus 70·6%, SMD=0·16).

The median follow-up time was similar between groups (41·0 [23·2] months for the exposed and 41·8 [23·2] months for the non-exposed). The percentage of children who were obese at least once during the study period was higher in the exposed group (19·7% versus 15·3%, SMD=0·12). The crude mean Z-scores were higher for the exposed group at all ages and peaked at the second year for both groups (0·81 [1·57] and 0·64 [1·45]) (Supplementary Table 7).

Cross-sectional analyses for age groups

Adjusted mean Z-scores were significantly higher in the exposed group at all age beyond the first year, with a difference of 0·23 (95%CI: 0·12–0·34) by the fifth year. Consistently, the odds of obesity were higher among exposed children, with 54% greater odds in the second year compared to non-exposed (95%CI: 1·29-1·83) (Figure 2).

Linear mixed models

The predicted Z-scores were in adequate range (±1 Z-score) for both exposed and non-exposed, but the curve of the exposed group was above that of the non-exposed by more than 0·1 Z-score. The largest difference was observed in the first year, with 0·28 [0·18–

0·38] Z-score difference. The difference diminished slightly between the second and third years, and the exposed group underwent a steeper increase in Z-score after the fourth year (Figure 3, the plots for the observed Z-score shown in Supplementary Figure 2).

Simulations of MNAR scenarios with delta adjustment

Even under the most extreme scenario, where all unobserved z-scores were assumed to be systematically 1·0 unit lower than those predicted under the Missing At Random (MAR) assumption, the estimated difference in z-scores by CHIK exposure remained statistically significant for most age groups (Figure 4).

Sensitivity analyses

The results for the sensitivity analyses are shown in Supplementary Figure 3 and 4. For both cross-sectional and LMM, analyses (i) using only individuals with complete baseline covariates and observed Z-score at all annualized intervals yielded statistically non-significant results. The analyses (ii) and (iii), which were analyses using all observed annualized Z-scores without requiring complete follow-up, yielded results like the main analyses with a larger confidence interval. The analyses (iv), which used all Z-score measures without annualizing yielded an unstable and therefore more uncertain model, likely due to the highly irregular timing and unequal number of observations across children. In the sex-stratified analyses (v), the Z-score trajectories were not different between males and females. The analyses excluding non-exposed from areas without CHIK cases (vi) was consistent with the main analyses. For the analyses stratified by urbanicity (vii), the effect of CHIK was similar in both strata but the confidence interval crossed null in the rural stratum (Supplementary Figures 5-7).

Discussion (1115)

In this nationwide cohort study, in-utero CHIK exposure was associated with an increased risk of obesity, reaching 54% higher odds in the second year of life and 41% at the fourth. CHIK-exposed infants had Z-scores 0·13 to 0·28 scores higher than the non-exposed after adjustment for confounders. These associations were robust across multiple sensitivity analyses and remained consistent under various MNAR scenarios.

Previous studies across multiple pathogens, including bacterial infections [6,32], seasonal influenza [8], SARS-CoV-2 [7,33], malaria [12,13], and syphilis [9], have reported trends toward increased adiposity among in-utero exposed offspring, potentially hinting at a shared obesogenic effect of in-utero infections. However, effect sizes are modest, study designs and settings vary widely, and causal conclusions cannot be drawn. HIV is the most studied pathogen in this context, yet findings remain widely inconsistent. Prospective cohorts in sub-Saharan Africa, where undernutrition is endemic, consistently report lower weight and length among HIV-exposed uninfected children [15,16], while studies from the United States and Europe report higher BMI in HIV-exposed uninfected adolescence [14,34]. For Zika virus, which is virologically closest to CHIK among previously reported pathogens, one cohort found that despite modest anthropometric differences, exposed children had altered lipid profiles strongly associated with BMI-for-age [11], hinting potential adipose effects beyond the well-known teratogenicity of Zika. Adding up to these prior studies, our findings suggest that CHIK infection during pregnancy may increase the risk of offspring obesity. Nevertheless, further research incorporating clinical and immunological data such as biomarkers of infection and inflammatory cytokines are needed to triangulate the

finding from our epidemiological data. In addition, studies exploring a broader range of pathogens are warranted to better understand the overall effects of in-utero infections on child obesity and the underlying mechanisms involved.

We hypothesize that several biological mechanisms may explain the observed obesogenic effect of in-utero CHIK exposure. First, CHIK infection in adults is known to exacerbate preexisting Type 2 DM.[18] It is possible that CHIK infection during pregnancy exacerbates gestational diabetes, which is a known cause for offspring obesity.[2] The larger percentage of newborns with macrosomia among the exposed group supports this pathway. Second, corticosteroid self-medication among CHIK patients may partially explain this association. A Brazilian study reports self-medicated analgesics use in 65% of CHIK patients, including corticosteroids.[35] Corticosteroid during pregnancy is known to increase offspring obesity,[36] and our study design could not disentangle the effect of medication from that of CHIK infection. Third, learning difficulties among CHIK-exposed infants may partially explain the association. A study from La Reunion cohort reports that 57% of children exposed to in-utero CHIK experienced learning difficulties.[22] Children with learning difficulty is shown to have higher obesity prevalence,[37] but the causal direction is unclear. Fourth, maternal immune activation (MIA) could mediate the association. CHIK infection can cause a rheumatoid arthritis-like chronic cartilage inflammation.[38] Studies on obesity have shown that maternal obesity during gestation may influence offspring obesity through chronic inflammation in the adipose tissues.[3] It is possible that despite different inflammatory mechanisms, the chronic inflammatory state from CHIK similarly affects the foetus metabolic system, leading to offspring obesity.

Further research is needed to establish a causality, including clinical and laboratory studies to elucidate underlying mechanisms. If confirmed, a causal link between in-utero CHIK infection and childhood obesity would have important global health implications, as this represents a potentially modifiable early-life risk factor. This is particularly relevant as Arboviruses, including CHIK, continue to expand into new regions, a process aggravated by climate change. In such a scenario, integrated prevention efforts across sectors, including public health, urban planning, environmental management, and vector control, may reduce both infection risk and downstream metabolic consequences.

This study has several strengths. First, it leverages a large nationwide Birth Cohort, including more than 3·3 million children and over 2,000 with in-utero CHIK exposure, providing substantial statistical power. Second, the longitudinal follow-up with repeated anthropometric measurements enabled the assessment of growth trajectories rather than relying on single time-point outcomes. Finally, triangulation of results across multiple analytical approaches designed to address informative missingness demonstrated consistency, supporting the robustness of the observed associations.

This study has several limitations. First, selection bias of anthropometric measurements in SISVAN remains a limitation despite multiple analytical approaches to overcome the differential follow-up. If this pattern varied by exposure status, estimates could be biased in either direction. Although delta adjustments suggested robustness to substantial MNAR departures, residual selection bias may persist. Second, CHIK diagnosis relied on passive surveillance, and pregnant women may not have sought care if asymptomatic or faced access barriers. Additionally, arbovirus diagnoses are typically clinical and subject to misclassification. Although we included only CHIK cases confirmed in the epidemiological

surveillance and excluded those with DEN or ZIK diagnoses, the risk of clinical misdiagnosis persists, and asymptomatic or undiagnosed CHIK infections would remain in the unexposed group. Such exposure misclassification would most likely bias our estimates toward the null. Third, we lacked data on pregnancy complications, especially gestational diabetes and excessive weight gain during gestation, which could be an effect modifier. Individuals with obesity or with T2 DM are known to have higher risk of severe and chronic CHIK infection,[39,40] and both obesity and diabetes during pregnancy are known to be associated with offspring obesity.[2–4] Thus, pregnancy complications such as gestational obesity and diabetes may be effect modifiers, with the obesogenic effect of CHIK infection being especially strong in those with preexisting conditions. However, we could not evaluate this effect modification in our study. Fourth, we lacked data on some relevant confounders such as family income, which may have resulted in residual confounding. Fifth, we did not have information on infections by other pathogens known to affect the foetus such as CMV and Toxoplasmosis. If these infections occurred at similar rates across exposure groups, they would likely attenuate estimates towards null.

In summary, our findings suggest that in-utero CHIK is associated with an increased risk of childhood obesity. These results support the broader concept that maternal infection during pregnancy may have lasting metabolic consequences for offspring, extending the recognized burden of CHIK during gestation beyond acute and neurodevelopmental outcomes. As CHIK burden continues to expand globally, consideration of long-term metabolic health may be important for assessing the life-course burden of early-life infections.

Data sharing statement

Raw data are available upon reasonable request to the Centro de Integração de Dados e Conhecimentos para a Saúde (CIDACS). Any person who wishes to receive authorisation must be affiliated to CIDACS or be accepted as collaborators, and present a detailed research project together with approval by an appropriate Brazilian institutional research ethics committee. For more information: https://cidacs.bahia.fiocruz.br/

Contributors

MK, OC, and EP conceptualized and designed the study. MK and OC conducted the statistical analyses. MK and EP wrote the manuscript. TCS, HBS, CSV, JFMS, VB, MGT, RS, and MB contributed to interpretation of findings and critically revised the manuscript for important intellectual content. EP, MB, RS, and MGT were responsible investigators in the construction of the CIDACS Birth Cohort. MK, EP, TCS, OC, and HBS had full access to all data in the study and verified the underlying data. All authors reviewed and approved the final version of the manuscript.

Declaration of interests

The authors declared no conflicts of interest.

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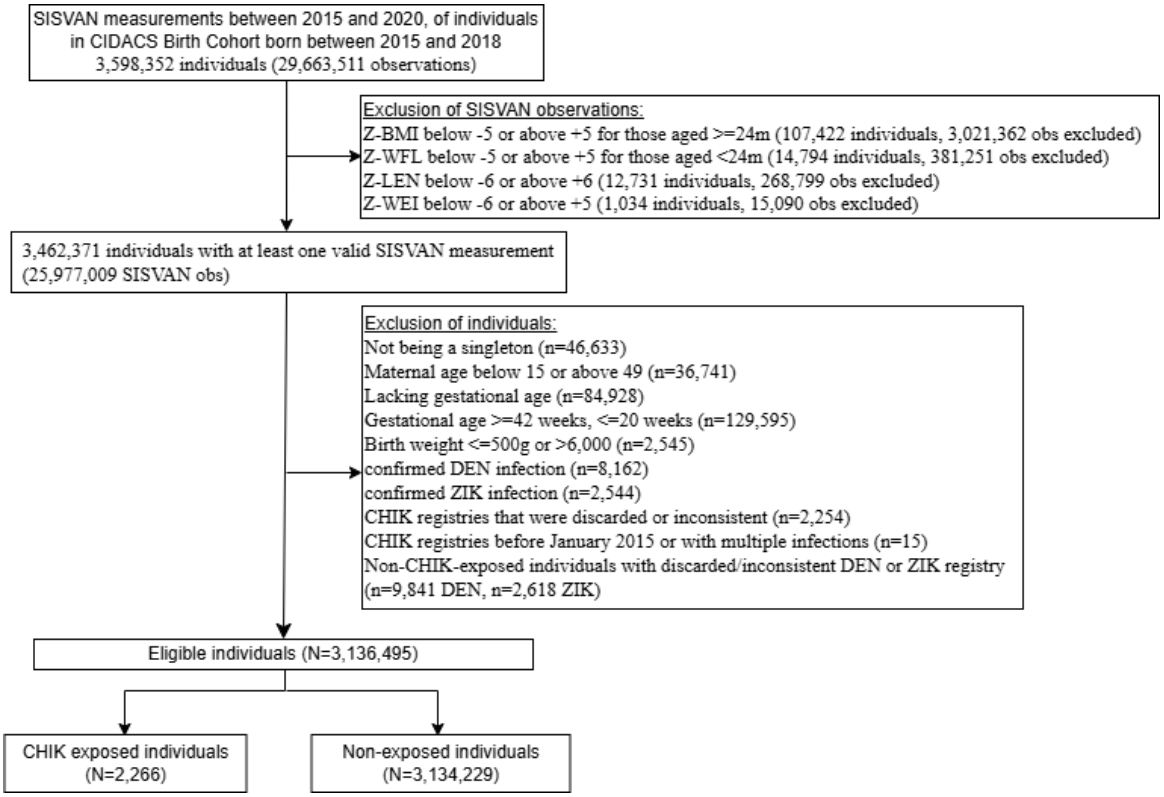
519 Table 1: Basic demographics of the population in the study.

		CHIK exposure status		
	Overall (N=3,136,495)	Non-exposed (N=3,134,229)	Exposed (N=2,266)	SMD
Sex				
Female	1532031 (48·8)	1530952 (48·8)	1079 (47·6)	0·0246
Male	1604464 (51·2)	1603277 (51·2)	1187 (52·4)	0·0246
Birth weight				
501-1000g	4383 (0·1)	4380 (0·1)	3 (0·1)	0·002
1001-1500g	14674 (0·5)	14663 (0·5)	11 (0·5)	0·0026
1501-2500g	200965 (6·4)	200834 (6·4)	131 (5·8)	0·0262
2501-4000g	2750234 (87·7)	2748255 (87·7)	1979 (87·3)	0·0106
4001-6000g	165305 (5·3)	165163 (5·3)	142 (6·3)	0·0428
Missing	934 (0·0)	934 (0·0)	0 (0·0)	0·0244
Mean (SD)	3224·78 (512·77)	3224·76 (512·77)	3251·61 (519·83)	0·052
Gestational weeks				
20-27wks	6589 (0·2)	6587 (0·2)	2 (0·1)	0·0316
28-31wks	25235 (0·8)	25213 (0·8)	22 (1·0)	0·0177
32-36wks	289511 (9·2)	289328 (9·2)	183 (8·1)	0·0411
37-41wks	2815160 (89·8)	2813101 (89·8)	2059 (90·9)	0·0376
Mean (SD)	38·60 (1·94)	38·60 (1·94)	38·70 (1·89)	0·0522
Marital status				
Divorced	28706 (0·9)	28694 (0·9)	12 (0·5)	0·0456
Married	585072 (18·7)	584655 (18·7)	417 (18·4)	0·0065
Single	1561904 (49·8)	1560850 (49·8)	1054 (46·5)	0·0658
Union	915273 (29·2)	914539 (29·2)	734 (32·4)	0·0696
Widowed	4471 (0·1)	4468 (0·1)	3 (0·1)	0·0027
Missing	41069 (1·3)	41023 (1·3)	46 (2·0)	0·0563
Maternal education				
None	20578 (0·7)	20560 (0·7)	18 (0·8)	0·0163
1-3 years	113767 (3·6)	113672 (3·6)	95 (4·2)	0·0292
4-7 years	762421 (24·3)	761903 (24·3)	518 (22·9)	0·0341
8-11 years	2034159 (64·9)	2032699 (64·9)	1460 (64·4)	0·0089
12 or more years	152814 (4·9)	152710 (4·9)	104 (4·6)	0·0133
Missing	52756 (1·7)	52685 (1·7)	71 (3·1)	0·0949

Maternal race				
Asian	7980 (0·3)	7977 (0·3)	3 (0·1)	0·0278
Black	187909 (6·0)	187845 (6·0)	64 (2·8)	0·1548
Indigenous	32089 (1·0)	32080 (1·0)	9 (0·4)	0·0746
Mixed	2024150 (64·5)	2022371 (64·5)	1779 (78·5)	0·3136
White	738954 (23·6)	738774 (23·6)	180 (7·9)	0·4391
Missing	145413 (4·6)	145182 (4·6)	231 (10·2)	0·2135
Maternal age				
15 to 19	693572 (22·1)	693134 (22·1)	438 (19·3)	0·0688
20 to 34	2140071 (68·2)	2138496 (68·2)	1575 (69·5)	0·0275
35 to 49	302846 (9·7)	302593 (9·7)	253 (11·2)	0·0495
NA	6 (0·0)	6 (0·0)	0 (0·0)	0·002
Mean (SD)	25·11 (6·41)	25·11 (6·41)	25·87 (6·55)	0·118
Number of ANC				
Adequate	2410247 (76·8)	2408337 (76·8)	1910 (84·3)	0·1891
One visit fewer than recommended	262556 (8·4)	262421 (8·4)	135 (6·0)	0·0937
Few than recommendation by more than two	395022 (12·6)	394836 (12·6)	186 (8·2)	0·1441
Missing	68670 (2·2)	68635 (2·2)	35 (1·5)	0·0477
Previous gestations				
None	975192 (31·1)	974501 (31·1)	691 (30·5)	0·013
1 or 2	1442292 (46·0)	1441257 (46·0)	1035 (45·7)	0·0062
3 or more	548232 (17·5)	547842 (17·5)	390 (17·2)	0·0071
Missing	170779 (5·4)	170629 (5·4)	150 (6·6)	0·0494
Urbanicity of residence				
Rural	836822 (26·7)	836371 (26·7)	451 (19·9)	0·161
Urban	2213458 (70·6)	2211718 (70·6)	1740 (76·8)	0·1416
Missing	86215 (2·7)	86140 (2·7)	75 (3·3)	0·0328
Year of conception				
2014	806371 (25·7)	806339 (25·7)	32 (1·4)	0·7595
2015	820050 (26·1)	819199 (26·1)	851 (37·6)	0·2469
2016	710059 (22·6)	709203 (22·6)	856 (37·8)	0·3345
2017	657824 (21·0)	657341 (21·0)	483 (21·3)	0·0084
2018	142191 (4·5)	142147 (4·5)	44 (1·9)	0·1469
Outcomes				
Ever-overweight	1091528 (34·8)	1090603 (34·8)	925 (40·8)	0·1245
Ever-obese	480979 (15·3)	480533 (15·3)	446 (19·7)	0·1147

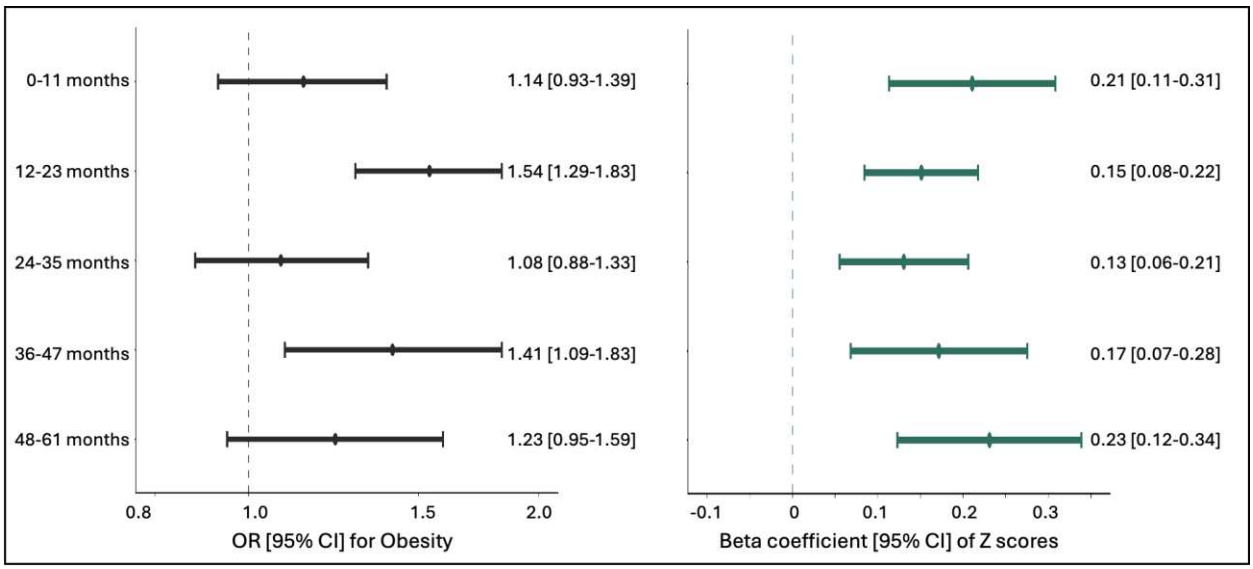
Footnote: * Outcomes of Ever-obese and ever-overweight are defined as individuals who had at least one anthropometric observation during the study period that was overweight (Z-score >+2) or obese (Z-score >+3). Abbreviations: CHIK, Chikungunya; SD, standard deviation; SMD, standard mean difference.

Figure 1: Inclusion flowchart of the participants.



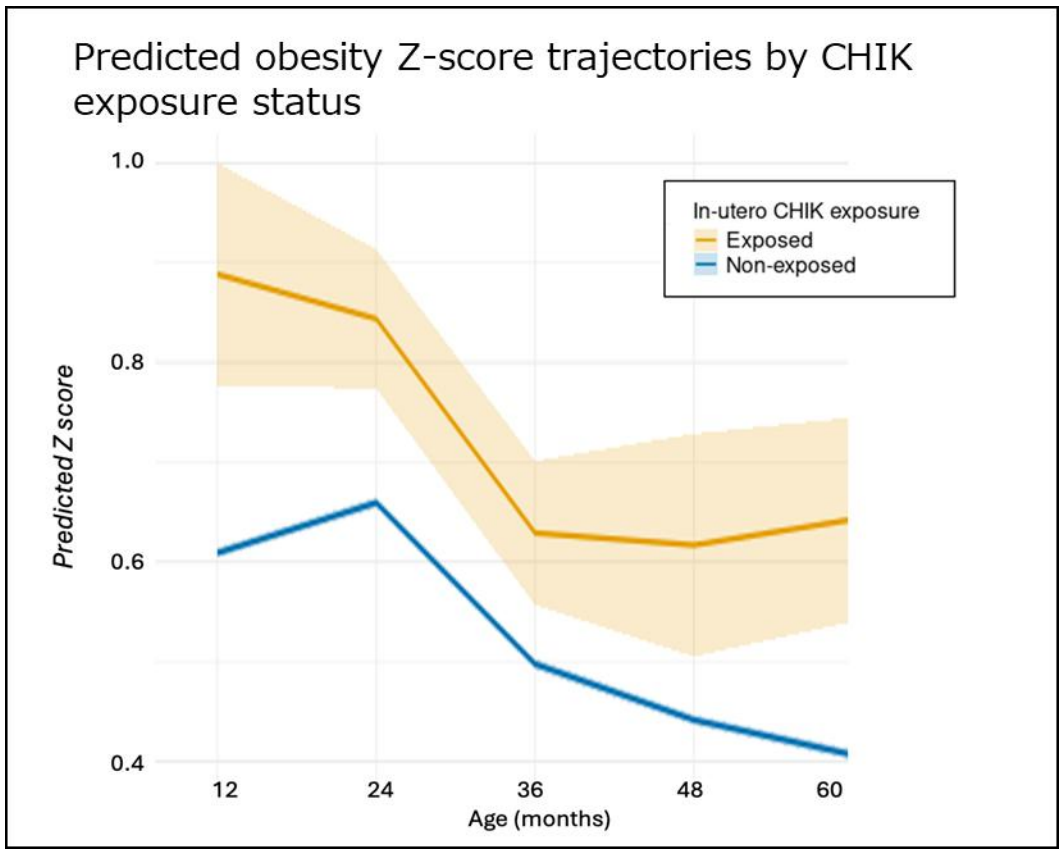
Footnotes: SISVAN registries with negative corrected age at visit (N=96,029) and those with mismatches in the date of birth in SISVAN and SINASC (N=160,191) are excluded merging with the Birth Cohort. Abbreviations: CADU, Cadastro Único para Programas Sociais (Brazilian national registry for social programs); CHIK, Chikungunya; DEN, dengue; obs, observations; SINASC, Sistema de Informações sobre Nascidos Vivos (Brazilian Live Birth Information System); SISVAN, Sistema de Vigilância Alimentar e Nutricional (Brazilian Food and Nutrition Surveillance System); ZIK, Zika.

Figure 2: OR and beta coefficient for the cross-sectional design



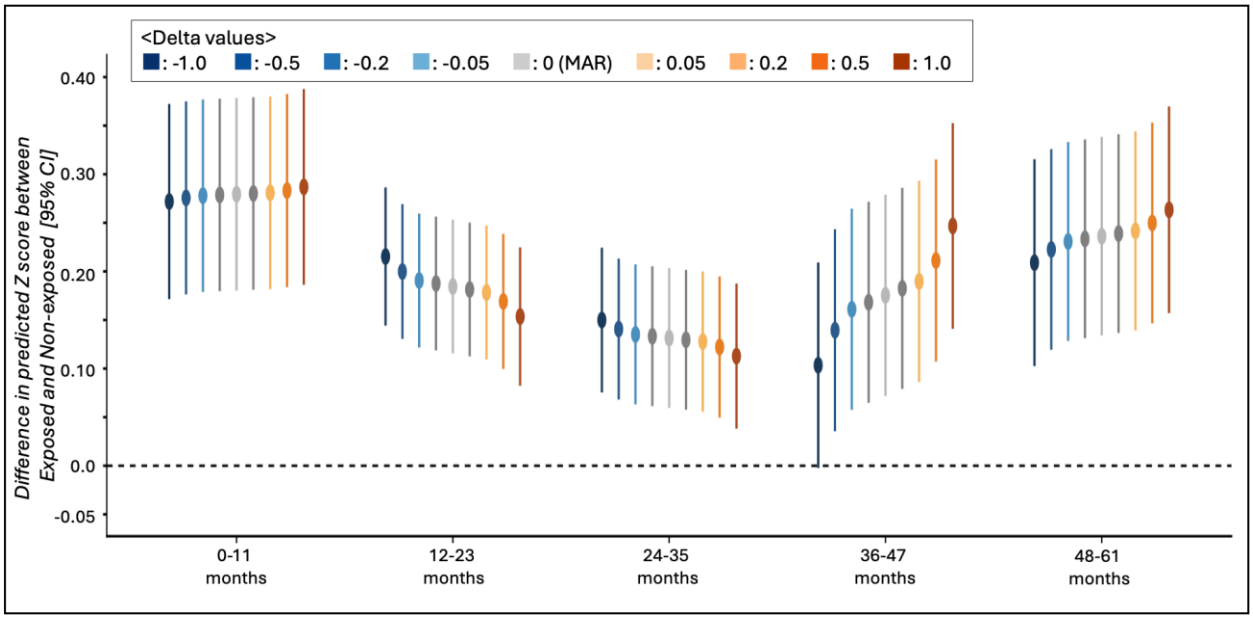
Abbreviations: CI, confidence intervals; OR, odds ratio.

Figure 3: Predicted conditional z-score trajectories by CHIK exposure



Footnote: the Z-score is a predicted conditional effect for the most common confounder combination (non-white, 20 to 34 years old mother with 8-11 years of education, in an urban area with adequate antenatal care visits, with conception date in June 2015).

Figure 4: departure from MAR for LMM model



Abbreviations: CI, confidence intervals; MAR, missing at random.

Supplementary Files

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