1   **The association between caesarean section delivery and later life obesity in**

2   **21-24 year olds in an Urban South African birth cohort**

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Abstract

Background: Obesity is an important public health problem and rates have reached epidemic proportions in many countries. Studies have explored the association between infants delivered by caesarean section and their later life risk of obesity, in many countries outside Africa. As a result of the increasing caesarean section and obesity rates in South Africa, we investigated the association in this country.

Methods: This was a retrospective analysis of data that were collected from a prospective South African birth cohort (Birth to Twenty Plus), established in 1990. A total of 889 young adults aged 21-24 years were included in the analysis. Multiple logistic regression models were fitted to assess the association between mode of delivery and early adulthood obesity.

Results: Of the 889 young adults, 106 (11.9%) were obese while 72 (8.1%) were delivered by CS; of which 14 (19.4%) were obese. Caesarean section delivery was significantly associated with obesity in young adults after adjusting for potential confounders like gestational age (at delivery), birth weight, sex, maternal age, parity and education (OR 1.99, 95% CI 1.00–3.94, p=0.049).

Conclusion: The association of caesarean section with early adulthood obesity should be interpreted with caution because data on certain key confounding factors such as mothers' pre-pregnancy body mass index and gestational diabetes were not available. Further research from Africa, with larger sample sizes and databases with useful linking of maternal and infant data, should be conducted.

Introduction

Obesity is an important public health problem and rates have reached epidemic proportions in many countries - one in every five young people was estimated to be obese in 2012 in high and middle income countries [1]. Globally, 39% and 13% of individuals aged 18 years and older were overweight and obese, respectively, in 2016 [2]. In South Africa, the rates of overweight or obesity in 2016 were higher among women (61% in women and 31% in men) [3]. Obesity has been associated with adverse health outcomes such as type 2 diabetes, cardiovascular disease cancer, and premature mortality, in both adults and children [4–8] . Diet (high energy foods), physical inactivity, birth weight, genetics, and parity are commonly explored risk factors of obesity [9–11]. Mode of delivery at birth has also been suggested to be associated with obesity in later life.

Due to the rising rates of obesity, any hypothesized risk factor, such as caesarean section (CS) as a mode of child delivery, is worth exploring. Acknowledging that CSs are sometimes performed to prevent birth complications, biased motives have been identified [12,13] and the use of the procedure is increasing globally [14]. As many as one in three births was reported to be by CS in high-income countries such as the United States of America (USA) in 2017 [15]. The rates of CS in South Africa in 2014, reported in the 2016 South African Health Review, were estimated to be 70.8% in the private health sector, and 24.7% in the public health sector (as reported by the District Health Information System (DHIS) which uses routinely collected health information to manage health services) [16]. An underlying mechanism for the proposed association between CS and later life obesity is the reported limited microbial diversity of offspring delivered by CS [17,18]. This is presumed to persist to adulthood [19].

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75   A number of studies have explored the association between CS and later life obesity. Three

76   systematic reviews and meta-analyses reported increased pooled effect size estimates in young

77   adults (YAs) delivered by CS (such individuals were more likely to be obese) [20–22]. Five

78   additional studies reported similar findings [19,23–26]. However, some studies did not find

79   significant associations, leading to inconsistent findings [27,28]. All previous studies have been

80   conducted in countries outside Africa [19,23–35] and, to our knowledge, nothing is known in

81   the African context. The aim of the study reported in this paper was to investigate the

82   association between CS delivery and early adulthood obesity among singletons in an ongoing

83   longitudinal birth cohort (Birth to Twenty Plus – Bt20+) with more than two decades of follow-

84   up in an urban region in South Africa [36].

85

86   **Methods**

87   *Study design and setting*

88   This was a retrospective analysis of data that were collected from a prospective cohort study

89   established in 1990. Birth to Twenty Plus (formerly Birth to Ten) is an ongoing prospective

90   South African birth cohort established in Soweto, Johannesburg, Gauteng in 1990 [36]. The

91   cohort comprises 3 273 singleton children of mothers who were recruited from antenatal clinics

92   and had an expected delivery date from 23 April to 8 June 1990. Consent to participate in the

93   study was provided by the mothers at enrolment; all subsequent data were also collected with

94   signed consent. Participants have been followed up through administered questionnaires,

95   contact with parents or caregivers, telephone calls, and field visits. Further information on the

96   cohort has been published elsewhere [36,37].

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100   *Exposure and outcome variables*

101   Information on mode of delivery was copied by the investigators of the Bt20+ cohort from the

102   official birth notification forms compiled at the local authority. Information on CS and vaginal

103   deliveries, i.e. normal (NVD) and assisted (AVD - forceps and vacuum) was available for this

104   study. A digital scale and wall mounted stadiometer were used to measure weight and standing

105   height, to the nearest 0.1 kg and 0.1 cm, respectively. These measurements were taken by

106   trained research personnel. Body Mass Index (BMI) was calculated using the formula

107   weight/height^2 (kg/m^2). We defined obesity (BMI $\geq$30 kg/m^2), as per the World Health

108   Organization (WHO) [38].

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110   The two sample proportion test was used to compute the power of the study, i.e. to check if the

111   study was adequately powered to answer the research question. Proportions of obese

112   participants were computed for each mode of delivery with 95% confidence intervals (CIs) and

113   80% power.

114

115   *Potential confounders*

116   We reviewed published literature on factors associated with obesity and mode of delivery, and

117   identified variables of interest from similar studies. Young adults' characteristics included

118   gestational age (at delivery), sex, ethnicity, age, education, alcohol consumption, cigarette

119   smoking, birth weight (low (<2.5 kg), normal (2.5-4.0 kg), macrosomic (>4 kg)), and

120   breastfeeding duration. Mothers' characteristics included parity, age at delivery, and education.

121   We generated infants' birth weight corrected for gestational age and sex (in centiles) by using

122   the INTERGROWTH-21st calculator to compare these variables with an international standard

123   [39]. Participant's age was calculated as the difference between date of birth and date of data

124   collection.

125 *Statistical analysis*

126 To examine if the study participants were different from those in the primary cohort, socio-

127 demographic characteristics were compared with those in the primary cohort. Using the

128 Kruskal-Wallis test, Pearson's Chi-square test, and Fisher's exact test, where appropriate, we

129 assessed the differences in participants' characteristics (early life, young adult and maternal)

130 across the modes of delivery and BMI categories, and compared the sex-stratified prevalence

131 of obesity for each mode of delivery. Regarding missing values, our study's covariates had less

132 than 10% missing values and additional 'unknown' categories were created for those covariates

133 with missing observations. Schafer *et al.* (1999) and Bennett *et al.* (2001) suggested that less

134 than 10% missing values in covariates is less likely to result in bias [40,41].

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136 To evaluate the association between CS and early adulthood obesity, we calculated the odds

137 ratio (OR) and 95% CIs, using logistic regression models. Young adults' sex and birth weight

138 in kg, mothers' parity, and education at YA's birth were included in the adjusted models.

139 Furthermore, we conducted a post-estimation (Wald) test to investigate the differences between

140 obesity rates across sex and birth weight categories (heterogeneity). This was done by

141 introducing cross product (interaction) terms between mode of delivery and YAs' sex or birth

142 weight in the final adjusted model. Sex and birth weight stratified models were then computed.

143 Additional analysis included NVD and AVD, combined, as the comparison group.

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145 Although lifestyle and behavioural characteristics, such as YAs' diet, physical activity,

146 smoking habits, and alcohol consumption, have been associated with obesity, it has been

147 suggested that they are not true confounders in the analysis of the association between mode

148 of delivery and later life obesity [19]. Nevertheless, to address the possibility of residual

149 confounding, these characteristics were adjusted for in the sensitivity analysis. Similarly,

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150   models adjusting exclusively for early life factors were computed. We also adjusted for YAs'

151   birth weight as a continuous covariate, and YA's breastfeeding duration at infancy, mother's

152   parity and mother's age at delivery as categorical covariates, in subsequent analyses. P values

153   <0.05 were considered statistically significant. All analyses were conducted using Stata® IC

154   14 (StataCorp LP College Station, TX).

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156   *Ethical considerations*

157   Prior to analysing the data, we obtained ethical approval from the Human Research Ethics

158   Committee of the University of the Witwatersrand (clearance certificate number M161184).

159   Anonymised data were received from the gatekeeper of the primary study and a data sharing

160   agreement was signed to ensure confidentiality and to limit access to the data.

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162   **Results**

163   The study participants comprised 889 21-24 year old YAs after excluding those in the primary

164   cohort with missing data; one cohort member was excluded for being older than 24 (Figure 1).

165   Of the final analytic sample, 72 (8.1%) were delivered by CS of which 14 (19.4%) were obese.

166   A 1.00 or 100% study power and an estimated sample size of 177 were obtained using the

167   proportions of obese participants delivered by NVD (11.1%) and CS (19.4%), in our final

168   sample.

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170   **Figure 1**: Flowchart showing the study population and selection of study participants

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172   The study participants' characteristics by mode of delivery category are presented in Tables 1

173   and 2. As seen in Table 1, CSs were more frequent than NVDs in those who had low birth

174   weight or macrosomia, and in Indians and Coloureds (non-Black participants).

Table 1: Socio-demographic characteristics by mode of delivery

	Mode of delivery								P value
	Total		NVD		AVD		CS		
	N=889		n=793		n=24		n=72		
	n	%	n	%	n	%	n	%	
Young adult characteristic									
Sex									0.890
Male	444	49.9	398	50.2	11	45.8	35	48.6	
Female	445	50.1	395	49.8	13	54.2	37	51.4	
Ethnicity									<0.001
Black	803	90.3	727	91.7	17	70.8	59	81.9	
Non-Black	87	9.7	66	8.3	7	29.2	13	18.1	
Alcohol intake									0.617
No	560	63.0	502	63.3	16	66.7	42	58.3	
Yes	264	29.7	231	29.1	8	33.3	25	34.7	
Unknown	65	7.3	60	7.6	0	-	5	6.9	
Smoking									0.479
No	530	59.6	472	59.5	12	50.0	47	59.5	
Yes	359	40.4	321	40.5	12	50.0	26	40.5	
Education									0.304
<grade 12	349	39.3	305	38.5	12	50.0	32	44.4	
≥ grade 12	531	59.7	479	60.4	11	45.8	40	55.6	
Unknown	10	1.1	9	1.1	1	4.2	0	-	
Early life and maternal Characteristic									
Mother's post-school education									0.187 [f]
No	792	92.2	709	89.4	23	95.8	59	81.9	
Yes	67	7.8	59	7.4	0	0.0	8	11.1	
Unknown	30	3.4	25	3.2	1	4.2	5	6.9	
Birth weight (kg)									0.018 [f]
LBW (<2.5)	74	8.3	63	7.9	4	16.7	7	9.7	
Normal (2.5 - 4.0)	798	89.8	718	90.5	20	83.3	60	83.3	
Macrosomia (>4)	16	1.8	11	1.4	0	-	5	6.9	
Unknown	1	0.1	1	0.1	0	-	0	-	
Birth weight (centile)									
SGA (<10th)	79	8.9	68	8.6	5	20.8	6	8.3	0.139 [f]
AGA (≥10th-≤90th)	680	76.5	610	76.9	18	75.0	53	72.2	
LGA (>90th)	129	14.5	114	14.4	1	4.2	14	19.4	
Unknown	1	0.1	1	0.1	0	-	0	-	

Non-black – Indians and Coloured, LBW – low birth weight, SGA – small for gestational age, AGA – appropriate for gestational age, LGA – large for gestational age, NVD/AVD – Normal/Assisted vaginal delivery
Fisher's exact (f)

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No statistically significant differences were observed for gestational age, parity, breastfeeding

duration or age at delivery (Table 2).

Table 2: Maternal characteristics of the study participants by mode of delivery

	Total N=889		NVD n=793		AVD n=24		CS n=72		P value
	Med	IQR	Med	IQR	Med	IQR	Med	IQR	
Gestational age (weeks) at delivery	38.0	38.0 – 39.0	38.0	38.0 – 39.0	38.0	38.0 – 40.0	38.0	37.5 – 39.0	0.074
Parity at delivery	2.0	1.0 – 3.0	2.0	1.0 – 3.0	1.0	1.0 – 3.0	2.0	1.0 – 3.0	0.136
Breastfeeding duration (months)	8.0	1.0 – 20.0	9.0	1.0 – 20.0	6.5	2.5 – 24.0	6.0	0.6 – 18.0	0.489
Age at delivery (years)	24.0	20.0 – 30.0	24.0	20.0 – 30.0	23.5	19.0 – 30.0	25.5	21.0 – 30.0	0.541
Med – median, IQR – interquartile range, NVD/AVD – Normal/Assisted vaginal delivery, CS – caesarean section									

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179   Compared to the primary cohort, the study participants were more likely to be Black (78.5%

180   vs 90.3%), smokers (19.3% vs 40.4%), have mothers who had no post school education (79.6%

181   vs 92.2%). They were also breast fed for a longer period, and had mothers who had longer

182   gestational age and were younger when they gave birth, than those in the primary cohort. There

183   were no differences between YAs sex, mode of delivery, education, alcohol intake, BMI and

184   birth weight, and mothers' parity, between the primary cohort and the study participants

185   (p>0.05). Certain characteristics were associated with BMI, such as YA's sex (p=<0.001),

186   ethnicity (p=0.039), smoking habit (p=<0.001), and education (p=<0.001); and mothers' parity

187   at delivery (p=0.019) (data not shown).

188

189   Sex-stratified prevalence of obesity and BMI across mode of delivery categories are presented

190   in Tables 3 and 4, respectively. Overall, the prevalence of obesity was higher in CS-delivered

191   participants than in those delivered through either AVD or NVD, but there were no differences

192   when the results were stratified by sex (Table 3).

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Table 3: Prevalence of obesity in each mode of delivery category among study participants, by sex

	N	n	%	95% CI	P value
Overall					0.042
NVD	793	88	11.1	9.1 – 13.5	
AVD	24	4	16.7	6.4 – 37.0	
CS	72	14	19.4	11.9 – 30.2	
Total	889	106	11.9	9.9 – 14.2	
Male					0.190
NVD	398	9	2.3	1.2 – 4.3	
AVD	11	1	9.1	1.3 – 44.0	
CS	35	3	8.6	2.8 – 23.5	
Total	444	13	2.9	1.7 – 5.0	
Female					0.133
NVD	395	79	20.0	16.3 – 24.2	
AVD	13	3	23.1	7.6 – 52.2	
CS	37	11	29.7	16.8 – 46.2	
Total	445	93	20.9	17.4 – 24.9	
CI – confidence interval, VD – vaginal delivery, CS – caesarean section					

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195 The median BMI of males (but not females) delivered by CS was higher than that of those

196 delivered by AVD or NVD (Table 4).

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Table 4: Body mass index of study participants by mode of delivery

	N	Med	IQR	P value
Overall				0.135
NVD	793	22.1	19.8 – 26.1	
AVD	24	21.6	19.0 – 27.4	
CS	72	23.3	20.7 – 23.3	
Total	889	22.2	19.9 – 26.3	
Male				0.018
NVD	398	20.8	19.3 – 23.3	
AVD	11	20.6	19.0 – 22.2	
CS	35	21.8	20.3 – 24.8	
Total	444	20.8	19.4 – 23.3	
Female				
NVD	395	24.6	21.0 – 28.9	0.861
AVD	13	25.6	19.0 – 28.0	
CS	37	25.2	21.4 – 30.0	
Total	445	24.2	21.0 – 29.0	
Med – median, IQR- interquartile range, BMI – body mass index				
CI – confidence interval, VD – vaginal delivery, CS – caesarean section				

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199   As seen in Table 5, birth by CS was associated with an almost two-fold increase in the odds of

200   obesity among YAs aged 21-24 years, in the crude analysis. After adjusting for YAs' sex and

201   birth weight, and mothers' parity and education at delivery as potential confounders, a similar

202   estimate was observed.

203

Table 5: The association between mode of delivery and early adulthood obesity, stratified by sex and birth weight (using normal BMI as reference)					
Variable	n_O/N_T	**%**	**OR**	**95%CI**	**P value**
Main analysis					
crude					
NVD	88/793	11.1	1.00	reference	
AVD	4/24	16.7	1.60	0.54 – 4.80	0.400
CS	14/72	19.4	1.93	1.04 – 3.61	0.039
Adjusted					
NVD	88/792	11.1	1.00	reference	
AVD	4/24	16.7	1.69	0.50 – 5.69	0.395
CS	14/72	19.4	1.99	1.00 – 3.94	0.049
Male					
NVD	9/397	2.3	1.00	reference	
AVD	1/11	9.1	4.70	0.44 – 50.68	0.203
CS	3/35	8.6	4.27	1.05 – 17.33	0.042
Female					
NVD	79/395	20.0	1.00	reference	
AVD	3/13	23.1	1.28	0.34 – 4.81	0.717
CS	11/37	29.7	1.77	0.82 – 3.85	0.149
Birth weight <3.1kg					
NVD	46/420	11.0	1.00	reference	
AVD	0/10	–		–	–
CS	5/30	16.7	1.41	0.47 – 4.25	0.542
Birth weight ≥3.1kg					
NVD	42/372	11.3	1.00	reference	
AVD	4/14	28.6	2.29	0.53 – 9.89	0.267
CS	9/42	21.4	2.74	1.07 – 7.01	0.036
OR – odds ratio, CI – confidence interval, NVD/AVD – Normal/Assisted vaginal delivery, CS – caesarean section. n_o – number of participants with outcome(s) in row group N_T – total number of participants in row group Adjusted for YAs' sex and birth weight; mothers' parity and education at YA's birth in all models.					

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205 Although no interaction was found between mode of delivery and either sex or birth weight in

206 the final adjusted models, obesity rates were statistically different across the sex (p=<0.001)

207 and birth weight (p=0.027) categories in these models, indicating heterogeneity (data not

208 shown). Among male YAs and participants who had a mean birth weight of at least 3.1 kg, CS

209 was associated with a statistically significant higher odds of obesity compared to NVD.

210

211 To address the possibility of residual confounding and to determine if the results held up under

212 different scenarios, a series of sensitivity analyses were conducted. The odds of being obese if

213 delivered by CS were 1.95 times the odds of being obese if delivered by AVD or NVD (Table

214 6). The additional adjustment for YA's breastfeeding duration, smoking habit and alcohol

215 intake, as well as treating certain covariates as linear or categorical in the sensitivity analyses,

216 did not change the conclusions reached from the results of the original analyses. The observed

217 association was not statistically significant when only early life factors (YAs' sex, birth weight

218 and breastfeeding duration; and mothers' parity, gestational age, age and education at delivery)

219 were adjusted for.

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221 Assuming causality, we found that 12 CS births would be required to have one case of YA

222 obesity (absolute risk increase 8.3%; numbers needed to harm 12; 95% CI 5.63 – 95.05).

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Table 6: Sensitivity analysis: examining the association between mode of delivery and early adulthood obesity under different scenarios

	OR	95% CI	P value
Combined normal and			
assisted vaginal delivery			
VD (normal and assisted)	1.00	reference	
CS	1.95	0.99 – 3.87	0.054
Controlling for confounders			
Lifestyle and behavioural			
characteristics + main analysis			
NVD	1.00	reference	
AVD	1.95	0.54 – 5.93	0.337
CS	1.80	0.99 – 3.65	0.053
Early life factors only			
NVD	1.00	reference	
AVD	1.73	0.61 – 4.93	0.304
CS	1.80	0.94 – 3.46	0.077
Covariates linear/categorical			
NVD	1.00	reference	
AVD	1.63	0.49 – 5.40	0.424
CS	1.98	1.00 – 3.91	0.049

OR – odds ratio, CI – confidence interval, NVD/AVD – Normal/Assisted vaginal delivery
Adjustment for confounders
i. Combined NVD and AVD – adjusted for YA's sex and birth weight; mothers' parity, age, gestational age, and education at YA's birth.
ii. Covariates linear/categorical – adjusted for YA's birth weight (continuous), breastfeeding duration at infancy (categorical); mother's parity and age at YA's birth (categorical) + other covariates in main analysis.
iii. Lifestyle and behavioural characteristics – adjusted for YA's breastfeeding duration during infancy, smoking habit, and alcohol intake + other covariates in main analysis.
iv. Early life factors only – adjusted for YA's sex, birth weight and breastfeeding duration at infancy; mothers' parity, gestational age, age and education at YA's birth.

230

Discussion

232 *Findings and evidence from previous studies*

233 In this analysis of 21-24 year old South Africans from a longitudinal urban birth cohort, CS

234 was associated with obesity in early adulthood. Among males and those with a birth weight

235 ≥3.1 kg, CS was statistically associated with an increased odds of obesity. The magnitude of

236 the association among females and those with a <3.1 kg birth weight is of particular clinical

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237 concern. The confidence intervals of the ORs in the stratified analyses were wide, indicating

238 low precision, due to the small sample size. Most of the sensitivity analyses supported the

239 finding of an association between CS and early adulthood obesity. A marginal statistical

240 significance was observed when early life and maternal characteristics were adjusted for,

241 regardless of their collinearity or correlation with other variables and their effect on the primary

242 predictor.

243

244 Significant associations between CS and obesity in early adulthood have been previously

245 reported, despite the inconsistencies in some studies [27,28]. In a systematic review and meta-

246 analysis by Darmasseelane *et al*. (2014), comprising studies published prior to 31 March 2012,

247 the odds of being obese among CS-delivered YAs (aged 18 years or older) from 11 studies,

248 was 22% higher than the odds of being obese among YAs delivered vaginally (OR 1.22, 95%

249 CI 1.05-1.42) [20]. Results from a meta-analysis by Li *et al.* (2013) support this association

250 among YAs aged 19 or older (OR 1.50, 95% CI 1.02-1.20) [21]. The studies included in these

251 reviews were conducted independently in different countries (Finland, England, Scotland,

252 Sweden, Brazil, Netherlands, China, India, and Denmark). Among Brazilian YAs aged 23-25

253 years old, Mesquita *et al*. (2013) and Bernardi *et al*. (2015) reported increase in fat

254 accumulation due to delivery by CS: measured by either waist-hip ratio (IRR 1.45, 95% CI

255 1.18-1.79) [23] or BMI (β coefficient 0.12, 95% CI 0.01-0.03) [24]. More recently, Yuan *et al.*

256 (2016) and Barros *et al.* (2017) reported increased risks of obesity in CS-delivered YAs (RR

257 1.15, 95% CI 1.06-1.26, n= 8 486; β coefficient 0.15, 95% CI 0.08-0.23, n= 1 794, respectively)

258 in Boston (USA) and Pelotas (Brazil) [19,26]. Finally, in a commentary published in 2017,

259 Kuhle *et al*. (2017) supported the association [42].

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261   The aforementioned studies were all conducted outside Africa. However, some of the study

262   sites were in upper-middle income countries, such as Brazil and China which are similar, socio-

263   economically, to South Africa, and hence their results are comparable to those from our study.

264

265   *Underlying mechanism*

266   It has been suggested that infants born via VD are exposed mainly to microorganisms in the

267   birth canal or vaginal environment, and that those delivered by CS are exposed to micro flora

268   on their mother's skin [43–45]. The abundance of *Coprococcus* and *Ruminococcus* of the

269   family Lachnospiraceae was also reported by Tun *et al.* (2018) in infants delivered through CS

270   – signifying dysbiosis in early life [44]. The investigators further explained the impact of family

271   Lachnospiraceae in promoting adiposity.

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273   Differences in intestinal bacterial colonisation; such as certain *Bifidobacteria spp.* that

274   contribute to digestion and infant intestine development have been reported to be absent in

275   infants delivered by CS [46]. Kalliomäki *et al.* (2008) reported that, compared to those of

276   normal BMI, overweight seven year old participants had lower Bifidobacteria counts at age

277   one and six years [47]. In addition, infants delivered by CS had almost no *Bifidobacteria spp.*

278   in their faecal samples in studies by Huurre *et al.* (2008) and Biasucci *et al.* (2008) [48,49].

279   Nonetheless, it is possible that the underlying reason or indication for CS delivery could be a

280   cause of later life obesity. This is because certain clinical states resulting in CS, as well as

281   antibiotics administered during CS, have been suggested to increase the tendency of offspring

282   obesity [50–52].

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286   *Limitations and strengths*

287   A limitation of this study is that the exposure and outcome assessments were dependent on the

288   accuracy of the data collected from the Bt20+ cohort. In addition, the current surge of CS in

289   South Africa was not reflected in the results; only 72 women gave birth through CS.

290   Consequently, the 95% CIs were wide, indicating low precision of the ORs. We did not have

291   the relevant data to examine the proposed mechanism underlying the association between CS

292   and obesity in later life (i.e. deprivation of CS-born infants of microorganisms essential for

293   regulating digestion). Caesarean delivery was not recorded as being elective or an emergency.

294   It has been proposed that differences in intestine microbiota composition might arise due to

295   prolonged delivery or ruptured fetal membranes [30,53], but this could not be investigated. In

296   addition, the proposed effect (obesity) of antibiotics administered during CS on offspring's

297   delivered through the procedure, could not be assessed due to lack of data. Furthermore, key

298   pre-pregnancy information was not available, e.g. mothers' BMI (height and weight);

299   gestational diabetes, preeclampsia, or pregnancy-induced hypertension; smoking habits;

300   information about previous CS; and family income. The absence of these variables might have

301   resulted in residual confounding, leading to higher point estimates than observed in previous

302   studies.

303

304   The strength of this analysis was the availability of data to estimate associations between CS

305   and obesity in later life. We were also able to demonstrate temporality as the exposure (CS)

306   preceded the outcome (obesity in early adulthood). Additional strengths of the study were the

307   availability of information on important early life factors of YAs, and prospectively collected

308   data in the cohort.

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Conclusion

311   Caesarean section as a mode of delivery was statistically associated with obesity in the study

313   participants. Further research is required in South Africa, and Africa in general, using routinely

314   collected data that provide useful linking of maternity data with information in other databases.

315   This will help to identify larger study populations and minimize costs, while investigating the

316   association across BMI categories and exploring the underlying mechanisms for the

317   association. Birth weight- and sex-stratified analyses, taking into account the potential

318   interaction with mode of delivery, and differences in obesity rates, should be performed, as

319   mean birth weights differ across and between populations. The reported increased odds of

320   obesity in later life after CS, including those found in this study, support the plausibility of a

321   biological link and should be considered as a motivating factor to reduce CS as a mode of

322   delivery unless clinically indicated.

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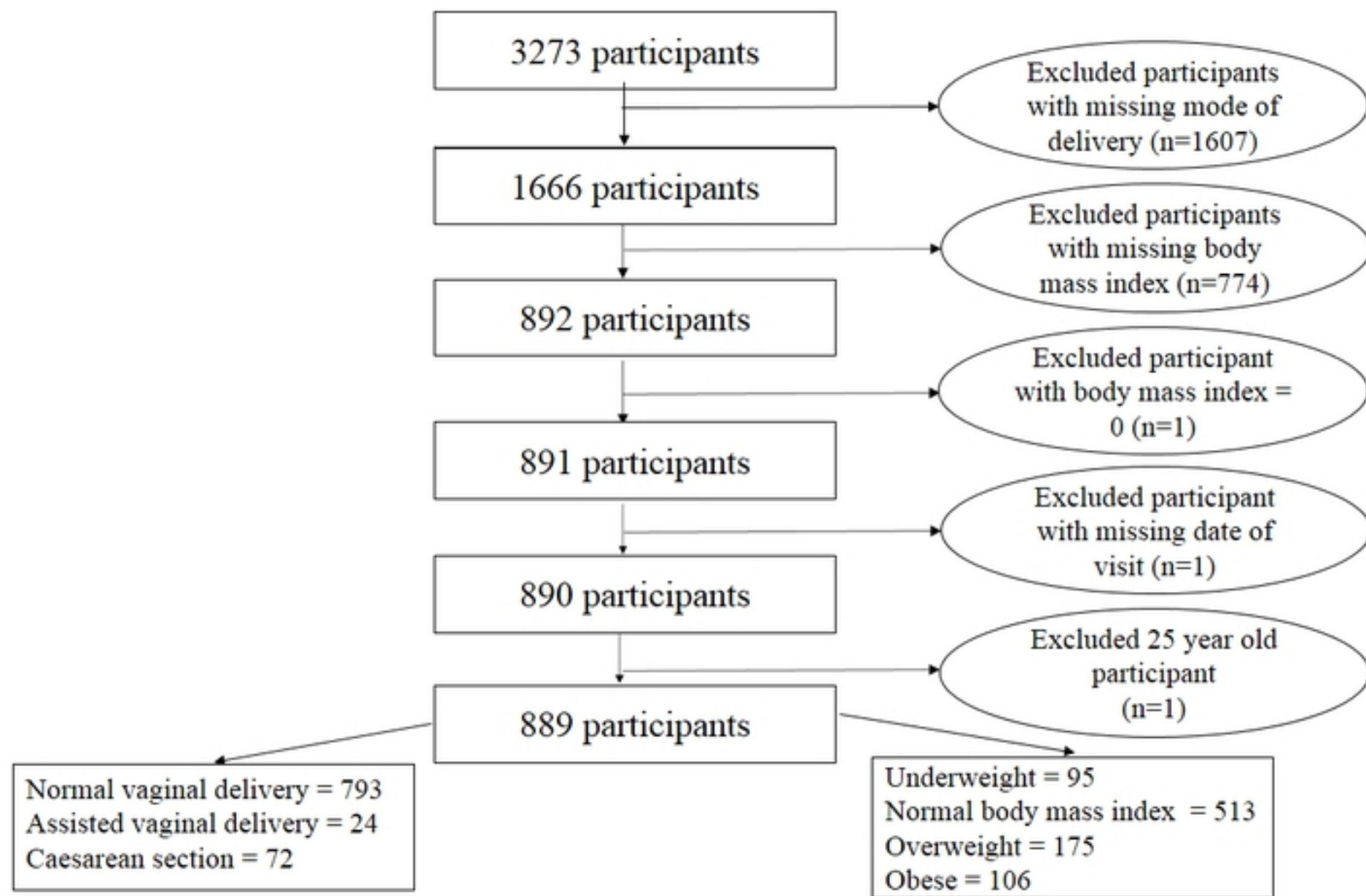
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Figure