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RESEARCH ARTICLE

Obesity and impairment of pancreatic β-cell function in early adulthood, independent of obesity age of onset: The Santiago Longitudinal Study

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Abstract

Aim: We investigated the relation of time of onset and length of obesity with biomarkers of β-cell function in early adulthood in an infancy cohort.

Material and methods: In 1039 23-year-olds, body-mass index (BMI) was measured at multiple time-points from enrollment. BMI trajectories were interpolated with cubic polynomials. Fasting glucose, insulin and adiponectin were measured at 23 years. Homeostatic model assessment-insulin resistance (HOMA-IR), HOMA-S, HOMA-β, HOMA-adiponectin (AD) and disposition index (DI) were estimated. IR and non-alcoholic fatty liver (NAFL) were diagnosed. According to the BMI trajectory, five groups were defined: participants who were never obese (NOB); participants with obesity starting in adolescence and remained obese into adulthood (recent-onset obesity, ROB); participants who were obese in early childhood but transitioned to non-obesity as preadolescents (former obesity, FOB); participants who were obese in early childhood and remained obese into adulthood (persistent obesity, POB); participants with obesity starting in preadolescence and transitioned to non-obesity as adolescents (transient obesity; TOB).

Results: Obesity was present in 47% of participants during at least one time-point. ROBs and POBs had higher insulin, HOMA-IR and HOMA-β, lower HOMA-S and DI, and higher prevalence of IR and NAFL at 23 years than NOBs, TOBs and FOBs. No differences were found in the β-cell functionality of NOBs, TOBs and FOBs.

Conclusions: Persistent and recent obesity are both related to IR, NAFL and a decline of β-cell function in emerging adulthood. Defeating obesity in childhood or adolescence allows reaching emerging adulthood with β-cell functioning similar to that of subjects who were NOB.

KEYWORDS

BMI trajectory, insulin resistance, obesity, β-cell function

1 | INTRODUCTION

The prevalence of type-2 diabetes (T2D) has tripled in the last 30 years closely related to the obesity epidemic and increasing socioeconomic disparities.[1-4] This increasing prevalence has affected younger age populations, with a substantial relative increase in all ethnic minority groups in the United States, the United Kingdom and significant increases in south-east Asia, Western Pacific Regions, and

sub-Saharan Africa.[2,5,6] In Chile, almost three-quarters of adults are either overweight or obese,[7] and the prevalence of T2D rose from 6% to 12.3% in 2003 to 2017.[8] Likewise, childhood obesity jumped from 4.5% in the mid-1980s to 33% in 2017,[9,10] and currently, 51% of preschoolers and first graders have some degree of excess weight.[10]

A progressive decline of β-cell function leads to T2D. Chronic exposure to obesity, leading to oxidative stress and inflammation, may result in impaired insulin secretion and impaired β-cell function.[11] Also, non-alcoholic fatty liver disease (NAFLD) in obese children may contribute to rising rates of impaired β-cell functionality.[12,13] Rates of NAFLD are 38% in US Hispanic children.[13] A substantial body of evidence associates a higher incidence of T2D with rapid foetal growth and excessive weight-gain in infancy.[14,15] However, several longitudinal studies suggest that early onset of impaired insulin response in adulthood is associated with the duration of obesity, independent of age at obesity onset. In a Swedish cohort, after 28 years of follow-up, Ohlsson et al found that obesity during puberty was a more significant determinant of T2D risk compared to early obesity or obesity before the age of 6 years.[16] It has also been proposed that predisposition to peripheral insulin resistance may lead to T2D, even before the subject becomes obese.[17]

T2D is a multi-systemic metabolic disorder, of heterogeneous aetiology, involving biological, genetic and environmental factors.[18] Likewise, recent evidence has suggested that disturbances in the composition of the gut microbiota due to the exposure to high-fat diets may cause of low-grade systemic inflammation that may predispose to obesity, metabolic disorders and T2D.[19] Hyperglycaemia in T2D is preceded by a phase of hyperinsulinemia secondary to increased β-cell activity in an attempt to maintain glucose control. Eventually, there is a progressive failure of β-cell functioning.[20,21] Both insulin resistance (IR) and β-cell dysfunction are early events associated with normal basal and post-stimulus glucose levels, especially in childhood and adolescence.[22,23] In obese adults, IR and β-cell dysfunction are likely to be strongly related to fasting hyperglycaemia and glucose intolerance.[24] To date, the influence of timing and duration of obesity on β-cell functioning has been poorly investigated. Here, we study the association of time of onset and length of obesity with insulin sensitivity and β-cell function in emerging adulthood under the hypothesis that the risk of impaired β-cell functioning is particularly high in individuals who were obese in early adulthood independent of age at obesity onset.

2 | METHODS

2.1 | Study design and population

We studied n = 1039 23-year-olds from the Santiago Longitudinal Study (SLS) (48% males) recruited as infants (4 months) in 1991 to 1995, from socially vulnerable neighbourhoods in the south-east area of Santiago (Chile). At enrolment, participants were healthy, full-term singletons, weighing ≥3 kg at birth, and free of acute or chronic health problems.[25] Growth and developmental assessments were performed at multiple time-points from enrolment through early adulthood.[25-30] At 23 years, they were assessed for the presence of cardiometabolic risk factors.[29] The IRBs of the Institute of Nutrition and Food Technology (University of Chile), University of Michigan and the University of California, San Diego approved this study. Informed and written consent was provided according to the norms for human experimentation, code of ethics of the World Medical Association.

2.2 | Measurements

2.2.1 | Anthropometric assessment

A research physician performed the anthropometric examination at 1, 5, 10, 12, 14, 16, 21 and 23 years using standardized procedures. Height (cm) was measured to the nearest 0.1 cm, with a Holtain Stadiometer, and weight (kg) to the nearest 0.1 kg, with a scale (Seca 725 and 703, Seca GmbH & co. Hamburg, Germany). Birthweight was obtained from health records. At 23 years, waist circumference (WC) was measured with a non-elastic flexible tape and recorded to 0.1 cm (Seca 201, Seca GmbH & co). Measurements were taken twice, with a third measurement if the difference between the first two exceeded 0.3 kg for weight, 0.5 cm for height and 1.0 cm for WC. Body-mass index (BMI) and BMI for age and sex (BMIz) were estimated. Obesity was diagnosed with 2006 and 2007 WHO standards. Participants having a BMIz > 2 SD before the age of six were categorized as having early obesity.

2.2.2 | Assessment of β-cell function at 23 years

Serum total glucose (Glu), insulin (Ins) and adiponectin (AD) were measured after an overnight fast of 8 to 12 hours. Glu was determined with an enzymatic colourimetric test (QCA S.A., Amposta, Spain), whereas RIA (Diagnostic Products Corporation, Los Angeles) was used for insulin determination. Total AD was determined with the Quantikine Human Total Adiponectin Immunoassay, a 4.5-hour solid-phase ELISA. The homeostatic model assessment (HOMA) was used to quantify insulin sensitivity and β-cell function. HOMA-IR, HOMA-β, HOMA-S, and disposition index (DI) were calculated by two methods: HOMA1 and HOMA2.[31,32] For HOMA1, the following formulae were used: HOMA-IR1 = [Ins(μU/L) × Glu(mg/dL) × 0.0555]/22.5]; HOMA-β1 = [20 × Ins(μU/L)]/[(Glu(mg/dL) × 0.0555)-3.5]; HOMA-S1 = [1/HOMA-IR] × 100%]; DI1 = [(HOMA-S1/100) × (HOMA-β1/100)]. HOMA-IR2, HOMA-β2 and HOMA-S2 were derived using the HOMA calculator (http://www.dtu.oc.ac.uk), and DI2 resulted by multiplying HOMA-S2/100 by HOMA-β2/100. Estimation of HOMA-AD was done as follows: HOMA-AD = [Glu (mmol/L) × Ins(mU/L)] / [22.5 x AD(μg/mL)].[33] Participants with HOMA-IR1 values ≥ 2.6 were considered to be insulin resistant.[28]

2.2.3 | Cardiometabolic risk evaluation at 23 years

Fifteen minutes after the anthropometric assessment and before other examinations, systolic and diastolic blood pressures (SBP/DBP) were measured three times using a standard mercury sphygmomanometer. Tryglideríces (TG) and HDL-cholesterol were also measured in the fasting state. Metabolic Syndrome (MetS) was diagnosed based on the IDF/AHA/NHLBI Joint Statement.[34] In a subset of n = 630 participants, an abdominal ultrasound was performed using a General Electric LogiQ ultrasonographer with a 4C RS convex multi-frequency probe (2-5.5 MHz) to investigate the presence of NAFL. All examinations were done by the same operator, who obtained standardized images that were analysed by two independent observers. The observers were gastroenterologists with training in abdominal ultrasound interpretation and scored liver brightness, diaphragm attenuation and vessel blurring according to Hamaguchi.[35] The maximum score possible was six. When there was disagreement between observers, the images were analysed jointly, and an agreement about the final score was reached. Participants having a total ultrasound score of ≥ 4 were considered as having NAFL.[36]

2.2.4 | Interpolation of BMI trajectory

BMI trajectory from birth to adulthood was interpolated using cubic splines.[37,38] This method was explained in detail in previous work and allowed for the modelling of smoothed, non-linear trajectories of BMI across different ages.[30] We got 1039 BMI trajectories and estimated the timing of obesity onset and the length of obesity in those participants who were obese or had obesity before the age of 6 years. Based on the observation of each interpolated trajectory, five mutually exclusive groups were defined: participants who were never obese (NOB); participants who were obese during adolescence or emerging adulthood (recent-onset obesity, ROB); participants who were obese in early childhood but transitioned to normal weigh as preadolescents (former obesity, FOB); participants with obesity starting in preadolescence and transitioned to non-obesity as adolescents (transient obesity; TOB) and participants who were obese in early childhood and remained obese (persistent obesity, POB).

2.3 | Data analysis

Data were analysed using Stata for Windows version 15.0 (Lakeway Drive College Station, Texas). The Shapiro-Wilk test was used to determine whether the variables were normally distributed. Ins, AD, HOMA-IR, HOMA-S, HOMA-β, HOMA-AD and DI were normalized by log transformation. Statistical analysis was done using transformed data, but untransformed data are provided here. Analysis of variance and the Kruskal-Wallis test were used for comparison of means and medians, respectively, of anthropometric and biochemical variables. χ^2 analysis evaluated differences in the prevalence IR, MetS and NAFLD.

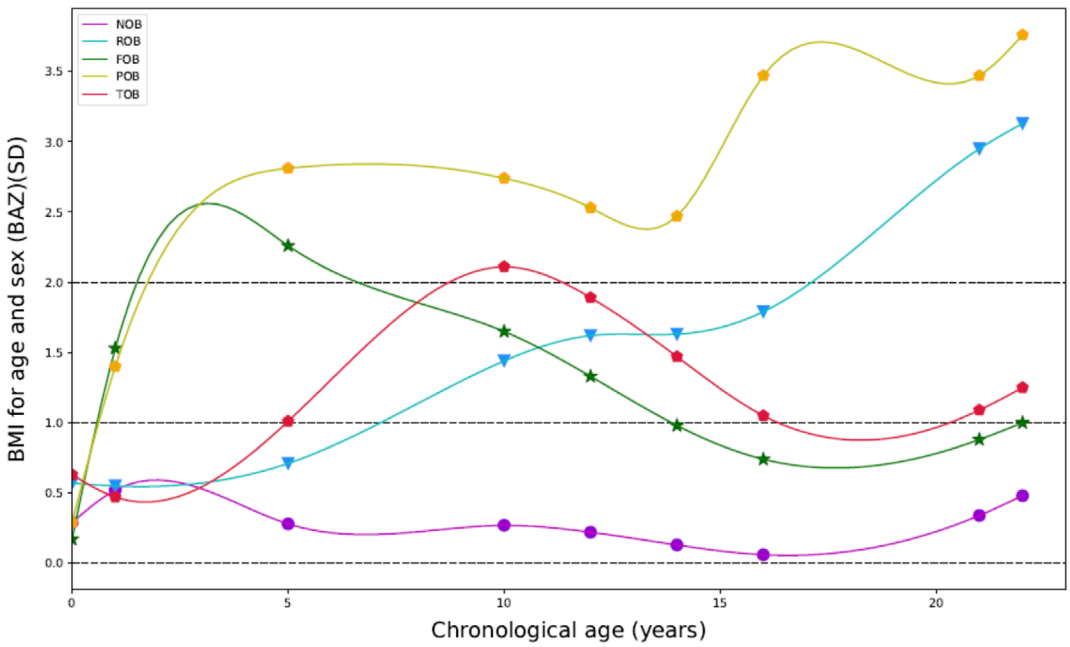

FIGURE 1 **BMI for age and sex (BAZ) from birth to early adulthood in the Santiago Longitudinal Study (n = 1039).** Participants who were never obese (NOB); participants with obesity starting in adolescence and remained obese into adulthood (recent-onset obese, ROB); participants who were obese in early childhood but transitioned to non-obesity as preadolescents (formerly obese, FOB); participants who were obese in early childhood and remained obese into adulthood (persistently obese, POB); participants with obesity starting in preadolescence and transitioned to non-obesity as adolescents (transiently obese; TOB). Bullets denote BMIz estimated with observed/measured weight and height. Measurements were taken at birth, 1y, 5y, 10y, 12y, 14y, 16y, 21y and 23y

TABLE 1 Anthropometric and metabolic profile in 23-years-old participants in the SLS, by obesity status (n = 1039)

	NOB (n = 552)(A)		ROB (n = 129)(B)		FOB (n = 155)(C)		POB (n = 158)(D)		TOB (n = 45)(E)		Between group comparison[e]	
	Mean or median	(SD) or [IQR]	Mean or median	(SD) or [IQR]	Mean or median	(SD) or [IQR]	Mean or median	(SD) or [IQR]	Mean or median	(SD) or [IQR]	*P* value[a]	ANOVA/KW test
Age (year)	23.0	(1.0)	23.0	(1.1)	23.2	(1.1)	23.0	(1.1)	22.9	(0.8)	NS	(…)
Sex distribution[b]	–	–	–	–	–	–	–	–	–	–	–	–
Males	257	51.6%	44	8.8%	90	18.1%	77	15.5%	30	6.0%	<.001[c]	(…)
Females	295	54.5%	85	15.7%	65	12.0%	81	15.0%	15	2.7%	–	–
Anthropometric profile: early adulthood	–	–		–	–	–	–	–	–	–	–	–
BMI 23 y	23.6	(3.1)	32.6	(4.3)	25.3	(2.7)	34.6	(4.7)	26.2	(3.3)	<.001	ABCDC
BMI 23 y (*z* score)	0.48	(1.0)	3.13	(1.2)	1.00	(0.8)	3.76	(1.4)	1.12	(1.0)	<.001	ABCDC
Waist-to-height ratio	0.45	(0.04)	0.57	(0.05)	0.48	(0.04)	0.59	(0.06)	0.49	(0.05)	<.001	ABCDC
Waist circumference (cm)	76.2	(7.9)	92.8	(8.6)	80.3	(7.5)	98.2	(10.1)	82.6	(8.6)	<.001	ABABA
Anthropometric profile: infancy, childhood and adolescence	–	–	–	–	–	–	–	–	–	–	–	–
Birthweight (*z* score)	0.29	(0.8)	0.57	(0.8)	0.17	(0.7)	0.29	(0.7)	0.43	(1.0)	ns	AAAAA
BMI 1 y (*z* score)	0.52	(0.8)	0.55	(0.6)	1.53	(0.9)	1.40	(0.9)	0.55	(0.8)	<.001	AACCA
BMI 5 y (*z* score)	0.28	(0.8)	0.71	(0.8)	2.26	(0.7)	2.81	(1.2)	1.17	(0.5)	<.001	ABCDE
BMI 10 y (*z* score)	0.27	(0.8)	1.44	(0.9)	1.65	(1.0)	2.74	(1.0)	2.03	(0.7)	<.001	ABBDE
BMI 14 y (*z* score)	0.13	(0.8)	1.93	(1.0)	0.98	(1.0)	2.53	(1.0)	1.47	(0.9)	<.001	ABCDB
BMI 16 y (*z* score)	0.06	(0.8)	2.09	(0.9)	0.74	(0.9)	2.47	(0.9)	1.05	(0.8)	<.001	ABCDC
Age at obesity onset (year)	d.n.a	d.n.a	14.6	(4.9)	1.9	(1.5)	2.3	(2.0)	9.4	(3.1)	<.001	BCCE
Obesity length (year)	d.n.a	d.n.a	8.5	(4.8)	6.2	(3.5)	20.7	(2.3)	3.2	(2.0)	<.001	BCDE
β-cell profile: early adulthood	–	–	–	–	–	–	–	–	–	–	–	–
Glycaemia (mg/dL)	88.2	(9.7)	89.4	(9.9)	88.6	(10.1)	90.0	(9.8)	88.5	(9.9)	ns	AAADA
Insulin (uUI/dL)	10.7	[6.9]	18.4	[15.0]	9.4	[6.9]	17.6	[15.2]	11.0	[6.5]	<.001[d]	ABABA
HOMA1-IR	2.34	[1.5]	4.07	[3.4]	2.06	[1.6]	3.71	[3.1]	2.27	[1.4]	<.001[d]	ABABA
HOMA1-S (%)	42.7	[30.3]	24.6	[23.9]	48.6	[36.8]	27.0	[23.3]	44.1	[28.7]	<.001[d]	ABABA
HOMA1-β (%)	160.5	[119]	228.0	[221]	139.8	[102]	247.9	[196]	172.7	[122]	<.001[d]	ABABA
HOMA-AD	0.42	[0.5]	0.76	[0.9]	0.35	[0.4]	0.86	[1.0]	0.47	[0.6]	<.001[d]	ABABA
Disposition index 1	0.67	[0.4]	0.62	[0.3]	0.65	[0.4]	0.58	[0.3]	0.65	[0.3]	.001[d]	AAADA
HOMA2-IR	1.36	[0.9]	2.42	[1.9]	1.21	[0.9]	2.25	[1.9]	1.41	[0.9]	.001[d]	ABABA
HOMA2-S	73.4	[49.2]	41.3	[31.2]	82.8	[57.0]	44.6	[36.2]	70.7	[48.0]	.001[d]	ABABA
HOMA2-β	126.5	[61.8]	174.0	[102.3]	112.4	[52.6]	170.0	[99.0]	128.8	[60.7]	.001[d]	ABABA

TABLE 1 (Continued)

	NOB (n = 552)(A)		ROB (n = 129)(B)		FOB (n = 155)(C)		POB (n = 158)(D)		TOB (n = 45)(E)		Between group comparison[e]	
	Mean or median	(SD) or [IQR]	Mean or median	(SD) or [IQR]	Mean or median	(SD) or [IQR]	Mean or median	(SD) or [IQR]	Mean or median	(SD) or [IQR]	*P* value[a]	ANOVA/KW test
Disposition index 2	0.90	[0.3]	0.75	[0.2]	0.93	[0.3]	0.75	[0.2]	0.95	[0.2]	.001[d]	ABABA
Adiponectin (μg/mL)	6.8	[4.3]	5.7	[3.4]	7.2	[4.5]	5.6	[4.3]	5.7	[3.6]	.002[d]	ABABA

[a]Analysis of variance with Bonferroni correction, except as indicated.
[b]Sex distribution expressed as number of participants and percentage.
[c]Pearson's Chi2 test. d.n.a. Does not apply.
[d]Kruskall-Wallis Test by ranks.
[e]A-E: Different letters indicate significant statistical differences. The same letter denotes means/medians that do not differ.
Abbreviations: BMI, body-mass index; FOB, formerly obese; HOMA, Homeostatic model assessment-insulin resistance; IR, Insulin resistance; NOB, never obese; POB, persistently obese; ROB, recent-onset obese; SLS, Santiago Longitudinal Study; TOB, transiently obese.

Analysis of covariance determined the contribution of recent-onset and long-term obesity to cardiovascular risk in emerging adulthood in the five groups. A first model was unadjusted and a second model adjusted for sex and meet criteria for the MetS at 23 years. The Bonferroni method was used to conduct post hoc analyses to test between groups differences. A P value of < .05 was used to denote statistical significance.

3 | RESULTS

Participants were 23.0 years (0.8 SD), 48% were males, and 31% had obesity at 23 years. In the sample, 47% were obese at some point in their life. As shown in Figure 1, mean obesity length was 20.7, 8.5, 6.2 and 3.3 years in POBs, ROBs, FOBs and TOBs, respectively. Mean age at obesity onset was 1.9, 2.3, 9.4 and 14.6 years in FOBs, POBs, TOBs and ROBs, respectively. FOBs transitioned to non-obesity at 8.1 years, whereas TOBs transitioned to non-obesity at 12 years.

Table 1 describes the anthropometric and β-cell profiles of NOBs (53%), ROBs (12.4%), FOBs (14.9%), POBs (15.2%) and TOBs (4.3%). A higher frequency of females was found among ROBs, whereas a higher frequency of males was found among FOBs and TOBs. As expected, BMIz differed across groups in infancy, childhood and adolescence. BMIz at 1 and 5 years were significantly higher in POBs and FOBs compared to NOBs, ROBs and TOBs. At 10 years, BMIz was significantly higher in POBs and TOBs compared to the other groups, whereas BMIz at 16 years was significantly higher in POBs and ROBs compered to NOBs, FOBs and TOBs.

The β-cell profile at 23 years (Table 1) showed differences in serum Ins, AD and all HOMA indicators, with ROB and POB participants having significantly unhealthier values (higher Ins, HOMA-IR, HOMA-β and HOMA-AD and lower HOMA-S) in all these biomarkers compared to NOBs, FOBs and TOBs. Likewise, POB participants had higher Gli and DI than the rest of the groups. It is also worth mentioning that although the prevalence of fasting hyperglycaemia was low overall in the sample (4.3%), it was significantly higher among ROBs (7.8%) and POBs (8.9%) compared to NOBs (1.3%), FOBs (3.2%) and TOBs (2.2%). Also, the prevalence of IR, MetS and NAFL was notably and significantly higher in ROBs (69.8%, 29.5% and 39%, respectively) and POBs (74.1%, 42.4% and 51.4% respectively) compared to the NOB, TOB and FOB groups (Figure 2).

Table 2 contains the estimated regression coefficients examining the association of age of onset and persistency of obesity with β-cell profile at 23 years. After accounting for the effect of sex and having MetS at 23 years we found that POBs had significantly higher Ins, HOMA1-IR, HOMA1-β and HOMA-AD and lower HOMA1-S, DI and AD compared to NOBs (reference group). ROB participants had significantly higher Ins, HOMA1-IR and HOMA1-β and lower values of HOMA1-S compared to the reference group. Also, we observed that TOBs did not differ in their β-cell profile compared to NOBs. Last, FOB participants had a similar DI, AD and HOMA-AD values than NOBs, significantly lower Ins, HOMA1-IR and HOMA1-β, and significantly higher HOMA1-S, denoting a β-cell profile as healthy as the

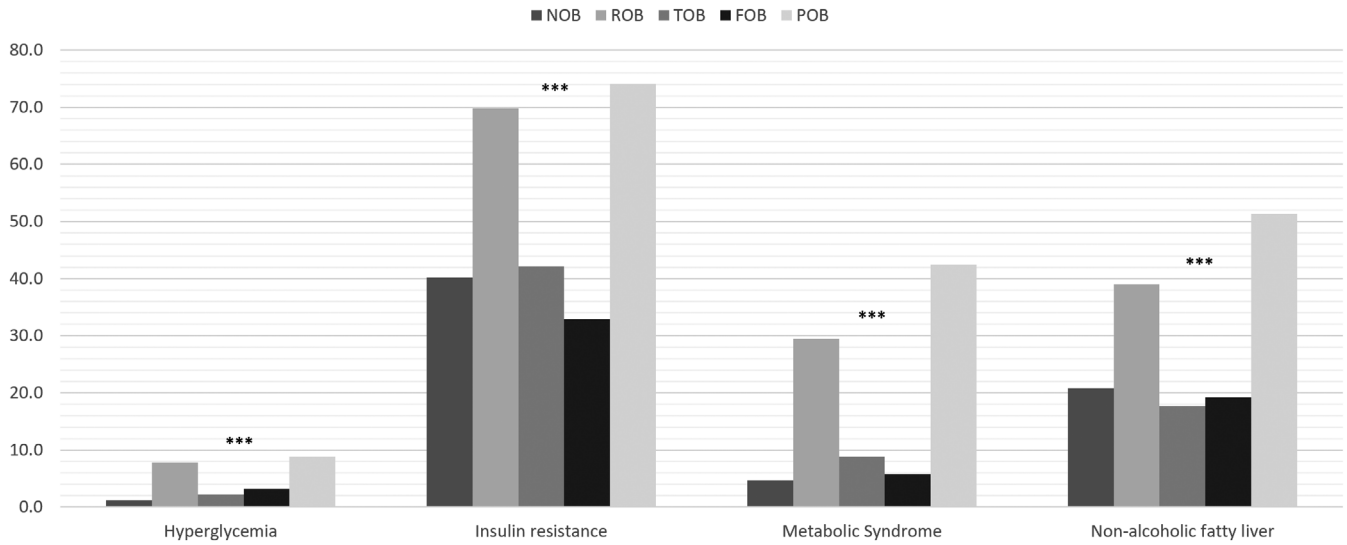

FIGURE 2 Impaired insulin sensitivity related conditions at 23 years by age of onset and persistency of obesity in the Santiago Longitudinal Study (SLS) (n = 1039). Metabolic syndrome and hyperglycaemia diagnosed with the AHA/IDF/ATP-III joint standard. Insulin resistance (IR) diagnosed with HOMA-IR values ≥2.6. NAFLD was diagnosed with Hamagushi score ≥ 4. Non-alcoholic fatty liver assessed in n = 630 participants. FOB, formerly obese; HOMA, Homeostatic model assessment-insulin resistance; NAFLD, non-alcoholic fatty liver disease; NOB, never obese; POB, persistently obese; ROB, recent-onset obese; TOB, transiently obese. Bold denotes between-group statistical differences as follows: *Significant at $\alpha < 0.05$. **Significant at $\alpha < 0.01$. ***Significant at $\alpha < 0.001$

reference group. The same pattern was observed when HOMA2 and DI2 were the dependent variables.

A between group comparison (Figure 3A,B), showed that: (a) ROBs and POBs had a similar β-cell functionality profile in emerging adulthood, (b) ROBs and POBs had significantly higher HOMA1-IR, HOMA1-β(%) and Ins, and lower values of HOMA1-S and DI compared to NOBs, TOBs and FOBs, (c) NOBs' β-cell profile was similar to that exhibited by TOBs and (d) FOBs were the group having the healthiest β-cell functionality profile, of all the groups, in emerging adulthood. Similar results were obtained when using HOMA2 and DI2 as dependent variables in the analysis (see Figure S1 in Supplementary Material).

4 | DISCUSSION

4.1 | Main findings

This study of participants in a prospective longitudinal study of a Chilean cohort found that both recent-onset and long-term obesity were associated with greater impairment of β-cell functionality in emerging adulthood compared to transient or FOB or never having been obese. In our sample, participants with obesity since adolescence had a β-cell profile similar to that of participants who were obese since early childhood and remained obese into their 20s. Also, we observed that participants who were transiently obese, with obesity starting in preadolescence and transitioning to normal weight or overweight status in adolescence, and those who were obese in early childhood but who transitioned normal weight or normal weight status as preadolescents (formerly obese) had no differences in their β-cell functionality profile compared to participants who were NOB.

Other longitudinal studies support our findings that the relationship between obesity in early childhood and T2D in adulthood is associated with the BMI trajectory. A study in Finnish adults showed that the cumulative incidence of T2D decreased progressively from 8.6% in individuals whose adiposity rebound occurred before the age of 5 years to 1.8% in those in whom it happened after the age of 7 years.[14] In the United Kingdom, the National Birth Cohort Study showed that a younger age at adiposity rebound was associated with increased rates of T2D in adulthood and the association was independent of sex, birth weight, father's socioeconomic status (SES), parental diabetes and participant's SES.[15] Conversely, a study in Swedish males observed that an increase in BMI at puberty related to an increased risk of T2D in adulthood independent of BMI in early childhood.[16] Similarly, in Denmark, a large-scale cohort study using data from the Copenhagen School Health Records Register found that a higher BMI between 7 and 12 years was associated with a higher risk of TD2 in adulthood. The associations were stronger in females than males but were not affected by birthweight.[39] A subsequent investigation in the same cohort observed that childhood overweight at 7 years was associated with increased risks of adult T2D only if overweight persisted in puberty or later.[40] Although a substantial body of evidence suggests that obesity in early childhood relates to higher T2D risk in the future, these studies do not differentiate between subjects who were obese in early childhood and stopped being obese later and those who were obese in early childhood and remained obese. Also, these studies do not consider the impact of obesity length on the risk of

TABLE 2 Estimated regression coefficients examining the association of age of onset and persistency of obesity with β-cell profile at 23 y (n = 1039)

	Obesity in early childhood (−)						Obesity in early childhood (+)			
	NOB[c]		ROB		TOB		FOB		POB	
	Intercept									
	Model 1[a]	*P*	Coeff.	*P*	Coeff.	*P*	Coeff.	P	Coeff.	P
Insulin (uUI/dL)	12.2	<.001	7.16	<.001	0.87	NS	−1.38	NS	7.99	<.001
HOMA1-IR	2.68	<.001	1.67	<.001	0.37	NS	−0.29	NS	1.95	<.001
HOMA1-S (%)	50.1	<.001	−15.6	<.001	−1.68	NS	4.87	NS	−18.7	<.001
HOMA1-β (%)	189.2	<.001	76.2	<.001	−3.86	NS	−23.2	.042	90.2	<.001
HOMA-AD	0.72	<.001	0.55	<.001	0.25	NS	−0.17	NS	0.99	<.001
Disposition index 1	0.77	<.001	−0.12	.002	−0.05	NS	−0.02	NS	−0.08	.019
HOMA2-IR	1.59	<.001	0.94	.001	0.08	NS	−0.20	.041	1.04	<.001
HOMA2-S (%)	83.0	<.001	−25.5	<.001	−1.58	NS	9.24	.022	−30.1	<.001
HOMA2-β (%)	134.9	<.001	42.5	<.001	−1.38	NS	−11.7	.022	44.9	<.001
Disposition index 2	0.95	<.001	−0.16	<.001	−0.02	NS	0.02	NS	−0.17	<.001
Adiponectin (μg/mL)	6.8	<.001	−1.1	.010	−1.1	NS	0.4	NS	−1.1	<.001
	Model 2[b]									
Insulin (uUI/dL)	9.7	<.001	3.1	<.001	0.8	NS	−1.5	.022	2.8	<.001
HOMA1-IR	2.1	<.001	0.7	.001	0.3	NS	−0.3	.030	0.6	.002
HOMA1-S (%)	59.1	<.001	−4.8	.042	−1.8	NS	5.2	.025	−5.8	.034
HOMA1-β (%)	147.2	<.001	37.2	.004	2.1	NS	−20.5	.032	46.4	<.001
HOMA-AD	0.66	<.001	0.19	NS	0.17	NS	−0.17	NS	0.45	.002
Disposition index 1	0.72	<.001	−0.13	.034	−0.03	NS	−0.01	NS	−0.09	.021
HOMA2-IR	1.25	<.001	0.42	<.001	0.08	NS	−0.21	.017	0.38	<.001
HOMA2-S (%)	92.1	<.001	−16.5	<.001	3.3	NS	7.9	.025	−19.6	<.001
HOMA2-β (%)	120.0	<.001	30.5	<.001	2.1	NS	−9.2	.046	31.8	<.001
Disposition index 2	0.96	<.001	−0.11	<.001	−0.01	NS	0.03	NS	−0.09	<.001
Adiponectin (μg/mL)	6.0	<.001	−0.8	NS	−0.6	NS	0.6	NS	−1.0	.016

[a]Model 1 is non-adjusted.

[b]Model 2 adjusted for sex, and cardiometabolic risk at 23 y (having the MetS).

[c]Never-obese participants (NOB) are the reference group. Coefficients are the mean difference between a given category and the reference group (Intercept).

Abbreviations: FOB, formerly obese; HOMA, Homeostatic model assessment-insulin resistance; NOB, never obese; POB, persistently obese; ROB, recent-onset obese; TOB, transiently obese.

developing T2D. The absence of these elements in the analysis may contribute in part to the disparity in the results.

In both POBs and ROBs, the prevalence of fasting hyperglycaemia, IR, NAFLD and MetS was remarkably high with significant differences when compared to NOBs, TOBs and FOBs. The accumulation of triacylglycerol in hepatocytes derived from the plasma non-esterified fatty acid pool, supplied mainly by the adipose tissue, could explain these results.[41] NAFLD and IR remain strong predictors of T2D that develops with the worsening of the hepatic regulation of glucose production.[42] A strong association of fatty liver with risk factors for T2D has been found in a sample of young obese African Americans (8-25 years) who had reduced HOMA-S and DI indicating a failure of compensatory insulin secretion/clearance in response to IR.[43] Because NAFLD is a highly prevalent obesity-related comorbidity in the paediatric population and is associated with a higher risk of T2D in adulthood, both the European Society of Endocrinology and the Paediatric Endocrine Society have stressed the need to rule out the presence of fatty liver in every child who is overweight or obese.[12,13]

Our results suggest that the presence of obesity, whether it is recent- or long-term, always carries a risk of major cardiometabolic complications. Interestingly, other cohort studies concluded that metabolically healthy obese subjects also have an increased risk of developing type-2 diabetes compared to normal weight subjects.[44-46] It seems that obesity never comes toll-free; therefore, the only options are to overcome or avoid it.

In our participants, long-term obesity was unrelated to greater β-cell dysfunctionality compared to ROB. T2D is characterized by

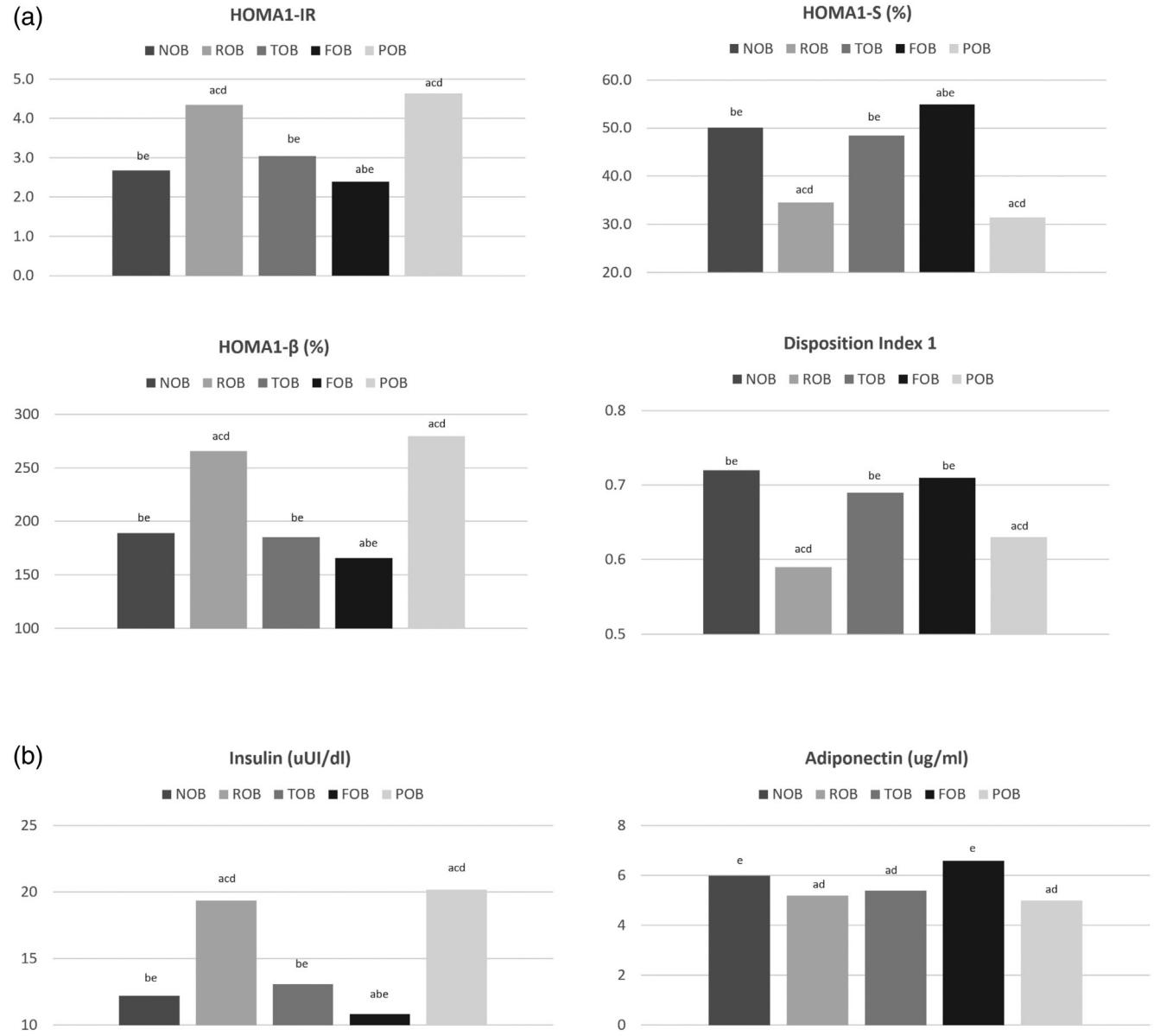

FIGURE 3 **Association of age of onset and persistency of obesity with β-cell profile in adulthood (n = 1039): between group comparison.** Participants who were never obese (NOB); participants with obesity starting in adolescence and remained obese into adulthood (recent-onset obese, ROB); participants who were obese in early childhood but transitioned to non-obesity as preadolescents (formerly obese, FOB); participants who were obese in early childhood and remained obese into adulthood (persistently obese, POB); participants with obesity starting in preadolescence and transitioned to non-obesity as adolescents (transiently obese; TOB). All models were adjusted for sex and having the MetS at 23 years. Between group comparison tested with Bonferroni adjustment. A, Significantly different from NOB. B, Significantly different from ROB. C, Significantly different from TOB. D, Significantly different from FOB. E, Significantly different from ROB

insulin deficiency in response to an increase in insulin demand induced by IR maintained over time, as a result of a disability of β-cells to increase mass and function.[21] For that reason, we cannot sustain that POBs will continue to have similar β-cell functionality profile than ROB group in the later stages of life.

Another significant result was that obesity in early childhood led to increased β-cell dysfunctionality in emerging adulthood only when obesity persisted through the years, as it was the case in the POB group. Instead, FOB participants, whose age at obesity onset was 1.9 years but transitioned to non-obesity at 8.1 years, had a β-cell functionality similar to participants who were NOB. A comparison of DXA-assessed fat mass percentage at 23 years in males and females after controlling age of onset and persistency of obesity (data not shown) indicated no significant differences between FOB and NOB participants. This suggests that β-cell impairment caused by early obesity can be prevented when children transition to a non-obese status. Nonetheless, these children should be followed as they grow into adults because although FOBs did not show a β-cell impairment compared to NOBs, they did have significantly higher values of BMI in preadolescence, adolescence and emerging adulthood than NOBs.

Thus, our findings emphasize the importance of promoting healthy dietary habits and regular exercise since the very beginning, particularly in children who had obesity before the age of 6 years. In developing countries, the prevalence of overweight and obesity among preschoolers exceeds 30%.[47] In Chile, more than one in four children < 6 years has obesity.[10]

4.2 | Limitations and strengths

We must acknowledge some limitations of our study. The results cannot be extrapolated to the overall Chilean population of young adults as our participants were of low-to-middle SES. However, this potential SES bias might be of especial interest, as the prevalence of obesity and T2D is higher in socially vulnerable individuals.[3,4] Second, our participants had normal birthweight, so our findings cannot be generalized to populations with extreme birthweights. Thus, we might have underestimated the β-cell dysfunctionality associated with long-term obesity. Despite these limitations, our study has several strengths. Our sample consists of participants born during a dramatic nutritional transition as Chile progressed from low-income to upper middle-income country.[48] Thus, the SLS is particularly useful to study the impact of obesity in early childhood on the future risk of impaired β-cell functioning or even T2D in individuals exposed to a thrifty phenotype. Another strength was the availability of BMI data from birth through adulthood, with multiple assessments that allowed estimation of BMI trajectories using models that provide a more realistic representation of BMI across the lifecourse.[36,37]

4.3 | Conclusion

In our sample of Chilean young adults followed since infancy, we found that both recent-onset and long-term obesity increased the risk of β-cell impairment in emerging adulthood. Moreover, ROB increased the risk of β-cell impairment to the same level as long-term obesity. Likewise, participants who had early obesity but transitioned to non-obesity in preadolescence had a β-cell profile in emerging adulthood similar to participants who were NOB. Our findings confirm that obesity prevention in infancy, childhood and adolescence might be quite helpful to decrease the risk of T2D in adulthood.

CONFLICT OF INTEREST

The authors certify that they have no affiliations with or involvement in any organization with any financial interest or non-financial interest in the subject discussed in this manuscript.

AUTHOR CONTRIBUTIONS

Conceptualisation, Raquel Burrows and Paulina Correa-Burrows; methodology, Raquel Burrows, Paulina Correa-Burrows, José Rogan; formal analysis, Paulina Correa-Burrows, José Rogan, Daniel Bunout; investigation, Raquel Burrows, Paulina Correa-Burrows; data collection, Raquel Burrows, Paulina Correa-Burrows, Daniel Bunout, Gladys Barrera; data curation, Raquel Burrows; writing—original draft preparation, Raquel Burrows; writing—review and editing, Estela Blanco, Elissa Kim, Sheila Gahagan, Paulina Correa-Burrows, José Rogan, Gladys Barrera, Daniel Bunout; supervision, Raquel Burrows, Sheila Gahagan; project administration, Raquel Burrows, Estela Blanco; funding acquisition, Sheila Gahagan, Raquel Burrows, Paulina Correa-Burrows, José Rogan.

DATA AVAILABILITY

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

ETHICS STATEMENT

Ethical approval was obtained by the IRBs of the University of Michigan, Institute of Nutrition and Food Technology (University of Chile), and the University of California, San Diego. Informed and written consent was provided according to the norms for Human Experimentation, Code of Ethics of the World Medical Association (Declaration of Helsinki, 1995).

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