Regression to the Mean Contributes to the Apparent Improvement in Glycemia 3.8 Years After Screening: The ELSA-Brasil Study

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OBJECTIVE

Glycemic regression is common in real-world settings, but the contribution of regression to the mean (RTM) has been little investigated. We aimed to estimate glycemic regression before and after adjusting for RTM in a free-living cohort of adults with newly ascertained diabetes and intermediate hyperglycemia (IH).

RESEARCH DESIGN AND METHODS

The Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) is a cohort study of 15,105 adults screened between 2008 and 2010 with standardized oral glucose tolerance test and HbA_{1c}, repeated after 3.84 ± 0.42 years. After excluding those receiving medical treatment for diabetes, we calculated partial or complete regression before and after adjusting baseline values for RTM.

RESULTS

Regarding newly ascertained diabetes, partial or complete regression was seen in 49.4% (95% CI 45.2–53.7); after adjustment for RTM, in 20.2% (95% CI 12.1–28.3). Regarding IH, regression to normal levels was seen in 39.5% (95% CI 37.9–41.3) or in 23.7% (95% CI 22.6–24.3), depending on use of the World Health Organization (WHO) or the American Diabetes Association (ADA) definition, respectively; after adjustment, corresponding frequencies were 26.1% (95% CI 22.4–28.1) and 19.4% (95% CI 18.4–20.5). Adjustment for RTM reduced the number of cases detected at screening: 526 to 94 cases of diabetes, 3,118 to 1,986 cases of WHO-defined IH, and 6,182 to 5,711 cases of ADA-defined IH. Weight loss ≥2.6% was associated with greater regression from diabetes (relative risk 1.52, 95% CI 1.26–1.84) and IH (relative risk 1.30, 95% CI 1.17–1.45).

CONCLUSIONS

In this quasi–real-world setting, regression from diabetes at ~4 years was common, less so for IH. Regression was frequently explained by RTM but, in part, also related to improved weight loss and homeostasis over the follow-up.

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Remission from diabetes (1–3) and intermediate hyperglycemia (IH) (4) has been reported in various clinical trials of patients undergoing intensive lifestyle interventions. However, in real-world settings, regression has been little investigated.

In one community-based cohort of individuals detected in a trial for screening and early treatment of diabetes, 30% of the initially detected and confirmed patients presented partial or complete remission from diabetes at 5 years (5). Additionally, in a community-based cohort of individuals with IH (6), remission to normal levels at 1 year was present in 54.0%. Although improvements may be interpreted as related to lifestyle changes, they may be explained, at least partially, by regression to the mean (RTM) (7), owing to the large variability that exists in glucose measures over time (8).

RTM is a statistical phenomenon in which extreme values tend to regress to the mean upon retesting. The Brazilian ELSA-Brasil (Longitudinal Study of Adult Health) study allows evaluation of the frequency of glycemic regression and factors related to it, including RTM. This large contemporary cohort study performed repeat glycemic evaluations by oral glucose tolerance test (OGTT) and HbA$_{1c}$ and advised those who had abnormal values to seek clinical attention and to change lifestyle (9), without performing any additional interventions aimed at changing behavior.

Thus, our objective was to estimate the fraction of ELSA-Brasil participants without known diabetes and meeting diabetes or IH cutoffs at baseline who showed glycemic regression at follow-up, before and after adjustment for RTM, and additionally, to assess the degree to which glycemic regression was associated with improved homeostasis, weight loss, and increased physical activity.

RESEARCH DESIGN AND METHODS

Study Design and Analytic Sample

ELSA-Brasil is a prospective occupational cohort study assembled between 2008 and 2010 (visit 1) in six capital cities of different regions of Brazil. We enrolled 15,105 active or retired civil servants, 35–74 years of age, of public universities or research institutions and performed a comprehensive set of questionnaires, clinical measurements, and laboratory tests. We recalled participants between 2012 and 2014 for a new set of interviews and examinations (visit 2), as previously described (10). Ethics committees of each institution approved the research protocols of both visits, and all subjects gave written consent to participate.

Measurements

Measurements obtained during visits 1 and 2 followed standardized protocols and regular quality control assessments (11). We ascertained age, race/skin color, educational achievement, medication use, and past medical history by standardized questionnaires. Medication use was verified against packages or prescriptions brought to the clinic. Weight, height, and waist circumference were measured with standard techniques, and physical activity was assessed in MET-minutes/week by the International Physical Activity Questionnaire (IPAC) using the leisure time and transport domains (10,12). BMI was defined as weight (kg)/height (m)^2.

We obtained an overnight fasting blood sample by venipuncture soon after arrival at the clinic and followed standardized procedures for a 2-h 75-g OGTT (13). Plasma glucose (PG) was measured using the hexokinase method, insulin by an immunoenzymatic assay (Siemens), and HbA$_{1c}$ by high-pressure liquid chromatography (Bio-Rad), a method certified by the NGSP. Intraclass correlation coefficients expressing between-person variance as a percentage of total variance, obtained analyzing blind replicate pairs of samples drawn at baseline, were 99% (95% CI 0.95–1.0) for glucose and 94% (95% CI 0.86–0.97) for HbA$_{1c}$ (14).

We estimated insulin resistance (IR) by HOMA2-IR and β-cell function by HOMA2-β calculations, using the program HOMA Calculator v2.2.3 for values of fasting PG (FPG) within the range of 3–25 mmol/L and of fasting insulin within the range of 20–400 pmol/L (https://www.dtu.ox.ac.uk/homacalculator/download.php). We calculated the disposition index (DI) as the product of HOMA2-β and 1/HOMA2-IR (15).

Ascertainment of Diabetes and IH

At visit 1, we ascertained diabetes based on laboratory measurements and self-reported information. A participant was considered to have previously diagnosed diabetes when reporting a previous medical diagnosis of diabetes or the use of medication for diabetes in the past 2 weeks. We did not consider as having a previous diagnosis those informing a diagnosis only while pregnant.

Those without a previous diagnosis of diabetes were classified as having diabetes if they reached the thresholds for

FPG (≥7.0 mmol/L; 126 mg/dL), 2 h PG (≥11.1 mmol/L; 200 mg/dL), or HbA$_{1c}$ (≥48 mmol/mol; 6.5%) (16,17). Among those not meeting diabetes criteria, IH was defined by both ADA and WHO criteria. For the ADA criteria, we defined impaired glucose tolerance as a 2-h PG ≥7.8 mmol/L (≥140 mg/dL), impaired fasting glucose (IFG) by a FPG ≥5.6 mmol/L (≥100 mg/dL), and elevated HbA$_{1c}$ by a value ≥39 mmol/mol (≥5.7%). For the WHO criteria, in addition to impaired glucose tolerance, IFG was defined by a FPG ≥6.1 mmol/L (≥110 mg/dL) and intermediate HbA$_{1c}$ as ≥42 mmol/mol (≥6.0%). At visit 2 we applied the same diagnostic criteria to classify diabetes and IH and ascertained regression by comparing categories between visits 1 and 2.

Information Given to Participants Regarding Abnormal Glucose Values

At baseline we provided all laboratory results to participants, alerting that eventual abnormal values in glucose or other tests needed confirmation to establish a clinical diagnosis and that lifestyle changes based on a healthy diet and regular physical activity were important to maintain normal glucose levels and health in general. Being enrolled in a longitudinal study to assess health, participants were aware that new evaluations would take place every 3–4 years.

Definition of Glycemic Regression From Diabetes or IH

We defined regression from diabetes as being complete (to normal glycemia by all three glycemic tests) or incomplete (to IH, but no longer meeting diabetes criteria by any of the three glycemic tests) (18). We defined regression from IH as normalization of all three glycemic tests.

Analyses

We calculated incidence of regression from diabetes and IH, and graphically displayed changes in the DI for those who reverted to normal, confirmed IH, or progressed to diabetes.

RTM was initially evaluated graphically by relating baseline with follow-up values using linear regression models. To account for RTM in the evaluation of glycemic changes from baseline to follow-up, we adjusted baseline values with the following formula (19,20):

$$X_a = X + (1 - r) * (\bar{X} - X)$$

where:

X_a = baseline value adjusted for RTM
X = baseline value
r = correlation between baseline and follow-up values
$\bar{X}$ = mean baseline value.

This adjustment permitted comparison of glycemic regression before and after these adjustments.

We evaluated the association of baseline characteristics with glycemic regression adjusting through Poisson regression with robust variance for baseline covariates, including age, sex, race/color, educational achievement, family history of diabetes, BMI, waist circumference, physical activity, and glycemic values. The latter were centered at their means. Finally, with similar models, we evaluated the association of larger changes (≥80th percentile) observed during follow-up in weight, waist circumference, physical activity, and the DI with glycemic regression. We fit three progressively adjusted models evaluating the change in exposures, first including age, sex, race/color, and educational achievement (model 1); next, family history of diabetes, baseline BMI, waist circumference, and physical activity (model 2); and finally, baseline fasting and 2-h glucose and HbA_{1c}.

We performed all analyses with SAS 9.4 for Windows (SAS Institute, Cary, NC).

RESULTS

A total of 15,090 participants had complete information to ascertain diabetes at visit 1, 13,618 not reporting a previous diagnosis of diabetes or medication use to treat diabetes during the previous 2 weeks. Among these, 950 met diabetes criteria, 7,165 met IH criteria by at least one laboratory test, and 5,503 had normoglycemic values. After additional exclusions, including those with a history of bariatric surgery or use of diabetes medication between visits, our analytic sample was composed of 526 subjects with newly diagnosed diabetes, 6,182 of IH and 4,937 of normoglycemia, thus totaling 11,645 participants (Supplementary Fig. 1).

Among these 11,645 participants free of known diabetes at baseline and not receiving medical treatment, there were

slightly fewer men (44.8%) than women (55.2%), most (66.9%) were between 45 and 64 years old, White (53.6%), with a university degree (55.5%), overweight or obesity (59.7%), and without a family history of diabetes (64.3%). Among the 526 participants with newly ascertained diabetes at baseline, there were slightly more men (54.9%) than women (45.1%), participants being most frequently aged 45–64 years (72.4%), White (42.1%), with less than a university degree (58.1%), and with overweight or obesity (80.2%). Similar characteristics were seen for the 6,182 subjects with IH at baseline, although the proportions of men and women were closer, and subjects tended to be younger and with less obesity. From crude and initial descriptive information, it is apparent that the cohort gained weight, increased physical activity, and worsened glycemic values between baseline and follow-up. Of note as well, mean FPG at baseline was at the level of the ADA cutoff to define IH (Supplementary Table 1).

As seen in Table 1, after a mean of 3.84 ± 0.42 years of follow-up, among those ascertained as having diabetes at baseline, we found substantial glycemic regression (to IH or to normal levels) when considering the results of each test separately: 41.3% (95% CI 34.6–48.0), 41.5% (95% CI 35.7–47.3), and 70.4% (95% CI 63.3–77.4) for FPG, 2-h PG, and HbA_{1c}, respectively. Regression to normal levels was considerably less frequent, 2.9%, 7.9%, and 24.1%, respectively. We also examined results of multiple tests at a single occasion to identify those less likely to regress from diabetes upon retesting. On the basis of having two positive tests, only 10.0–17.5% regressed, complete regression to normoglycemia being virtually absent. With three positive tests, only 11.6% regressed, none to normal levels.

As also seen in Table 1, regression from IH varied according to the criteria used to define it. When we used the WHO criteria, regression to normal levels was seen in 44%, 43.8%, and 80% for FPG, 2-h PG, and HbA_{1c}, respectively, and when we defined by the ADA criteria, in 27.0%, 43.8%, and 61.3%, respectively. Multiple testing also reduced the likelihood of regression, although less effectively than when used for detecting diabetes.

Scatter plots of baseline and follow-up glycemic values for the three tests (Fig. 1)

illustrate far-from-perfect correlations ($r = 0.62$ for FPG and 2-h PG, and $r = 0.46$ for HbA_{1c}) and downward inclinations ($\beta = 0.84$, 0.75 and 0.54 for FPG, 2-h PG, and HbA_{1c}, respectively) of the estimated regression line from the diagonal, indicative of RTM.

To evaluate the importance of RTM in overall regression, we estimated the frequency of glycemic regression after accounting for RTM. To do so, we adjusted baseline glycemic values according to the equation described in Research Design and Methods, here defining diabetes and IH when detected by at least one of the three tests. Figure 2 shows these results, on the left depicting categories based on the observed glycemic values at baseline and on the right, categories based on those adjusted to account for RTM.

Among the 526 participants (top circles) meeting diabetes cutoffs at baseline, 260 (49.4%; 95% CI 45.2–53.7) regressed: 234 (44.5%; 95% CI 40.0–38.1) to IH and 26 (4.9%; 95% CI 3.1–6.8) to normoglycemia. After adjustment for RTM, the frequency of diabetes at baseline decreased substantially, with only 94 of 526 of the initially defined participants (17.9%) now meeting diabetes cutoffs. Glycemic regression was still present, albeit of lower proportions: 19 (20.2%; 95% CI 12.1–28.3) regressed, 17 (18.1%; 95% CI 10.3–25.9) to IH and 2 (2.0%; 95% CI 0–5.0) to normal.

Among the 3,118 subjects (middle circles) meeting WHO IH cutoffs at baseline, 1,234 (39.5%; 95% CI 37.9–41.3) regressed, reaching normal values, and 404 progressed to diabetes (13.0%; 95% CI 11.8–14.1). After adjustment for RTM, 1,986 of 3,118 of the initially defined participants (63.7%) now met IH cutoffs, with 519 (26.1%; 95% CI 22.4–28.1) regressing to normal and 492 progressing to diabetes (24.3%; 95% CI 22.4–26.2).

Among the 6,182 subjects (bottom circles) meeting the ADA criteria for IH, 1,464 (23.7%; 95% CI 22.6–24.3) regressed, reaching normal values, and 499 progressed to diabetes (8.1%; 95% CI 7.4–8.7). After adjustments, 5,711 of 6,182 of the initially defined participants (92.4%) now met IH cutoffs, with 1,110 (19.4%; 95% CI 18.4–20.5) regressing to normal and 649 progressing to diabetes (11.4%; 95% CI 10.5–12.2).

Thus, after accounting for RTM, the fraction of those regressing decreased

Table 1—Glycemic regression at 3.8 years of follow-up of those meeting cutoffs for diabetes or IH at baseline

Diabetes at baseline	All (N = 526)	Any regression		Regression to IH		Regression to normal	
	N	N	%	N	%	N	%
Multiple tests on the same occasion: FPG, 2-h PG, and/or HbA$_{1c}$							
Abnormal by one of the three tests							
FPG ≥7.0 mmol/L	206	85	41.3	79	38.4	6	2.9
2-h PG ≥11.1 mmol/L	277	115	41.5	93	33.6	22	7.9
HbA$_{1c}$ ≥48 mmol/mol	162	114	70.4	75	46.3	39	24.1
Abnormal by two tests							
FPG ≥7.0 and 2-h PG ≥11.1 mmol/L	97	17	17.5	16	16.5	1	1
FPG ≥7.0 and HbA$_{1c}$ ≥48 mmol/mol	50	7	14	7	14	0	0
2-h PG ≥11.1 mmol/L and HbA$_{1c}$ ≥48 mmol/mol	50	5	10	5	10	0	0
Abnormal by all three tests	43	5	11.6	5	11.6	0	0

IH at baseline defined by the WHO criteria	All (N = 3,118)					Regression to normal	
	N					N	%
Multiple tests on the same occasion: FPG, 2-h PG, and/or HbA$_{1c}$							
Abnormal by one of the three tests							
FPG ≥6.1 mmol/L	1,078					474	44
2-h PG ≥7.8 mmol/L	2,031					889	43.8
HbA$_{1c}$ ≥42 mmol/mol	603					485	80.4
Abnormal by two tests							
FPG ≥6.1 and 2-h PG ≥7.8 mmol/L	457					85	18.6
FPG ≥6.1 and HbA$_{1c}$ ≥42 mmol/mol	127					46	36.2
2-h PG ≥7.8 mmol/L and HbA$_{1c}$ ≥42 mmol/mol	124					38	30.7
Abnormal by all three tests	66					7	10.6

IH at baseline defined by the ADA criteria	All (N = 6,182)					Regression to normal	
	N					N	%
Multiple tests on the same occasion: FPG, 2-h PG, and/or HbA$_{1c}$							
Abnormal by one of the three tests							
FPG ≥5.5 mmol/L	4,811					1,298	27
2-h PG ≥7.8 mmol/L	2,031					889	43.8
HbA$_{1c}$ ≥38.8 mmol/mol	1,678					1,028	61.3
Abnormal by two tests							
FPG ≥5.5 and 2-h PG ≥7.8 mmol/L	1,344					154	11.5
FPG ≥5.5 and HbA$_{1c}$ ≥38.8 mmol/mol	939					142	15.1
2-h PG ≥7.8 mmol/L and HbA$_{1c}$ ≥38.8 mmol/mol	338					72	21.3
Abnormal by all three tests	336					19	5.7

Data are based on FPG, 2-h PG, and HbA$_{1c}$ in ELSA-Brasil, 2008–2020.

substantially (59.1%; from 49.4% to 20.2%) for participants initially labeled as having diabetes; moderately (34.0%) for those labeled as having IH by the WHO cutoffs, and less so (17.9%) for those labeled as having IH by the ADA cutoffs.

We then investigated whether changes in glucose homeostasis accompanied glycemic regression during the follow-up. From a mean DI at baseline of 47.4 (Supplementary Table 1), for those ascertained as having diabetes at baseline (left panels, Supplementary Fig. 2) who regressed to normal, the median DI increased by 11.3 (P < 0.001), with improvements in both β-cell function and insulin sensitivity. For those regressing to

IH, the median DI increased less (6.8%; P < 0.001), with more modest improvement in insulin sensitivity and a minor worsening in β-cell function. For those with diabetes confirmed at reevaluation, DI decreased (−5.3; P < 0.001), reflecting worsened β-cell function and stable insulin sensitivity (Supplementary Fig. 2).

Similarly, among those classified as having IH at baseline (Supplementary Fig. 2, right panels), from a mean baseline DI of 65.4, for those who regressed to normoglycemia, the median DI increased slightly (4.3; P < 0.001), with both improved insulin sensitivity and β-cell function. For those who confirmed IH, DI decreased somewhat (−3.0; P < 0.001),

and for those who progressed to diabetes, the median DI decreased (−13.0; P < 0.001), with β-cell function and insulin sensitivity both worsened.

We also evaluated whether changes in lifestyle between visits could explain part of the regression from diabetes and IH among those not reporting bariatric surgery and antidiabetic medication at follow-up. We ran three separate sets of progressive models, each one evaluating three changes that occurred between visits—weight loss, reduced waist circumference, and increased physical activity. As seen in Table 2, in the final adjusted model, the likelihood of regression from diabetes, compared with those
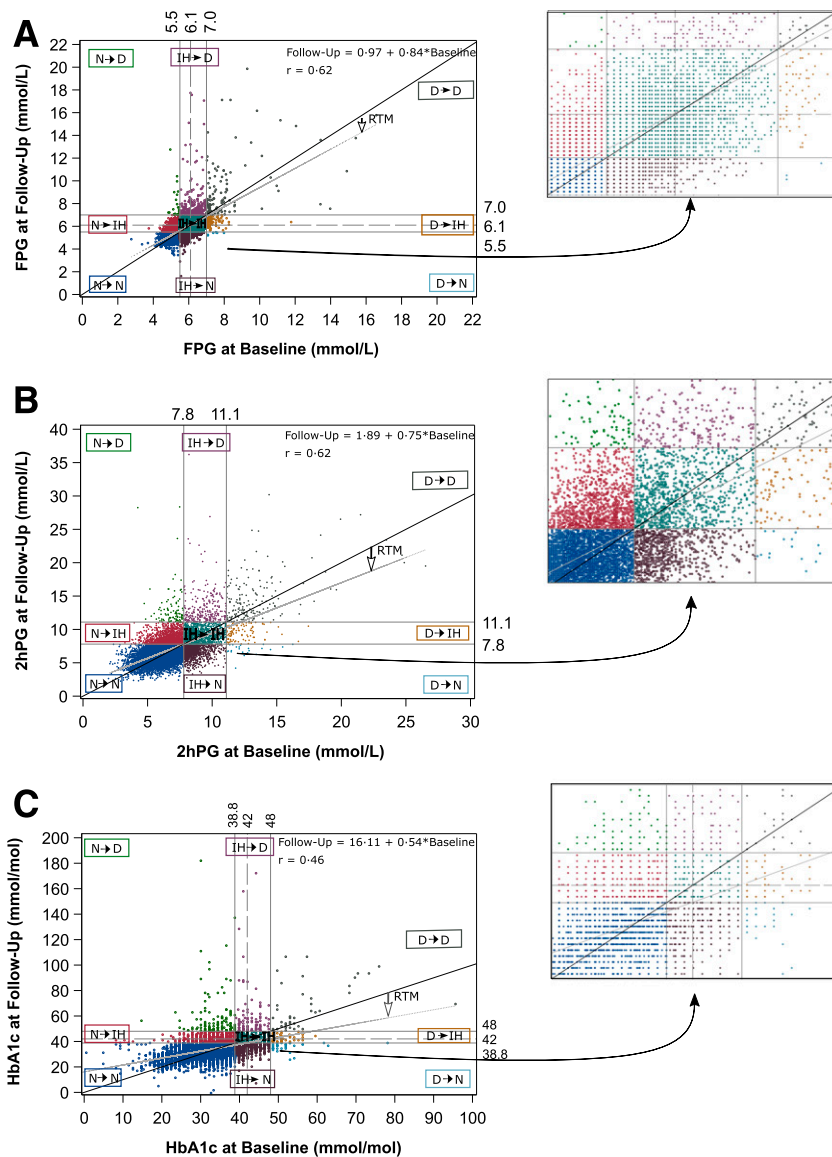
Figure 1—Scatter plots of baseline and follow-up glycemic values and estimated parameters of linear regression for FPG (*A*), 2-h PG (*B*), and glycated hemoglobin (HbA$_{1c}$) (*C*). The dark line is the 45° diagonal; the fine line is the predicted fit. Additional graphs show details of central portions. D, diabetes; N, normal.

with lesser or unchanged values, was greater for those with a larger (≥80 percentile) change between visits: a ≥2.6% loss of initial weight (relative risk [RR] 1.52; 95% CI 1.26–1.84), a ≥1.4 cm decrease in waist circumference (RR 1.33; 95% CI 1.07–1.67); and a ≥552 MET-min/week increase in physical activity (RR 1.29; 95% CI 1.08–1.55).

The likelihood of regression from IH was greater in the final model only for those with a larger weight loss (RR 1.30; 95% CI 1.17–1.45) and a larger reduction in waist circumference (RR 1.22; 95% CI 1.08–1.38).

In similar models, a larger improvement in the DI (≥12.5; ≥80 percentile)

was associated with regression from diabetes (RR 1.91; 95% CI 1.63–2.23) and IH (RR 2.84; 95% CI 2.60–3.09).

CONCLUSIONS

Within the context of a cohort study of adults tested with an OGTT and an HbA$_{1c}$, at 3.8 years of follow-up, 49.4% of those ascertained as having diabetes had regressed (15.4% to normal and 34% to IH). After adjustment for RTM, regression decreased considerably, with only 20.2% regressing, 5% to normal and 15% to IH. Among those ascertained as having IH, regression was also frequent when defined by WHO criteria, 39.5% and 26.1% after adjustment for RTM; but less so

when defined by the ADA criteria, 23.7%, and 19.4% after adjustment for RTM. The use of more than one test helped identify those more likely to regress. To our knowledge, this is the first evaluation of RTM among individuals with new-onset diabetes and IH detected in a large and contemporary observational study and receiving no structured intervention.

The regression from diabetes we found after adjusting for RTM (20%) is comparable to that of those enrolled in a trial of community-based screening (Anglo-Danish-Dutch Study of Intensive Treatment In People with Screen Detected Diabetes in Primary Care [ADDITION]-Cambridge study), in which 30% of participants initially detected were below diagnostic cutoffs (HbA$_{1c}$ <6.5%; <43 mol/mol off antidiabetic medication) at the 5-year follow-up (5). Their slightly greater frequency of glycemic regression may be due to the more intensive intervention offered in the treatment arm of the trial. On the other hand, both our and the ADDITION results show a greater frequency of regression than that seen in an integrated health care delivery system, which found diabetes remission at 7 years under usual care in only 4.6% of individuals, probably in part due to less focus on identifying these patients (21).

The regression from IH we found before adjustment for RTM (27.0–80.4%, depending on the criteria used for FPG, 2-h PG, or HbA$_{1c}$) (Table 1) is comparable to that found for IH in the CRONICAS (Center of Excellence in Chronic Diseases) cohort study (31.4–66.9% depending on the diagnostic criteria used for FPG and HbA$_{1c}$) at 2.2 years. Although they estimated RTM to be small, the contribution of RTM to regression to normal was not evaluated (22). Our results are also comparable to those found in the ADDITION-Leicester study, which followed up at 1-year individuals with IH (defined by a single OGTT with WHO cutoffs) in a community screening program, finding that 54.0% had regressed to normal levels.

Of note, the adjustment for RTM we adopted here resulted in a marked reduction (59.1%) in the fraction of diabetes cases regressing, a moderate one (34.0%) when considering WHO-defined IH, and a discrete one (17.9%) for ADA-defined IH. That the effect of RTM is more pronounced among subjects with diabetes and WHO-defined IH is consonant
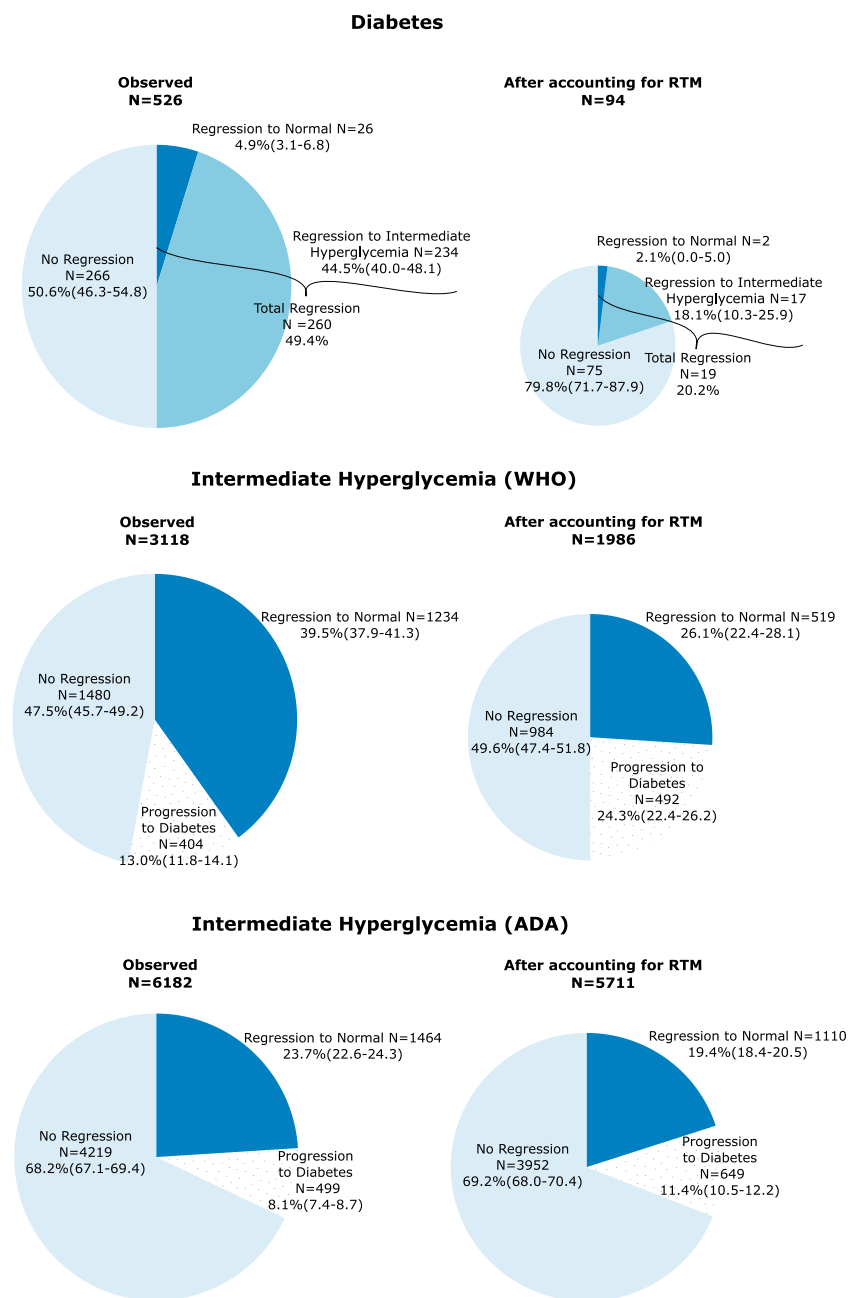
Diabetes

Observed
N=526

Regression to Normal N=26
4.9%(3.1-6.8)

Regression to Intermediate
Hyperglycemia N=234
44.5%(40.0-48.1)

No Regression
N=266
50.6%(46.3-54.8)

Total Regression
N =260
49.4%

After accounting for RTM
N=94

Regression to Normal N=2
2.1%(0.0-5.0)

Regression to Intermediate
Hyperglycemia N=17
18.1%(10.3-25.9)

No Regression
N=75
79.8%(71.7-87.9)

Total Regression
N=19
20.2%

Intermediate Hyperglycemia (WHO)

Observed
N=3118

Regression to Normal N=1234
39.5%(37.9-41.3)

No Regression
N=1480
47.5%(45.7-49.2)

Progression
to Diabetes
N=404
13.0%(11.8-14.1)

After accounting for RTM
N=1986

Regression to Normal N=519
26.1%(22.4-28.1)

No Regression
N=984
49.6%(47.4-51.8)

Progression to
Diabetes
N=492
24.3%(22.4-26.2)

Intermediate Hyperglycemia (ADA)

Observed
N=6182

Regression to Normal N=1464
23.7%(22.6-24.3)

No Regression
N=4219
68.2%(67.1-69.4)

Progression
to Diabetes
N=499
8.1%(7.4-8.7)

After accounting for RTM
N=5711

Regression to Normal N=1110
19.4%(18.4-20.5)

No Regression
N=3952
69.2%(68.0-70.4)

Progression
to Diabetes
N=649
11.4%(10.5-12.2)

Figure 2—Proportions of participants with diabetes and IH at baseline and their glycemic regression at follow-up, before and after adjustments for RTM. Top, diabetes at baseline. Bottom, IH at baseline. The size of the circles illustrates the relative reduction in baseline cases after accounting for RTM.

with the understanding that those with more extreme initial values are more likely to have larger RTM upon retesting. Of note also, adjustment for RTM and the use of multiple tests in the same occasion, although reducing the number of individuals likely to regress from diabetes or IH, also reduces substantially the number of subjects ascertained at screening as having diabetes or IH. Important implications of these findings merit discussion.

First, the substantial proportion of subjects meeting diabetes cutoffs at baseline regressing upon retesting reiterates the need to confirm a positive test before labeling diabetes, as recommended in current clinical guidelines. Although clinicians in busy day-to-day practice may skip confirmation, our findings illustrate that lack of confirmation will result in a large proportion of individuals receiving pharmacological treatment who do not really have diabetes.

That 34.6% of those reporting diabetes in a recent National Health and Nutrition Examination Survey (NHANES) survey presented HbA$_{1c}$ values of ≤6.5% suggests that some degree of overdiagnosis may be present (23). Additionally, it is possible that the fraction of success achieved in clinical trials aiming for diabetes remission will be somewhat exaggerated if diabetes-level glycemia off medication is not confirmed before randomization. In settings where a confirmatory test on a subsequent occasion is not viable, our findings support the use of multiple tests for the diagnosis of diabetes, an option now included in the ADA recommendations (24,25).

Second, our findings further document that the prevalence and incidence of diabetes and IH, when based on a single test, overestimate true rates. In fact, taking the short-term between-day variability of FPG into account in NHANES led to an estimated 24% lower prevalence of diabetes (8). Yet major groups, such as the Non-Communicable Disease Risk Factor Collaboration (NCD-RisC) (26), the Global Burden of Disease Study (27), and the International Diabetes Federation Atlas (28), which characterize prevalence of diabetes worldwide, do not make adjustments for this problem or discuss its relevance. Using multiple tests on the same occasion (Table 1) may be useful to avoid errors in both epidemiologic studies and clinical trials.

Third, our findings among those with IH showing glycemic regression related to RTM or to small changes in lifestyle, as discussed later, highlight the importance of confirming IH before prescribing a structured diabetes prevention program or a medication to prevent diabetes.

Of note also, our finding of glycemic regression not explained by medical treatments after adjustment for RTM in a quasi–real-world scenario is also novel and merits discussion. The glycemic regression we found after taking RTM into account could be interpreted as due to changes in lifestyle during follow-up. Associations of glycemic regression with >5% weight loss and an improved DI support this interpretation and give further evidence that simple, real-world interventions have significant metabolic benefits for diabetes prevention (29). Whether increased insulin sensitivity and/or improved β-cell function underlie these changes deserves further

Table 2—Poisson regression with robust variance estimates of the associations between changes from baseline and regression from diabetes and IH

	Model 1		Model 2		Model 3	
	RR	95% CI	RR	95% CI	RR	95% CI
Regression from diabetes ($n = 526$)						
Weight loss vs. stable						
≥2.6% loss	1.29	1.05 1.59	1.29	1.05 1.58	1.52	1.26 1.84
Reduced waist vs. stable						
≥1.4 cm loss	1.11	0.88 1.4	1.09	0.86 1.38	1.33	1.07 1.67
Increased physical activity vs. stable						
≥552 MET-min/week increase	1.35	1.12 1.63	1.3	1.07 1.58	1.29	1.08 1.55
Increased DI vs. stable						
≥12.5 increase	1.89	1.63 2.21	1.85	1.59 2.17	1.91	1.63 2.23
Regression from IH ($n = 6,182$)*						
Weight loss vs. stable						
≥2.6% loss	1.18	1.06 1.32	1.23	1.1 1.38	1.3	1.17 1.45
Reduced waist vs. stable						
≥1.4 cm loss	1.19	1.04 1.36	1.27	1.11 1.45	1.22	1.08 1.38
Increased physical activity vs. stable						
≥552 MET-min/week increase	1.1	0.99 1.22	1.07	0.96 1.19	1.03	0.93 1.15
Increased DI vs. stable						
≥12.5 increase	2.83	2.6 3.08	2.62	2.4 2.86	2.84	2.6 3.09

Data are shown after 3.8 years of follow-up among those not reporting bariatric surgery or initiating medication for diabetes in ELSA-Brasil, 2008–2014. Model 1, weight loss, reduced waist, increased physical activity, or DI plus age, sex, race/color, educational achievement, and family history of diabetes. Model 2, model 1 plus baseline BMI, waist circumference, and physical activity. Model 3, model 2 plus centered baseline FPG and 2-h PG, and HbA$_{1c}$. *IH based on the ADA criteria.

evaluation, particularly regarding IFG, which is less likely to improve with standard lifestyle changes (30).

A final note regarding the definition used here for glycemic regression: For diabetes, we considered partial or complete regression as a decrease below standard diagnostic cutoffs, FPG (<7.0 mmol/L; 126 mg/dL), 2-h PG (<11.1 mmol/L; 200 mg/dL), or HbA$_{1c}$ (<48 mmol/mol; 6.5%). For complete regression from diabetes, we required a 2-h PG <7.8 mmol/L (140 mg/dL), an FPG <5.6 mmol/L (100 mg/dL), or an HbA$_{1c}$ <39 mmol/mol (5.7%), unless analyses referred specifically to changes based on the WHO criteria, for which cutoffs for FPG and HbA$_{1c}$ are higher. There is no consensus yet on what should be considered "normal values" for each test. Our use of the most stringent ADA definition underestimates glycemic regression when based on the WHO (16) or National Institute for Health and Care Excellence (NICE) cutoffs (31).

Limitations to our findings need to be considered. First, because we excluded approximately one-third of those ascertained as having diabetes at baseline due to subsequent medical treatment, frequencies of regression observed are probably overestimates. However, even if none of those treated would have regressed,

the frequency of regression would remain large.

Second, when generalizing our results, population mean glycemic values must be considered. Given the high mean glycemia in our sample, RTM would be greater in other populations in which IH and diabetes represent a smaller fraction of the whole.

Third, because our study was observational, with greater or lesser lifestyle change occurring without investigator input, it does not permit ascribing changes in glycemia directly to specific changes in behavior/lifestyle. However, that we also observed regression from hypertension related to the modest weight losses during the same time frame (32) further supports the contention that unstructured and low-intensity real-world lifestyle interventions can exert clinically relevant change. In the absence of a control group and considering the small weight changes observed, there remains the possibility of our findings being explained by residual confounding and or incomplete adjustment for RTM.

Strengths of our findings also deserve attention. ELSA-Brasil is a large contemporary cohort, with standardized measurements, low attrition, and glycemia assessed with all three standard diagnostic tests. Our analyses provided

adjustments for RTM in the evaluation of glycemic regression from diabetes and IH, which to our knowledge have rarely been conducted within the context of observational studies in the field of diabetes.

In conclusion, after an average of 3.8 years, in those without medical treatment, glycemic regression had occurred in many of those meeting diabetes and IH cutoffs at baseline. RTM accounted for an important part of this regression. Some of the remaining regression probably resulted from modest weight loss achieved during follow-up.

Author Contributions. M.I.S. drafted the report. M.I.S., P.B., J.S.Y., and B.B.D. designed the analytic plan. M.I.S., S.M.B., D.C., R.G., and B.B.D. are principal investigators of ELSA-Brasil. P.B. and S.C. conducted the data analysis. M.I.S., P.B., S.C., J.M.N.G., S.M.B., D.C., R.G., J.S.Y., and B.B.D. interpreted the data and made meaningful revisions to the manuscript. M.I.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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