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Liver steatosis as a predictor of incident diabetes in adults: a prospective evaluation in the *Brazilian Longitudinal Study of Adult Health* (ELSA-Brasil)

Esteatose hepática como preditor de diabetes incidente em adultos: avaliação prospectiva no *Estudo Longitudinal de Saúde do Adulto* (ELSA-Brasil)

Esteatosis hepática como predictor de diabetes incidente en adultos: evaluación prospectiva en el *Estudio Longitudinal de Salud del Adulto* (ELSA-Brasil)

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Abstract

Increasing epidemiological evidence suggests a bidirectional relationship between non-alcoholic fatty liver disease (NAFLD) and type 2 diabetes, and that NAFLD may precede and/or promote the development of diabetes. This study aimed to investigate whether liver steatosis is associated with the incidence of diabetes in the Brazilian Longitudinal Study of Adult Health *(ELSA-Brasil). The ELSA-Brasil is an occupational cohort study of active or retired civil servants, aged 35-74 years, in six capital cities in Brazil. We excluded participants with diabetes at baseline, those who reported excessive alcohol consumption or with missing information on relevant covariates, and those with self-referred hepatitis or cirrhosis. In total, 8,166 individuals participated, and the mean duration of follow-up was 3.8 years. The Cox proportional regression model was used to estimate the adjusted hazard ratio (HR) for the associations. Abdominal ultrasonography was used to detect liver steatosis. In the follow-up period, the cumulative incidence of diabetes was 5.25% in the whole sample, 7.83% and 3.88% in the groups with and without hepatic steatosis, respectively ($p < 0.001$). Compared to those without steatosis, individuals with hepatic steatosis had an increased risk of developing diabetes (HR = 1.31; 95%CI: 1.09-1.56) after adjustment for potential confounders, including body mass index (BMI). Hepatic steatosis was an independent predictor of incident diabetes in the ELSA-Brasil cohort study. Physicians should encourage changes in lifestyle and screen for diabetes in patients with fatty liver.*

Liver Steatosis; Non-alcoholic Fatty Liver Disease; Type 2 Diabetes Mellitus; Insulin Resistance; Obesity

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Introduction

Non-alcoholic fatty liver disease (NAFLD) has become the leading cause of chronic liver disease worldwide, affecting 17-46% of adults [1]. About 20% of people with NAFLD have non-alcoholic steatohepatitis (NASH), which is associated with fibrosis and can evolve to cirrhosis and hepatocellular carcinoma [2].

Prevalence of type 2 diabetes increased over the last decades and is still increasing globally [3]. Diabetes has been linked to a shorter life expectancy mainly because of its complications, including heart disease, stroke, and kidney failure [4]. Lifestyle changes and medications – such as metformin – are shown to reduce diabetes incidence [5]. Brazil is experiencing a rapid nutritional transition, with marked increases in overweight and obesity across all social strata, particularly in the low socioeconomic stratum. Not surprisingly, diabetes prevalence and associated mortality increased in the last decades [6,7].

NAFLD and diabetes share many cardiometabolic risk factors and pathophysiological pathways. Moreover, increasing epidemiological evidence suggests a bidirectional relationship between NAFLD and diabetes, and that NAFLD may precede and/or promote the development of diabetes [8,9,10,11]. Early identification of individuals at high risk for diabetes would help prevent further complications. Ultrasonography-diagnosed NAFLD has been independently associated with diabetes development, mainly in Asian populations [12,13,14,15,16,17,18,19,20,21,22,23]. This study aimed to determine whether hepatic steatosis is associated with the incidence of diabetes in a Brazilian cohort study, the *Brazilian Longitudinal Study of Adult Health* (ELSA-Brasil).

Methods

Study design and analytic sample

The ELSA-Brasil is a prospective, occupational cohort study aimed at investigating the incidence and progression of diabetes, cardiovascular disease, and other chronic conditions over time. The cohort study was conducted from August 2008 to December 2010, in six capital cities of different Brazilian regions. In total, 15,105 active or retired civil servants of public universities or research institutions aged 35-74 years participated. A comprehensive set of questionnaires, clinical measurements, and laboratory tests were carried out at baseline visit (visit 1). From September 2012 to December 2014, the cohort study was recalled for a new set of interviews and examinations (visit 2), as previously described [24]. ELSA-Brasil was approved by the Brazilian National Research Ethics Commission (CONEP; 976/2006) and by the research ethics committee of each institution: São Paulo University (USP; 669/06), Oswaldo Cruz Foundation (Fiocruz; 343/06), Espírito Santo Federal University (UFES; 041/06), Minas Gerais Federal University (UFMG; 186/06), Rio Grande do Sul Federal University (UFRGS; 194/06), and Bahia Federal University (UFBA; 027/06).

At visit 1, 6,250 participants were excluded: 1,811 participants who had diabetes (confirmed at visit 2), four without enough information to confirm diabetes status, 2,558 who did not undergo liver ultrasonography, 751 who reported excessive alcohol consumption (> 20g/day for women and > 30g/day for men), 275 with missing information on relevant covariates (i.e., daily or weekly alcohol consumption, self-identified race/skin color, weight and/or height, physical activity level), 841 with self-referred hepatitis or cirrhosis, and 10 who had values four times higher or equal to the upper limit of normality for alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST), resulting in 8,855 participants at risk of developing diabetes. Of these, 689 did not attend to the scheduled visit 2 or provided insufficient information to confirm diabetes status or relevant covariates at visit 2. Thus, considering the overlap in exclusion criteria, our final sample totaled 8,166 participants (92.2% of those at risk of diabetes at baseline). Compared to the study participants, those who did not return to visit 2 were slightly older, had higher body mass index (BMI), were more frequently men and had lower schooling level; difference regarding race/skin color was not significant.

Procedures

Data collection included face-to-face interviews, clinical examinations, and laboratory tests conducted by trained certified professionals using standardized instruments during visits 1 and 2 [24]. They recorded age (years), race/skin color (self-declared following the Brazilian census categories as being white, black, mixed-race ["*pardo*"], Asian, and indigenous), sex, schooling level (≥ 12 years [higher education]; 9-11 years [high school]; ≤ 8 years [elementary school]), and family history of diabetes in first degree relatives. Alcohol consumption was assessed by the semi-quantitative food frequency questionnaire (g/day); smoking status (never, former, and current smoker) and current leisure physical activity were also assessed by questionnaires. Prescribed and nonprescribed medication use was verified against medication blisters/boxes and/or medical prescriptions brought to the clinic. Weight and height, BMI (kg/m^2), and waist circumference (WC, in cm) were objectively assessed following standard procedures [24].

An overnight fasting blood sample by venipuncture was obtained soon after the participant's arrival at the clinic and followed standardized procedures for a two-hour 75g oral glucose tolerance test (OGTT) [25]. Fasting plasma glucose (FPG) concentrations were measured with the hexokinase method, insulin concentrations with an immunoenzymatic assay (ADVIA, Siemens: https://www.siemens.com); triglyceride and total and high density lipoprotein cholesterol (HDL) concentrations with enzymatic methods (Siemens); glycated hemoglobin (HbA1c) with high pressure liquid chromatography (Bio-Rad: https://www.bio-rad.com); AST and ALT by Modified International Federation for Clinical Chemistry technique (enzymatic assay) (Siemens). Insulin resistance was assessed using the homeostasis model assessment-insulin resistance (HOMA-IR), estimated by the equation [FPG (mg/dL) ×0.0555×fasting insulin (mIU/L)]/22.5. Low-density lipoprotein cholesterol (LDL) levels were estimated by the Friedewald equation when triglyceride levels were ≤ 400mg/dL. Otherwise, LDL was measured using the homogeneous enzymatic colorimetric method, without precipitation (Siemens). Ultrasensitive C-reactive protein (CRP) was measured by immunochemistry using nephelometry (nephelometer BN II Siemens).

Hypertension was defined as systolic blood pressure ≥ 140mmHg or diastolic blood pressure ≥ 90mmHg (sum of two measures), and/or use of anti-hypertensive drugs during the previous two weeks.

Leisure time physical activity was assessed using the *International Physical Activity Questionnaire* (IPAQ), in the long-modified version. Participants were categorized into two groups: low and moderate/high activity according to the sum of the metabolic equivalents per week (combination of type of activity, frequency, and duration) [26].

Hepatic ultrasound protocol and fatty liver assessment

Liver ultrasound examinations on the participants were performed by board-certified radiologists or by radiology technicians, after adequate training, using the same models of equipment: a high-resolution B-mode scanner (SSA-790A, Aplio XG, Toshiba Medical System: https://www.toshiba.com/tic/industries-served/medical) and a convex array transducer (model PVT-375BT), with a central frequency of 3.5MHz, and a fundamental frequency of 1.9-5.0MHz. After acquisition, the B-mode hepatic ultrasound images were read by board-certified radiologists at the ELSA-São Paulo research center, which was established as the ELSA-Brasil ultrasound reading center. A senior ultrasound radiologist verified the quality control protocol was verified by crosschecking the data. The liver ultrasound scanning protocol was set up in accordance with the following criteria, as previously validated [27].

Hepatic attenuation of the ultrasound beam: a standard B-mode ultrasound evaluation was conducted using a 4-point visual grading system based on the degree of diaphragm visible posterior to the right hepatic lobe. The hepatic attenuation was classified as normal (diaphragm completely visible) or abnormal as: mild (partial, i.e., diaphragm > 50% visible); moderate (partial, i.e., diaphragm < 50% visible); or severe (no visible diaphragm). Liver steatosis was defined by the presence of abnormal hepatic attenuation [27].

Confirmation of diabetes

Diabetes was confirmed based on laboratory measurements and self-reported information at visit 1. Participants were considered to have previously diagnosed diabetes when answering yes to either "Have you been previously told by a physician that you had/have diabetes (sugar in the blood)?" or "Have you used medication for diabetes in the previous two weeks?". For women who reported having only gestational diabetes, they were not considered as having had previously diagnosed diabetes. Those without a previous diagnosis were assessed for undiagnosed diabetes based on their laboratory values and then confirmed as having newly diagnosed diabetes if they reached the thresholds for FPG ≥ 126mg/dL; 7.0mmol/L, OGTT ≥ 200mg/dL; 11.1mmol/L, or HbA1C ≥ 6.5%; 48mmol/mol [11,25]. Participants whose diagnosis of diabetes has not been confirmed at visit 2 were not considered cases of diabetes and were included at baseline. Type 1 diabetes was not recorded among incident cases but, given that participants were all aged at least 35 years, these participants were unlikely to have type 1 diabetes. After excluding those with diabetes at visit 1 that were confirmed at visit 2, incident diabetes was confirmed based on the same criteria at visit 2 (2012-2014) [28].

Statistical analysis

Kolmogorov-Smirnov and Shapiro-Wilk tests were used to test normality of data. Continuous variables were presented as means and standard deviation or medians and ranges, and dichotomic variables were presented as absolute numbers and percentages. Group differences for continuous variables were analyzed using Student's t-test or the Mann-Whitney U test and, for categorical variables, using the chi-square test. Univariate logistic regression was performed to assess the characteristics associated with liver steatosis at baseline. Variables with a p-value < 0.20 in the univariate analysis were included as independent variables into the regression model. Multivariate logistic regression was used to evaluate the association of independent factors (age, sex, race/skin color, schooling level, BMI or WC, physical activity level, hypertension, smoking status, fasting plasma glucose, HDL cholesterol, and triglyceride levels) with liver steatosis. Statistical significance was set at two-sided p-value less than 0.05.

Time to event (detection of diabetes) was estimated as the time elapsed from visit 1 to the reported date of diagnosis obtained during yearly telephone interviews or at visit 2. When this date was unavailable, time to event was defined as half of the time elapsed from visit 1 to the follow-up contact point at which diabetes was reported. For incident cases defined only by laboratory values at visit 2, the estimated time to event (assuming a linear increase of glycemia from baseline to follow-up) was interpolated as the first date in which one of the three measures of glycemia reached its diagnostic threshold. Cumulative incidence (risk) over the whole analysis period was estimated as the number of new cases of diabetes divided by the total number of participants without diabetes at baseline.

Cox regression models were used to estimate the adjusted hazard ratio (HR) for incident diabetes based on two models. In the first model, adjustments were made for baseline BMI, sex, age, race/skin color, schooling level, hypertension, smoking status, leisure physical activity, FPG, and familiar history of diabetes. In the second model, BMI was replaced by WC and maintained the same variables. A sensitivity analysis was conducted, including CRP at model 1. We excluded participants with CRP ≥ 20mg/dL, which could indicate acute inflammation, totalizing 7,879 individuals for the final sample (Supplementary Material: http://cadernos.ensp.fiocruz.br/static//arquivo/suppl-0905-22_9379.pdf).

Proportional hazards assumptions were guaranteed using the Schoenfeld residual analysis. Statistical analysis was performed with Stata, version 14.0 (https://www.stata.com).

Results

Among ELSA-Brasil participants, the prevalence of liver steatosis was 35.1% and it was higher in males with obesity and lower schooling and physical activity levels. The group with liver steatosis had higher baseline BMI, WC, aminotransferases, triglycerides, total and LDL cholesterol, FPG, and HOMA-IR levels. Table 1 shows the baseline characteristics of the 8,166 participants.

Table 1

Baseline characteristics of the subjects at risk of developing diabetes according to the presence of hepatic steatosis. *Brazilian Longitudinal Study of Adult Health* (ELSA-Brasil), 2008-2010 (N = 8,166).

Characteristics	Total n (%)	Participants with hepatic steatosis n (%)	Participants without hepatic steatosis n (%)	p-value
Total	8,166 (100.00)	2,866 (35.10)	5,300 (64.90)	
Sex				
Male	3,327 (40.74)	1,381 (48.19)	1,946 (36.72%)	**< 0.001**
Female	4,839 (59.26)	1,485 (51.81)	3,354 (63.28)	
Age group (years) [mean±SD]	51.12±8.96	51.83±8.75	50.73±9.05	**< 0.0001**
35-44	2,090 (25.59)	621 (21.67)	1,469 (27.72)	
45-54	3,256 (39.87)	1,173 (40.93)	2,083 (39.30)	**< 0.001**
55-64	2,107 (25.80)	808 (28.19)	1,299 (24.51)	
65-74	713 (8.73)	264 (9.21)	449 (8.47)	
Race/Skin color				
White	4,544 (55.65)	1,593 (55.58)	2,951 (55.68)	
Mixed-race ("*pardo*")	2,115 (25.90)	766 (26.73)	1,349 (25.45)	
Black	1,208 (14.79)	405 (14.13)	803 (15.15)	0.378
Asian	216 (2.65)	69 (2.41)	147 (2.77)	
Indigenous	83 (1.02)	33 (1.15)	50 (0.94)	
Schooling level				
Higher edcuation	4,414 (54.05)	1,476 (51.50)	2,938 (55.43)	
High school	2,877 (35.23)	1,031 (35.97)	1,846 (34.83)	**< 0.001**
Elementary school	875 (10.72)	359 (12.53)	516 (9.74)	
BMI (kg/m^2) [mean±SD]	26.61±4.60	28.84±4.94	25.41±3.90	**< 0.0001**
Underweight or normal (< 18.5-24.9)	3,276 (40.12)	615 (21.46)	2,661 (50.21)	
Overweight (25.0-29.9)	3,277 (40.13)	1,263 (44.07)	2,014 (38.00)	**< 0.001**
Obesity (≥ 30.0)	1,613 (19.75)	988 (34.47)	625 (11.79)	
Waist circumference (cm) [mean±SD]	89.28±12.24	95.65±12.26	85.83±10.75	**< 0.0001**
Male	93.62±11.31	98.78±11.08	89.96±9.95	**< 0.0001**
Female	86.29±11.96	92.73±12.60	83.44±10.47	**< 0.0001**
Hypertension	2,380 (29.16)	1,085 (37.88)	1,295 (24.44)	**< 0.001**
Smoking				
Current	963 (11.79)	321 (11.20)	642 (12.11)	**< 0.001**
Former	2,286 (27.99)	906 (31.61)	1,380 (26.04)	
Leisure physical activity				
Low	6,230 (76.29)	2,282 (79.62)	3,948 (74.49)	**< 0.001**
Moderate/High	1,936 (23.71)	584 (20.38)	1,352 (25.51)	
AST (U/L) [median±IQR]	23 (9-133)	24 (9-133)	23 (9-109)	**< 0.0001**
ALT (U/L) [median±IQR]	23 (4-170)	26 (7-170)	21 (4-139)	**< 0.0001**
GGT (U/L) [median±IQR]	24 (3-903)	28 (5-903)	22 (3-820)	**< 0.0001**
Cholesterol (mg/dL) [mean±SD]				
Total	213.69±39.93	217.81±40.92	211.47±39.20	**< 0.0001**
HDL	57.09±14.23	53.96±13.00	58.78±14.58	**< 0.0001**
LDL	131.36±33.68	133.98±34.26	129.94±33.28	**< 0.0001**
Triglyceride (mg/dL) [median±IQR]	108 (26-1,714)	131 (26-1,222)	99 (26-1,714)	**< 0.0001**
FPG (mg/dL) [mean±SD]	99.21±8.95	101.35±9.19	98.05±8.60	**< 0.0001**
HbA1c (%) [mean±SD]	5.28±0.56	5.34±0.57	5.25±0.56	**< 0.0001**
HOMA-IR [median±IQR]	2.34 (0.33-42.18)	3.10 (0.74-23.84)	2.00 (0.33-42.2)	**< 0.0001**
CRP [median±IQR]	1.33 (0.69-2.99)	1.73 (0.91-3.78)	1.16 (0.60-2.57)	**< 0.0001**
First degree relative with diabetes	2,956 (36.20)	1,105 (38.56)	1,851 (34.92)	**0.001**

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; CRP: C-reactive protein; FPG: fasting plasma glucose; GGT: gamma-glutamyltransferase; HbA1c: glycated hemoglobin; HDL: high density lipoprotein cholesterol; HOMA-IR: homeostasis model assessment of insulin resistance; IQR: interquartile range; LDL: low density lipoprotein cholesterol; SD: standard deviation.
Note: statistically significant indicators are represented by bold emphasis.

The factors independently associated with liver steatosis at baseline were BMI and WC, sex, race/skin color, hypertension, leisure physical activity, triglycerides, HDL cholesterol, and FPG (Table 2).

The cumulative incidence of diabetes was 5.25% in the whole sample, 7.83% and 3.88% in the groups with and without hepatic steatosis, respectively ($p < 0.001$).

In the multivariate model adjusted for sex, age, race/skin color, schooling level, BMI, hypertension, smoking status, leisure physical activity, FPG, subjects with liver steatosis had higher risk of diabetes incidence compared to the group without hepatic steatosis (HR = 1.31; 1.09-1.56). The association persisted in the model adjusted for WC instead of BMI (HR = 1.29; 1.08-1.54) (Table 3).

Sensitivity analysis including CRP did not change the association between steatosis and diabetes incidence (Supplementary Material: http://cadernos.ensp.fiocruz.br/static//arquivo/suppl-0905-22_9379.pdf).

Table 2

Association of sociodemographic and clinical factors with the presence of hepatic steatosis at baseline of the *Brazilian Longitudinal Study of Adult Health* (ELSA-Brasil) (N = 8,166).

Characteristics	Model of logistic regression with BMI		
	OR	95%CI	p-value
Age	1.01	1.00-1.01	0.06
Females	0.71	0.63-0.79	**< 0.001**
Race/Skin color			
White	1.00		
Mixed-race ("*pardo*")	0.98	0.87-1.11	0.80
Black	0.78	0.67-0.90	**0.001**
Asian	1.17	0.85-1.61	0.33
Indigenous	0.92	0.56-1.49	0.73
BMI (kg/m^2)	1.18	1.16-1.19	**< 0.001**
Hypertension	1.15	1.02-1.29	**0.02**
Leisure physical activity			
Moderate/High	0.85	0.75-0.95	0.006
Triglycerides	1.00	1.00-1.00	**< 0.001**
HDL cholesterol	0.99	0.99-1.00	**0.02**
FPG	1.01	1.01-1.02	**0.001**
Characteristics	**Model of logistic regression with waist circumference**		
	OR	**95%CI**	**p-value**
Age	1.00	0.99-1.00	0.397
Females	1.13	1.02-1.26	**0.024**
WC	1.07	1.07-1.08	**< 0.001**
Triglycerides	1.00	1.00-1.00	**< 0.001**
FPG	1.01	1.00-1.02	**0.001**

95%CI: 95% confidence interval; BMI: body mass index; FPG: fasting plasma glucose; HDL: high density lipoprotein cholesterol; OR: odds ratio; WC: waist circumference.

Note: adjusted for age, sex, skin color or race, schooling level, BMI (in the first model), waist circumference (in the second model), hypertension, leisure physical activity, triglycerides, HDL cholesterol and fasting plasma glucose levels, smoking, familiar history of diabetes. Statistically significant indicators are represented by bold emphasis.

Table 3

Cox regression analysis for the adjusted association between hepatic steatosis at ELSA-Brasil (*Brazilian Longitudinal Study of Adult Health*) baseline and diabetes incidence.

Characteristics	Model 1		Model 2	
	HR (95%CI)	p-value	HR (95%CI)	p-value
Hepatic steatosis	1.31 (1.09-1.56)	0.004	1.29 (1.08-1.54)	**0.006**
Females	1.38 (1.16-1.64)	< 0.001	1.59 (1.33-1.88)	**< 0.001**
Age	1.02 (1.01-1.03)	0.002	1.01 (1.00-1.02)	**0.008**
FPG	1.10 (1.09-1.11)	< 0.001	1.10 (1.08-1.11)	**< 0.001**
BMI	1.04 (1.03-1.06)	< 0.001	-	-
WC	-	-	1.02 (1.01-1.03)	**< 0.001**

95%CI: 95% confidence interval; BMI: body mass index; FPG: fasting plasma glucose; HR = hazard ratio; WC: waist circumference.

Note: adjusted through Cox regression analysis for: Model 1 – sex, age, race/skin color, schooling level, hypertension, BMI, smoking, leisure physical activity, FPG, first degree relative with diabetes; Model 2 − same adjustments replacing BMI by WC. Statistically significant indicators are represented by bold emphasis.

Discussion

Of the 8,166 participants without diabetes at baseline in the ELSA-Brasil, a contemporary, occupational cohort study of people aged 35-74 years living in a middle-income country, 35.1% presented liver steatosis detected by liver ultrasound, and fatty liver was associated with diabetes incidence. Due to unhealthy lifestyles, both NAFLD and diabetes have shown an increasing prevalence in the past decade, which is expected to increase further in the near future. Previous studies have shown that diabetes and cardiovascular disease are the most common outcomes and causes of death in patients with NAFLD [10,29].

The factors independently associated with the presence of hepatic steatosis at baseline were components of the metabolic syndrome (MetS): BMI and WC, triglycerides and FPG levels, which is consistent with the concept of NAFLD as a hepatic manifestation of MetS [30].

This study, based on the ELSA-Brasil, showed that having hepatic steatosis at baseline increased the risk of diabetes development by 29-30% after adjustments. To our knowledge, this is the first prospective study that confirms fatty liver as a risk factor for diabetes development in a South American population.

A recent meta-analysis with 19 unique observational studies (17 from Asian countries and two from the United States) provided evidence of a significant association between image-diagnosed fatty liver and the long-term risk of incident diabetes [22]. They found that the presence of NAFLD conferred a HR = 2.2 for incident diabetes, a risk that seemed to increase further with growing NAFLD "severity" (assessed in four observational studies using either the ultrasonographic or the NAFLD fibrosis score). The association between NAFLD and diabetes risk was stronger in studies with a follow-up longer than five years [22]. This might explain why we found a lower HR for diabetes in our study, as our mean follow-up was about four years.

It remains uncertain whether NAFLD causally increases diabetes risk or if it is a marker of other shared risk factors. The association between NAFLD and the development of diabetes can be explained in several ways. NAFLD, especially NASH with varying levels of hepatic fibrosis, exacerbates hepatic insulin resistance and causes the release of proinflammatory mediators and prodiabetogenic hepatokines that may promote the development of diabetes [23,31,32]. Although CRP is a biomarker of inflammation for ELSA-Brasil, the sensitivity analysis including it did not modify the association between NAFLD and diabetes incidence. Intrahepatic fat accumulation also increases insulin resistance by stimulating inflammatory pathways regulated by nuclear factor-β [31,32,33]. How-

ever, whether improvement or resolution of NAFLD could decrease the risk of incident diabetes remains uncertain.

This study has several strengths. Firstly, a standard protocol of investigation was designed and strictly followed by specially trained epidemiologists, doctors, and nurses. All questionnaires and physical examinations were carried out according to a standard procedure. Secondly, the strict criteria of diabetes incidence included FPG, OGTT, and HbA1c, meaning fewer missing cases. Thus, excluding 689 participants who could not be evaluated at visit 2, all the participants who developed diabetes could be found and robust estimates of HR were obtained. Finally, this study had a large sample size, which gave us enough power to build a stable Cox model to estimate HRs.

This study also has its limitations. Viral hepatitis B and C serologies and laboratory investigations to exclude other etiologies of chronic liver diseases were not routinely performed. Some chronic liver diseases can lead to hepatic steatosis, such as alcoholic liver disease, infection by genotype 3 of the hepatitis C virus, Wilson's disease, among others. However, participants were excluded if they reported excessive alcohol consumption or referred hepatitis or cirrhosis.

In conclusion, this study showed that in the ELSA-Brasil, liver steatosis is associated with an increased risk of developing diabetes. Showing that fatty liver is an independent risk factor for incident diabetes is important to justify strengthened NAFLD prevention strategies and to increase physicians' awareness on the need to implement adequate preventive measures to decrease future diabetes incidence and related disease burden in patients with NAFLD. Lifestyle changes and sustained weight loss are the most effective ways to prevent diabetes and treat NAFLD.

Contributors

L. C. Faria contributed to the study planning, data analysis, and writing; and approved the final version. M. F. H. S. Diniz contributed to the study planning, data analysis, writing, and review; and approved the final version. L. Giatti contributed to the writing and review; and approved the final version. M. I. Schmidt contributed to the writing and review; and approved the final version. A. C. Goulart contributed to the writing and review; and approved the final version. B. B. Duncan contributed to the writing and review; and approved the final version. S. M. Barreto contributed to the study planning, data analysis, and writing; and approved the final version.

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Resumo

Evidências epidemiológicas crescentes sugerem uma relação bidirecional entre a doença hepática gordurosa não alcoólica (DHGNA) e o diabetes tipo 2 e que a DHGNA pode preceder e/ou promover o desenvolvimento de diabetes. O objetivo deste estudo foi investigar se a esteatose hepática está associada à incidência de diabetes no Estudo Longitudinal de Saúde do Adulto *(ELSA-Brasil). O ELSA-Brasil é um estudo de coorte ocupacional com servidores públicos ativos ou aposentados, com idades entre 35 e 74 anos, de seis capitais do Brasil. Foram excluídos os participantes com diabetes no início do estudo, aqueles que relataram consumo excessivo de álcool ou com falta de informações sobre covariáveis relevantes e indivíduos com hepatite ou cirrose autorreferida. No total, 8.166 indivíduos participaram e o tempo médio de seguimento foi de 3,8 anos. O modelo de regressão proporcional de Cox foi utilizado para estimar a razão de risco (HR) ajustada para as associações. A ultrassonografia abdominal foi utilizada para detectar esteatose hepática. No período de seguimento, a incidência cumulativa de diabetes foi de 5,25% em todo o grupo de participantes e de 7,83% e 3,88% nos grupos com e sem esteatose hepática, respectivamente (p < 0,001). Em comparação com aqueles sem esteatose, os indivíduos com esteatose hepática apresentaram um risco elevado de desenvolver diabetes (HR = 1,31; IC95%: 1,09-1,56) após o ajuste para potenciais fatores de confusão, incluindo o índice de massa corporal (IMC). A esteatose hepática foi um preditor independente de diabetes incidente no ELSA-Brasil. Os médicos devem incentivar mudanças no estilo de vida e a triagem para diabetes para pacientes com fígado gorduroso.*

Esteatose Hepática; Hepatopatia Gordurosa não Alcoólica; Diabetes Mellitus Tipo 2; Resistência à Insulina; Obesidade

Resumen

La creciente evidencia epidemiológica sugiere una relación bidireccional entre la enfermedad del hígado graso no alcohólica (EHGNA) y la diabetes tipo 2 y que la EHGNA puede preceder y/o desarrollar la diabetes. El objetivo de este estudio fue investigar si la esteatosis hepática está asociada con la incidencia de diabetes en el Estudio Longitudinal de Salud del Adulto *(ELSA-Brasil). ELSA-Brasil es un estudio de cohorte ocupacional, realizado con funcionarios públicos activos o jubilados, con edades entre 35 y 74 años, de seis capitales en Brasil. Se excluyeron a los participantes con diabetes al inicio del estudio, aquellos que informaron consumir excesivamente alcohol o que carecían de información sobre las covariables relevantes, y los individuos con hepatitis o cirrosis autorreportada. En total participaron 8.166 sujetos, y el tiempo medio de seguimiento fue de 3,8 años. Se utilizó el modelo de regresión proporcional de Cox para estimar la razón de riesgo ajustada (HR) en las asociaciones. Se realizó ecografía abdominal para detectar esteatosis hepática. En el periodo de seguimiento, el grupo de participantes tuvo incidencia acumulada de diabetes del 5,25%, y en los grupos con y sin esteatosis hepática fueron del 7,83% y el 3,88%, respectivamente (p < 0,001). Los individuos con enfermedad de hígado graso tuvieron mayor riesgo de desarrollar diabetes (HR = 1,31; IC95%: 1,09-1,56) después de ajustar los posibles factores de confusión, incluido el índice de masa corporal (IMC), en comparación con aquellos sin esteatosis. La esteatosis hepática fue un predictor independiente de diabetes incidente en ELSA-Brasil. Los médicos deben alentar cambios en el estilo de vida y la detección de diabetes a los pacientes con hígado graso.*

Hígado Graso; Enfermedad del Hígado Graso no Alcohólico; Diabetes Mellitus Tipo 2; Resistencia a la Insulina; Obesidad

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