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Original Research

The risk of cardiometabolic disorders in lean non-alcoholic fatty liver disease: A longitudinal study

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ABSTRACT

Background: Recent studies suggest that non-alcoholic fatty liver disease (NAFLD) in lean (BMI<25 kg/m^2) individuals presents a distinct phenotype. We sought to determine the cardiometabolic consequences of lean NAFLD in a population cohort of relatively young asymptomatic individuals who participated in a voluntary routine health promotion evaluation in Brazil.

Methods: We analyzed data in our population collected from 2004 to 2016. Medical and demographic history, anthropometric measures, and fasting blood samples were obtained. Participants had ultrasonography to assess for fatty liver. We defined NAFLD as fatty liver in individuals scoring below 8 on the alcohol use disorders identification test (AUDIT). We included data from 9137 individuals who had complete data at baseline and at follow-up.

Results: The prevalence of lean NAFLD in our cohort was 3.8%. Over the median follow-up period of 2.4 years (range 0.5–9.9 years), lean individuals had 74% (HR: 1.74 (1.39–2.18)) and 67% (1.67 (1.29–2.15)) greater risk of developing elevated BP and elevated glucose, and nearly 3 times the risk of atherogenic dyslipidemia (HR: 2.98 (2.10–4.24)) compared to lean individuals without NAFLD. Lean NAFLD individuals also had higher risk of developing elevated glucose (HR: 1.37 (1.07–1.75)) and atherogenic dyslipidemia (1.46 (1.05–2.01)) compared to non-lean individuals without NAFLD. However, there was no significant difference in the risk of elevated BP, elevated glucose or atherogenic dyslipidemia between lean NAFLD and non-lean individuals with NAFLD in fully adjusted models.

Conclusion: Lean NAFLD is not metabolically benign. Further cardiovascular risk stratification and appropriate preventive measures should be considered in lean individuals who present with NAFLD.

1. Background

Non-alcoholic fatty liver disease (NAFLD), defined by hepatic accumulation of lipids among individuals without heavy alcohol consumption, is a common metabolic disorder with a global prevalence of about 24% [1,2]. NAFLD is associated with adverse cardiovascular events (including myocardial infarction, stroke, coronary revascularization), atherosclerotic disease, cardiomyopathy, and cardiac arrhythmias [3,4]. The prevalence, incidence, and mortality from NAFLD continues to rise, largely driven by progressively increasing obesity, metabolic syndromes, and diabetes mellitus rates [5]. Analysis of the National Health and Nutrition Examination Survey shows that the prevalence of NAFLD

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among normal weight (body mass indices [BMI]18.5 kg/m^2 – 24.9 kg/m^2) individuals is about 7–8% and increases with weight in a linear fashion such that the prevalence of NAFLD is over 4 times greater among those with BMI ≥35 kg/m^2 [6].

Emerging data suggest that lean NAFLD (BMI<25 kg/m^2) poses a distinct clinical phenotype, one that is characterized by lower levels of metabolic abnormalities such as insulin resistance and metabolic syndrome compared to non-lean individuals with NAFLD. In addition, lean NAFLD is associated with the presence of genetic polymorphisms such as the rs738409 variant of the phospholipase domain-containing protein 3 (PNPLA3) gene, which in turn is associated with a higher rate of hepatic fibrosis [7]. However, recent studies have suggested that lean NAFLD may not follow a benign course. Studies on mortality from lean NAFLD are scarce, but suggest that lean NAFLD has similar or greater mortality risk compared to non-lean NAFLD [8,9]. Considering the risks, there is renewed interest in understanding the epidemiology and metabolic consequences associated with the lean NAFLD phenotype.

Studies assessing cardiometabolic disease in lean NAFLD are limited. Most of these are cross-sectional studies, and several are conducted in symptomatic populations or those with elevated liver enzymes. Only a few studies have focused on asymptomatic populations and even fewer have examined the longitudinal cardiometabolic consequences of lean NAFLD. Since cardiovascular disease (CVD) is the most common cause of mortality among persons with NAFLD, it is paramount to assess these intermediates which may give insights as to the mechanisms of mortality and elucidate prevention targets in persons with NAFLD.

In this study, we seek to determine the cardiometabolic consequences of lean NAFLD in a relatively young, asymptomatic population.

2. Methods

2.1. Study design

We analyzed data from a routine health promotion evaluation that occurred at the Preventive Medicine Center of the Hospital Israelita Albert Einstein in São Paulo, Brazil from 2004 to 2016. Participants took part in this exercise voluntarily and had multiple visits. At each visit, participants filled out questionnaires on demographics, lifestyle including smoking history and physical activity, assessed using the short form of the international physical activity questionnaire (IPAQ), and medical history including medication use. Anthropometric measures including weight, height and abdominal circumference were also obtained. Fasting blood samples were also obtained for lipid profile, hepatic enzyme levels, blood glucose and high sensitivity C-reactive protein (HsCRP). Other details of the study methodology have been published elsewhere [10]. Analyses were restricted to participants with complete data at baseline visit and a follow-up visit that was at least 6 months after the baseline visit. The study was approved by the institutional review board of the local institution.

2.2. Exposure assessment

All participants had ultrasonography to assess for the presence of fatty liver. This was done after a 6 h fast using a Siemens ACUSONXP-10 device (Siemens AG, Mountain View, California). The images were read by board certified radiologists who were unaware of the clinical or laboratory data of the participants. Fatty liver was assessed according to conventional methods, based on the presence of increased hepatic echogenicity making it distinguishable from the renal parenchyma of the liver [11]. We defined NAFLD as fatty liver in individuals whose alcohol use disorders identification test (AUDIT) score was less than 8. The presence of an AUDIT score greater than 8 is associated with habitual harmful alcohol drinking [12]. Body mass index (BMI) was calculated as the weight in kg divided by the square of the height in meters (expressed as kg/m^2). Based on their BMI, participants were categorized as lean (BMI 18.5–24.9 kg/m^2) or non-lean (BMI 25 kg/m^2 and above).

2.3. Outcome assessment

The main outcomes studied were cardiometabolic disorders such as elevated blood pressure (BP), elevated glucose, atherogenic dyslipidemia (defined as a combination of elevated triglycerides and low HDL cholesterol) and elevated HsCRP. BP was obtained as a mean of three resting measures, the first of which was obtained after a 5-min rest and in accordance with the American Heart Association guidelines [13].

Plasma lipid, glucose, gamma glutamyl transferase (GGT), liver transaminases (alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and alkaline phosphatase levels were measured by standardized automated laboratory tests using a VITROS platform (Johnson & Johnson Clinical Diagnostics, New Brunswick, New Jersey). Total cholesterol was measured by an enzymatic colorimetric method, HDL-cholesterol was measured by a precipitation method while LDL-cholesterol was calculated using the Friedewald formula (for triglyceride levels less than 400 mg/dl). High-sensitivity C-reactive protein (HsCRP) levels were determined by immunonephelometry (Dade-Behring GmbH, Mannheim, Germany). All laboratory testing was performed at the Central Laboratory of the Hospital Israelita Albert Einstein.

Elevated BP was defined as a systolic BP of 130 mmHg or more, a diastolic BP of 80 mmHg or more, the use of medications to treat hypertension, or a self-reported history of hypertension. Considering that some society guidelines such as the European society of cardiology/European Society of Hypertension define hypertension as systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg, we also created an alternately defined elevated blood pressure. This alternately defined elevated BP was characterized as a systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg, the use of medications to treat hypertension, or a self-reported history of hypertension. Elevated blood glucose was defined as a fasting blood glucose above 100 mg/dl, a history of diabetes, or use of glucose lowering medication. Atherogenic dyslipidemia (AD) was defined as a combination of elevated triglycerides (>150 mg/dl) and low HDL-cholesterol levels (<40 mg/dl for men and <50 mg/dl for women). Finally, the presence of low-grade inflammation was determined if HsCRP levels were >2.0 mg/L [14].

2.4. Statistical analysis

We excluded participants without complete data on variables of interest. We also excluded participants with BMI less than 18.5 kg/m^2, and those with AUDIT scores ≥8 and those with follow-up less than 6 months leaving a sample size of 9137 participants (see Fig. 1).

Participants were then categorized into 4 groups based on their BMI and NAFLD status – Lean, without NAFLD; lean NAFLD; non-lean without NAFLD; non-lean with NAFLD.

All collected data were assessed for normality. Means with standard deviations (SD) were used to describe normally distributed continuous variables, while medians with interquartile ranges (IQR) were computed for non-normally distributed continuous variables. The analysis of

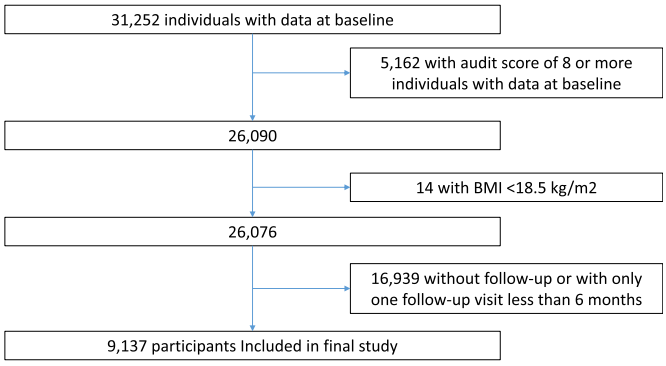

Fig. 1. Participant selection into the study.

variance (ANOVA) was used to compare means across BMI-NAFLD groups while the Kruskal-Wallis test was employed for comparing medians across groups. For categorical variables, the frequencies (%) were computed across the BMI-NAFLD groups and compared using chi-square test.

We analyzed the incidence of the cardiometabolic disorders and elevated HsCRP defined as the number of new cases in the population at risk per person-year (PY). Next, we used the Cox proportional hazards model to calculate hazard ratios (HR) and 95% confidence intervals (95% CI) for the relationship between NAFLD groups and each of the aforementioned cardiometabolic disorders. We compared lean NAFLD to the each of the other BMI-NAFLD groups. From the data, we created three models: the first was a univariate analysis, the second was adjusted for age, sex, cigarette smoking, physical activity level, abdominal circumference, and blood glucose (except for elevated blood glucose analysis). The full model additionally adjusted for lipids – LDL-cholesterol, HDL-cholesterol, triglycerides and total cholesterol (except in the AD analysis), use of lipid lowering therapy, and for liver enzymes gamma glutamyl transferase (GGT), aspartate transaminase (AST), alanine transaminase (ALT) and alkaline phosphatase (ALP). All incidence and hazard ratio analysis excluded persons who had the outcome at baseline. For instance, where elevated BP was the outcome, persons with elevated BP at baseline were excluded but those with other cardiometabolic outcomes (elevated glucose, HsCRP >2 or AD) were not excluded if they did not have elevated BP at baseline. All statistical analysis was carried out on Stata software version 16.

3. Results

3.1. General characteristics

The final study sample size of 9137 participants had a median follow-up period of 2.4 years (IQR:1.6–4.0 years, range 0.5–9.9 years). At baseline, the prevalence of lean NAFLD was 3.8%. The mean age of participants was 42 years, and 75% were male. Lean NAFLD individuals were older and more likely to be males compared to lean and non-lean groups without NALFD. Waist circumference was larger among lean NAFLD compared to lean without NAFLD. The prevalence of cigarette smoking at baseline was generally low. Details on the baseline characteristics can be found in Table 1.

3.2. Lean NAFLD and the relationship with cardiometabolic disorders

3.2.1. Elevated blood pressure

The incidence of elevated BP was 16 per 100PY in the entire population, rising to 22 per 100PY and 26 per 100PY among lean NAFLD and non-lean NAFLD. The incidence was lower (10 per 100PY) among lean individuals without NAFLD. Details are shown in Fig. 2. In multivariate analysis, the risk of elevated BP was 74% greater among lean NAFLD compared to lean without NAFLD (HR 1.74 [95% CI:1.39–2.18]). There was no statistically significant difference in the risk of elevated BP between lean NAFLD and non-lean individuals without NAFLD (HR:1.02 [95% CI:0.82–1.23]) and between lean NAFLD and non-lean individuals with NAFLD (HR: 1.08 [95% CI: 0.85–1.36]). Details can be found in Table 2.

When the definition of elevated blood pressure was modified to increase the BP threshold ≥140 mmHg or diastolic BP ≥ 90 mmHg the incidence of elevated BP was much lower overall (4.3 per 100PY), however, the results of univariate and multivariate analysis comparing Lean NAFLD to other BMI-NAFLD groups were similar. See Supplementary Tables S1 and S2 for details.

3.2.2. Elevated blood glucose

As shown in Fig. 2, the incidence of elevated blood glucose was 7.6 per 100PY in the entire population. The highest incidence was among non-lean individuals with NAFLD (12.7 per 100PY), followed by lean NAFLD individuals (9.3 per 100PY). Lean individuals without NAFLD had the lowest incidence (4.0 per 100PY). In multivariate analysis, lean NAFLD had 1.8 and 1.4 times the risk of elevated blood glucose compared to lean, no NAFLD and non-lean no NAFLD respectively (HRs: 1.67 [95%

Table 1
Comparisons of demographic and metabolic characteristics of participants in Lean NAFLD compared to other groups at baseline among participants with follow-up data.

N	ALL	Lean, No NAFLD	Lean NAFLD	Non-Lean, no NAFLD	Non-Lean, NAFLD	P value
	9137	3372	349	2880	2536	
Mean Age (years, SD)	42 (9)	40 (8)	44 (9)	42 (9)	45 (8)	<0.001
Sex (F %)	24.9	45.2	12.0	17.8	7.9	<0.001
Mean BMI (kg/m^2, SD)	26.2 (4.0)	22.6 (1.6)	23.7 (1.1)	27.5 (2.3)	29.8 (3.7)	<0.001
Mean abdominal circumference (cm, SD)	91.5 (12.4)	81.0 (8.0)	88.0 (6.2)	94.6 (8.1)	102.6 (10.2)	<0.001
Mean SBP mmHg (SD)	117 (13)	111 (11)	118 (11)	119 (12)	124 (13)	<0.001
Mean DBP mmHg (SD)	76 (8)	72 (7)	77 (7)	77 (7)	81 (8)	<0.001
Mean Glucose (mg/dl, SD)	88.1 (13.7)	84.0 (9.4)	91.4 (18.5)	87.3 (9.5)	94.1 (18.7)	<0.001
Smoker (%)	7.7	6.5	6.3	8.7	8.5	0.003
Minimally active or sedentary (%)	59.7	55.5	61.0	57.3	67.9	<0.001
Median total cholesterol (mg/dl, IQR)	195 (172–220)	188 (167–211)	199 (172–224)	197 (175–222)	202 (178–227)	<0.001
Median LDL-c (mg/dl, IQR)	120 (100–144)	113 (93–135)	124 (101–144)	124 (104–148)	127 (105–150)	<0.001
Median HDL-c (mg/dl, IQR)	47 (39–56)	53 (45–63)	45 (39–52)	46 (39–54)	41 (36–48)	<0.001
Median triglycerides (mg/dl, IQR)	110 (79–157)	88 (66–119)	128 (93–186)	108 (80–149)	152 (111–205)	<0.001
Median GGT (mg/dl, IQR)	27 (19–39)	21 (16–29)	31 (23–44)	27 (20–38)	36 (27–50)	<0.001
Median Alkaline Phosphate (mg/dl, IQR)	63 (53–74)	60 (51–70)	64 (55–75)	64 (54–74)	67 (57–78)	<0.001
Median Aspartate Aminotransferase (mg/dl, IQR)	27 (23–33)	25 (21–30)	29 (25–35)	27 (23–32)	31 (26–37)	<0.001
Median Alanine Aminotransferase (mg/dl, IQR)	36 (27–47)	29 (23–37)	40 (33–54)	35 (28–45)	46 (36–61)	<0.001
Median HsCRP (mg/dl, IQR)	1.2 (0.6–2.5)	0.8 (0.4–1.8)	1.0 (0.5–1.9)	1.2 (0.6–2.4)	1.8 (1.0–3.3)	<0.001
Elevated BP (%)	54.4	32.8	58.2	59.3	76.9	<0.001
Elevated Glucose (%)	14.2	5.9	20.1	11.4	27.6	<0.001
Atherogenic Dyslipidemia (%)	14.8	4.4	20.3	12.9	30.2	<0.001
HsCRP≥2 (%)	30.9	22.4	23.1	30.2	44.1	<0.001
Use of Antihypertensive Medication (%)	11.0	3.8	8.9	10.0	22.0	<0.001
Use of Lipid lowering medication	9.9	5.1	10.9	1.7	15.1	<0.001
Glucose lowering medication	2.8	0.9	5.7	1.9	5.8	<0.001

Atherogenic Dyslipidemia: Defined as a combination of elevated triglycerides (≥150 mg/dl) AND low HDL-c (<40 mg/dl in men or <50 mg/dl in women).
LDL-c, low density lipoprotein cholesterol; HDL-c high density lipoprotein cholesterol; SD, standard deviation; IQR, interquartile range.
SBP systolic blood pressure, DBP diastolic blood pressure.

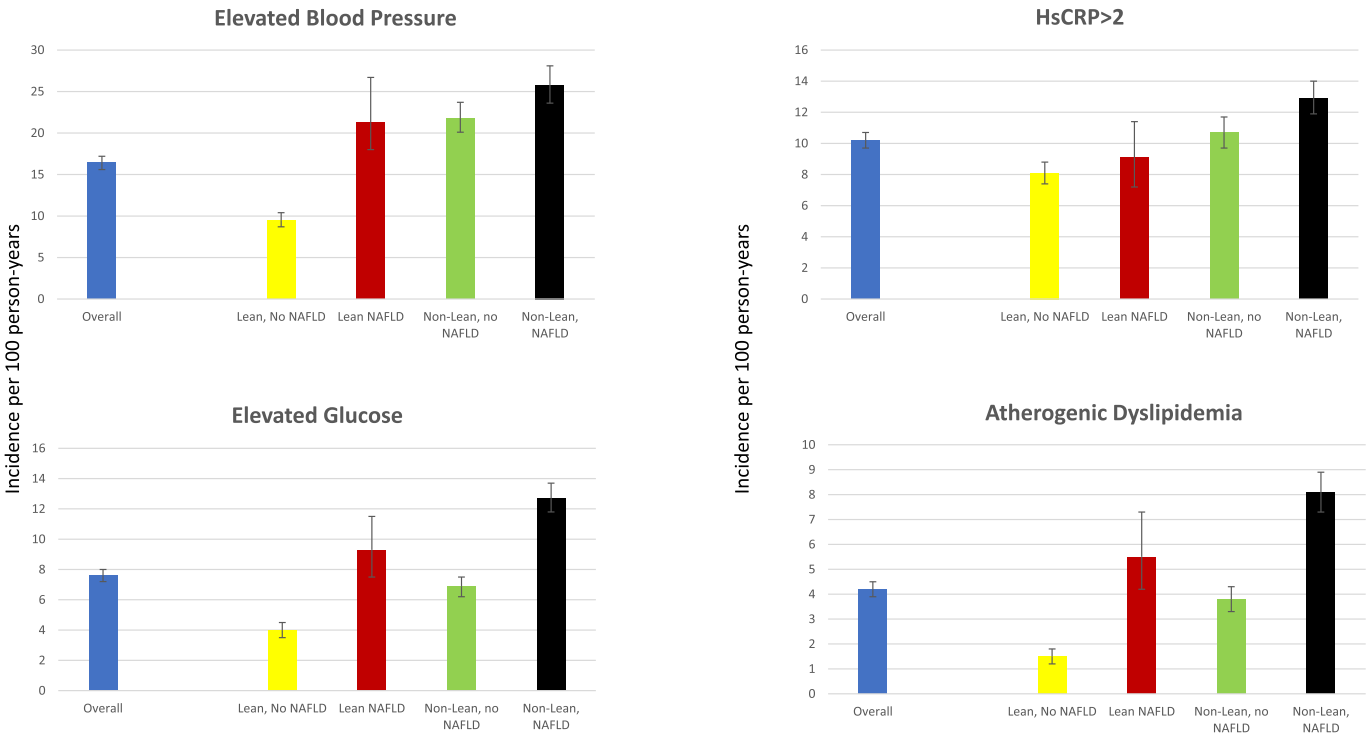

Fig. 2. The incidence of cardiometabolic abnormalities (per 100 person-years) across BMI-NAFLD groups.

Table 2
Hazard ratios for the longitudinal relationship between baseline NAFLD and new-onset cardiometabolic disorders.

Outcome Variable	Models	Lean NAFLD Vs. Lean, No NAFLD	Lean NAFLD Vs. Non-Lean, No NAFLD	Lean NAFLD Vs. Non-lean, NAFLD
Elevated Blood Pressure[a]	Univariate	2.41 (1.94–3.00)	1.02 (0.82–1.26)	0.97 (0.70–1.08)
N = 4436	Minimally Adjusted[e]	1.79 (1.43–2.24)	1.03 (0.83–1.29)	1.05 (0.83–1.33)
	Fully Adjusted[f]	1.74 (1.39–2.18)	1.02 (0.82–1.23)	1.08 (0.85–1.36)
Elevated Blood Glucose[b]	Univariate	2.36 (1.85–3.02)	1.36 (1.07–1.73)	0.74 (0.59–0.93)
N = 8113	Minimally Adjusted	1.83 (1.42–2.35)	1.41 (1.10–1.79)	0.92 (0.72–1.12)
	Fully Adjusted	1.67 (1.29–2.15)	1.37 (1.07–1.75)	0.96 (0.75–1.23)
HsCRP > 2[c]	Univariate	1.15 (0.90–1.46)	0.86 (0.67–1.10)	0.72 (0.56–0.92)
N = 6648	Minimally Adjusted	1.17 (0.91–1.50)	0.98 (0.77–1.26)	0.89 (0.69–1.16)
	Fully Adjusted	1.09 (0.84–1.41)	0.93 (0.73–1.02)	0.89 (0.69–1.15)
Atherogenic Dyslipidemia[d]	Univariate	3.85 (2.73–5.42)	1.49 (1.09–2.04)	0.70 (0.52–0.95)
N = 8058	Minimally Adjusted	3.26 (2.30–4.63)	1.55 (1.12–2.14)	0.85 (0.62–1.18)
	Fully Adjusted	2.98 (2.10–4.24)	1.46 (1.05–2.01)	0.86 (0.63–1.19)

Lean = BMI 18.5 kg/m2 to <25 kg/m2. Non-lean = BMI≥25kg/m2. NAFLD: Non-alcoholic Fatty Liver Disease.
Ns are sample sizes after excluding participants with the outcome at baseline.
[a] Persons with elevated blood pressure at baseline were excluded from the analyses.
[b] Persons with elevated blood glucose at baseline were excluded from the analyses.
[c] Persons with HSCRP >2 at baseline were excluded from the analyses.
[d] Persons with atherogenic dyslipidemia at baseline were excluded from the analyses.
[e] Minimally adjusted models were adjusted for age, sex, physical activity, smoking status, and abdominal circumference.
[f] Fully adjusted models had covariates as in minimally adjusted model plus lipids (total cholesterol, LDL-c, HDL-c, triglycerides except when AD [atherogenic dyslipidemia] was modeled as outcome variable), liver enzymes (GGT, Alkaline Phosphatase, Aspartate transaminase, Alanine transaminase), elevated blood glucose (except when elevated blood glucose was modeled as outcome variable), elevated blood pressure (except when elevated blood pressure was modeled as the outcome variable) and the use of cholesterol lowering medication for all 4 outcome variables.

CI:1.29–2.15] and HR:1.37 [95%CI:1.07–1.75]). Although the risk of elevated glucose was lower among lean NAFLD compared to non-lean NALFD on univariate analysis, the statistical significance was lost after adjusting for possible confounders. Details can be found in Table 2.

3.2.3. *Atherogenic dyslipidemia*

The incidence of atherogenic dyslipidemia (defined here as elevated triglycerides and low HDL) was 4.2 per 100PY in the entire population. Persons without NAFLD had the lowest incidence (lean, no NAFLD 1.5 per 100PY and non-lean no NAFLD was 3.8 per 100PY). The incidence was highest among non-lean individuals with NAFLD (8.1 per 100PY), while lean NAFLD had an incidence of 5.5 per 100PY. In multivariate analysis, lean NAFLD individuals were 3 times as likely to develop AD compared to lean individuals without NAFLD (HR: 2.98 [95%CI: 2.10–4.24]). They were also 1.5 times as likely to develop AD compared to non-lean individuals without NAFLD (HR: 1.46 [95%CI:1.05–2.01]). Similar to the findings with elevated blood glucose, lean NAFLD, compared to non-lean individuals with NAFLD, had a significantly reduced risk of atherogenic dyslipidemia. However, the statistical significance was lost after adjusting for potential confounders. See Fig. 2 and Table 2.

3.2.4. Elevated HsCRP

Lean persons with and without NAFLD had roughly similar incidence of elevated HsCRP (9.1 and 8.1 per 100PY). This was lower than the incidence in non-lean individuals with (12.9 per 100PY) and without NAFLD (10.7 per 100PY). Details can be found in Fig. 2. There was no statistically significant difference in the risk of elevated HsCRP between lean NAFLD and lean, no NAFLD, and between lean NAFLD and non-lean without NAFLD. Lean NAFLD had significantly reduced risk of elevated HsCRP compared to non-lean individuals with NAFLD in univariate analysis only. The statistical significance was lost after adjusting for potential confounders (Table 2).

4. Discussion

In this longitudinal study of asymptomatic individuals, there was elevated cardiometabolic (elevated BP, atherogenic dyslipidemia and elevated glucose) risk among lean individuals with NAFLD compared to lean individuals without NAFLD and to a lesser extent non-lean (overweight and obese) individuals without NAFLD. Lean and non-lean individuals with NAFLD had similar cardiometabolic risk. These results suggest that lean NAFLD has significant cardiometabolic consequences and raising further questions about its proposed benign course.

Several studies have demonstrated an association between lean NAFLD and BP. In a previous cross-sectional study of working class Brazilians, prevalent NAFLD was associated with BP in the hypertension range among individuals with BMI <30 kg/m^2 [10]. Other studies have validated the cross-sectional association between elevated BP and NAFLD in lean individuals [15,16]. However, only a few studies have investigated the risk of incident hypertension or elevated BP among lean NAFLD. One such study from Sri Lanka which compared 50 individuals with lean NAFLD at baseline with 260 non-lean NAFLD and 544 individuals without NAFLD showed no statistically significant difference in the incidence of hypertension over a seven-year period among groups [17]. By contrast, the present study, which has a larger sample size and greater number of lean NAFLD participants, showed significant risk of incident elevated BP among lean NAFLD compared to lean and non-lean groups without NAFLD. The reason for the dissimilarity in findings remains unclear. However, in addition to the present study having a larger population of individuals with lean NAFLD, elevated BP was defined using less strict criteria and participants were considerably younger (42 years vs 54 years). Changing the definition of elevated BP to one with higher systolic and diastolic BP thresholds did not significantly alter the results of regression analysis.

Atherogenic dyslipidemia, defined as elevated levels of triglycerides, and small-dense LDL with low levels of HDL-cholesterol is a central feature in the development of diabetes and is a marker of both metabolic syndrome and insulin resistance [18]. AD is associated with increased risk of coronary artery disease [19]. Numerous studies have shown a relationship between lean NAFLD and measures of insulin resistance such as HOMA-IR [20–22]. While several studies have demonstrated cross-sectional relationships between lean NAFLD and lipids in general, to our knowledge, the present study is the first to assess the temporality of atherogenic dyslipidemia in lean NAFLD. The increased risk of AD in lean NAFLD over those who were non-lean but without NAFLD suggests that NAFLD may be a greater marker of atherogenicity than BMI and lends credence to the theory of insulin resistance as one of the drivers of lean NAFLD [23].

Low-grade inflammation, often measured by an elevation in HsCRP, is associated with cardiovascular disease onset and is regarded as a marker of subclinical atherosclerosis [14]. NAFLD in general has been linked to increase in the risk of low-grade inflammation [24–26]. We found no studies specifically examining relationships between lean NAFLD and low-grade inflammation. In the present study, there was no difference in the risk of elevated HS-CRP between lean NAFLD and lean individuals without NAFLD, and between lean NAFLD and non-lean individuals without or with NAFLD.

At the heart of the definition of lean NAFLD is a BMI measure of leanness. Our study shows that among lean individuals, those with NAFLD had higher waist circumference compared to those without NAFLD. It is unclear if a shift in the definition of lean NAFLD from a BMI-based measure to waist circumference-based definition will yield different results. Several large epidemiologic studies indicate that waist circumference is a better predictor of CVD and all-cause mortality [27,28]. This suggests that a waist circumference-based definition of lean NAFLD may be more predictive of cardiometabolic outcomes than the current definition. This needs to be explored further however, it is beyond the scope of the present study.

Diabetes and hypertension have been linked with all-cause mortality in lean NAFLD [17,29,30]. At least one study suggests that diabetes may be a predictor of cardiovascular mortality in lean NAFLD and a recent study in individuals with biopsy proven NAFLD showed that hypertension was an independent risk of mortality [31]. Thus, cardiometabolic disorders in lean NAFLD have significant prognostic implications. The findings from this study highlight the importance of lean NAFLD in the development of cardiometabolic disorders and adds mechanistic insight to the elevated CVD risk associated with lean NAFLD. The present study, which shows that lean NAFLD poses greater cardiometabolic risk than non NAFLD groups regardless of BMI, but exhibits similar risk of low-grade inflammation compared to non NAFLD groups, suggests that lean NAFLD is phenotypically distinct from the other BMI-NAFLD groups. The findings of this study should spur providers who manage lean NAFLD patients to monitor closely for the development of cardiometabolic disorders. There is obviously more work needed to fully understand the relationships between NAFLD in lean/non-obese adults and cardiometabolic risk and how this risk translates to the occurrence of CVD later in life. For instance, there is no data measuring the incidence or progression of coronary artery calcification, a surrogate marker of atherosclerosis plaque burden and an independent marker of CVD events, in lean NAFLD.

The main strengths of this study include its longitudinal nature that has allowed for assessment of the temporal relationship between lean NAFLD and cardiometabolic disorders. The large sample size allows for a more robust comparison of multiple subgroups. In addition, the present study adjusted for several important covariates in regression analyses including central obesity (waist circumference) and the use of lipid lowering medication. It is one of only a few population-level studies to longitudinally assess cardiometabolic risk associated with lean NAFLD in an otherwise asymptomatic population.

Our study is limited by its retrospective design in which data on several variables were not collected. Hepatic steatosis was determined by ultrasound which has limited sensitivity for the diagnosis of steatosis [32]. Nonetheless, ultrasound estimation is an affordable and safe way to diagnose liver fat and is commonly used in clinical practice. Beyond BMI, waist circumference and hepatic steatosis, there were no other measures of adiposity collected in this study. Thus, we are unable to account for these other measures in our definition of leanness or in our multivariate analyses. In most clinical and public health settings, BMI and waist circumference are the most often assessed measures of adiposity used in clinical and public health/policy decision making. Thus, we deem our findings are of clinical and public health relevance regardless of this limitation. The participants in our study were young (average age was 42 years), largely male (75%) and Brazilian thus our findings cannot be generalized to older adults, largely female populations, or other ethnicities. Finally, approximately 65% of participants who did not have a follow-up were excluded from the study which may have introduced selection bias.

5. Conclusions

The risk of cardiometabolic disorders among lean persons with NAFLD is greater than individuals without NAFLD regardless of their BMI status. This suggests that lean NAFLD is not a metabolically benign

condition. Health care providers who treat lean NAFLD patients should strongly consider further cardiovascular disease risk stratification, appropriate preventative measures and monitoring even if their patients are asymptomatic. Future investigative efforts should focus on the mechanisms driving increased cardiometabolic risk and how this translates to hard CVD outcomes in lean individuals with NAFLD.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: RDS has received honoraria related to consulting, speaking, and research activities from Ache, Amgen, AstraZeneca, Esperion, Kowa, Merck, Novo-Nordisk, Pfizer, PTC, and Sanofi/Regeneron. MSB has received honoraria related to consulting, speaking and research activities from Boston Scientific, Sanofi, GE HealthCare, EMS and Novo-Nordisk.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajpc.2020.100097.

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