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Longitudinal association between overweight years, polygenic risk and NAFLD, significant fibrosis and cirrhosis

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Summary

Background: Adiposity amplifies the genetic risk of non-alcoholic fatty liver disease (NAFLD).

Aim: We evaluated the association between overweight-years, a cumulative exposure based on the product of the duration and severity of excess body weight (body mass index (BMI) ≥ 25 kg/m^2), and genetic risk on liver fat and fibrosis.

Methods: This is a longitudinal analysis derived from a prospective cohort of adults in the Framingham Heart Study who underwent genotyping and vibration-controlled-transient-elastography with controlled attenuation parameter. Univariable and multivariable linear and logistic regression analyses were used to assess the association between overweight-years and liver fat and fibrosis. The association between genetic variants of liver fat (*PNPLA3*, *TM6SF2*, *GCKR*) and fibrosis (*PNPLA3*, *TM6SF2*, *HSD17B13*) was also assessed using a polygenic risk score.

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AUTHORSHIP

Guarantor of the article: Veeral Ajmera, MD, MAS. All the authors approved the final version of the manuscript.

AUTHOR CONTRIBUTIONS

Veeral Ajmera: Conceptualization (lead); investigation (equal); methodology (equal); project administration (equal); supervision (equal); writing – original draft (lead); writing –review and editing (lead). **Na Wang:** Data curation (equal); formal analysis (equal); methodology (equal); writing – review and editing (equal). **Hanfei Xu:** Data curation (equal); formal analysis (equal); methodology (equal); writing – review and editing (equal). **Ching-Ti T Liu:** Data curation (equal); formal analysis (equal); methodology (equal); writing – review and editing (equal). **Michelle Long:** Conceptualization (equal); data curation (equal); funding acquisition (equal); methodology (equal); writing – review and editing (equal).

CONFLIC T OF INTEREST STATEMENT

MT works full-time for Novo Nordisk, however, this analysis was completed before she initiated working Novo Nordisk.

SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

Results: Our sample included 2478 participants (54% women) with mean age and BMI of 40 (±8.5) years and 26.5(±5.1) kg/m^2, respectively. The mean follow-up was 14(±0.9) years, and each participant underwent three study visits. The prevalence of NAFLD was 28.3% (n = 700), and 207 (8.4%) had clinically significant fibrosis. In age-, sex- and diabetes-adjusted multivariable analyses, overweight-years (per SD) had a strong association with NAFLD (aOR 3.53 [95% CI: 3.10–4.02], $p < 0.001$), clinically significant fibrosis (aOR 1.60 [95% CI: 1.40–1.84], $p < 0.001$) and cirrhosis (aOR 1.81 [95% CI: 1.38–2.37], $p < 0.001$). High-polygenic risk was significantly associated with liver fat and clinically significant fibrosis ($p < 0.05$).

Conclusion: Overweight-years is strongly associated with NAFLD and clinically significant fibrosis and combined with polygenic risk may assist in defining the trajectory of NAFLD.

1 | INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a leading cause of chronic liver disease worldwide; however, only approximately 25% of patients with nonalcoholic steatohepatitis (NASH) are at the greatest risk for disease progression to cirrhosis and liver cancer.[1] To date, liver biopsy remains the only reliable way to identify patients with NASH. However, it is impractical to scale to the affected population, and the association between histologic NASH and long-term liver-related outcomes has been equivocal.[2,3]

NAFLD has strong genetic underpinnings with twin studies demonstrating that hepatic steatosis and hepatic fibrosis are heritable.[4,5] In addition, multiple single nucleotide polymorphisms (SNPs), including those in *PNPLA3* and *TM6SF2*, are associated with the presence and severity of NAFLD.[6,7] In addition a SNP, in *GCKR*,[8] is associated with increased liver fat. More recently, a protective variant in *HSD17B13*[9,10] was found to protect against NAFLD cirrhosis. Despite the strong association between genetic risk and disease severity, genetic testing results have not been integrated into clinical risk stratification. Rather, genetic risk may be used to better understand disease trajectory.[10,11] Importantly, in cross-sectional studies adiposity amplifies the genetic risk associated with variants in *PNPLA3* and *TM6SF2*, and patients with risk alleles who are not overweight or obese have a low risk of NAFLD.[12] However, as BMI increases, the impact of the risk alleles on liver fat increases, suggesting that the combined evaluation of adiposity and genetic risk may have greater prognostic value.

To date, studies evaluating the association between adiposity, genetic risk and NAFLD have primarily evaluated BMI at a single time point. The combination of intensity and duration of other risk factors, most notably, pack-years for cigarette smoking, has been shown to improve clinical risk prediction. BMI trajectory is associated with NAFLD risk,[13] yet the effect of excess body weight over time and genetic risk on liver fat and fibrosis in patients with NAFLD has not been evaluated. In this study, we propose to examine the association between overweight-years defined as the product of the duration and severity of excess body weight (BMI > 25 kg/m^2) on liver fat and fibrosis and evaluate if the association differs based on genetic risk of liver fat and fibrosis among participants of the Framingham Heart Study.

2 | MATERIALS AND METHODS

2.1 | Study design

This is a longitudinal analysis derived from well-characterised adult (age ≥ 18 years) cohorts of participants from the Framingham Heart Study Third Generation and Omni 2 cohorts.[14] Participants took part in an ancillary study to evaluate liver fat and fibrosis using vibration controlled transient elastography (VCTE) between April 2016 and March 2019. All the participants, excluding those with overt ascites, implanted medical devices, or who were pregnant, were offered a VCTE exam and underwent a standardised research visit, including history, anthropometric assessment, and fasting blood collection. All patients provided written informed consent prior to enrolling in the study, and the study was approved by the Boston University Medical Center Institutional Review Board.

2.2 | Inclusion and exclusion criteria and covariates

We included all participants with VCTE data in this study. Participants meeting the following criteria were excluded from the study: significant alcohol consumption (defined as >21 drinks/week for men or >14 drinks/week for women) or missing alcohol use data; missing or poor quality VCTE data, or missing genetic data (Appendix S1). Participants were excluded if they did not attend all three exams over the study period. Co-variates included in the characterisation of the study population and analysis included; age, sex, ethnicity, alcohol, physical activity index, body mass index (required for each visit), waist circumference, alanine aminotransferase, aspartate aminotransferase, plasma glucose, glycosylated haemoglobin, total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, presence of hypertension (defined as systolic blood pressure >= 140 mm Hg, diastolic blood pressure >= 90 mm Hg, or being on antihypertensive medications), presence of diabetes (fasting glucose ≥126, or use of diabetic, hypoglycemic medications including insulin or HbA1c ≥ 6.5) and smoking status.

2.3 | Overweight-years assessment

All patients underwent a standardised clinical evaluation, including a detailed history and anthropometric measurements, performed by a trained clinical investigator. BMI was defined as the body weight (in kg) divided by height (in m) squared. **Overweight-years** were quantified from the time of enrollment into the study at the exam 1 visit (2002–2005). Overweight-years is a concept similar to pack-years of smoking that integrates the exposure with time. Specifically, the average BMI over the time interval was calculated. Then to calculate excess weight, 24 was subtracted because it is the highest whole number BMI considered normal weight. The degree of excess weight was multiplied by time interval to obtain overweight-years. For example, if a participant had a BMI of 26 kg/m^2 at study visit 1 and 30 kg/m^2 at study visit 2, 6 years later the overweight-years would = [(30 + 26)/2–24] × 6 = 24. All participants had three study visits, and total overweight-years was the sum of the values calculated from visits 1 to 2 plus visits 2 to 3. A similar concept quantifying obese-years in the Framingham cohort was associated with incident diabetes.[15]

2.4 | Genetic risk assessment

To create a polygenic risk score, we first selected single nucleotide polymorphisms (SNPs) with established associations with liver fat (*PNPLA3* rs738409, *TM6SF2* rs58542926, *GCKR* rs1260326) and liver fibrosis (*PNPLA3* rs738409, *TM6SF2* rs58542926, *HSD17B13* rs72613567). Data on *MBOAT7* rs641738 had low-imputation quality (0.191) and was excluded from analysis as a minimum threshold of 0.30 was required for inclusion. Genotyping in the Framingham Heart Study was performed with the Affymetrix 550 K Array.[16] SNPs were imputed to the 1000 Genomes project reference panel phase 3 version 5. Genotypes were coded additively using a continuous dosage scale from 0 to 2 using an additive model based on prior published data.[8,10,17]

2.5 | VCTE assessment

We used VCTE (Fibroscan 502 Touch; Echosens) performed by a research coordinator certified by Echosens to obtain measurements of liver fat (controlled attenuation parameter [CAP]) and liver fibrosis (liver stiffness measurement [LSM]) as previously described.[18] Participants fasted for >3 h before the examination. For all examinations, the M probe was applied first; however, the operator switched to the XL probe if needed based on the recommendations of the device's probe selection tool. Each exam was evaluated for quality by an experienced hepatologist (M.T.L.), and the operator obtained a minimum of 10 measurements from each participant. The device calculated the median CAP, LSM values, and interquartile range. Examinations that did not meet quality criteria, defined as an interquartile range/median ratio >0.30 when the median LSM is ≥7.1 kPa, were excluded.[19]

2.6 | Outcome measures

We chose the cutoff values of LSM≥ 8.2 kPa and LSM≥ 13.6 kPa for clinically significant fibrosis and cirrhosis, respectively. Optimal cut-points have varied between studies. A large biopsy proven cohort of NAFLD patients utilised the aforementioned cut-points for fibrosis stage ≥2 and cirrhosis and the cut-points have been utilised in a previous published study from this cohort.[18,20] Similarly, the optimal CAP cut-off for any steatosis in high-quality NAFLD cohorts with the use of the XL probe ranges from 285 dB/m,[21] 288 dB/m[22] to 302 dB/m.[20] The cut-point ≥290 dB/m for any hepatic steatosis was chosen for this study as had been utilised in a previous published study from this cohort.[18] Participants with CAP ≥ 290 dB/m but LSM< 8.2 kPa were considered to have hepatic steatosis without clinically significant fibrosis. Those with CAP < 290 dB/m and LSM< 8.2 kPa were considered to have neither hepatic steatosis nor clinically significant fibrosis.

The **primary outcomes** were significant fibrosis (VCTE ≥ 8.2 kPa), cirrhosis (VCTE > 13.6 kPa) and NAFLD (CAP ≥ 290 dB/m) after the exclusion of significant alcohol use.

Secondary outcomes included VCTE and CAP assessed as continuous measures in linear regression.

2.7 | Statistical analysis

Descriptive statistics described participants' characteristics, including demographics, anthropometrics, exposures and covariates. Continuous variables were presented as mean

and standard deviation, or median and interquartile ranges in case of non-normal distribution. Categorical variables were expressed as percentages and frequencies. Exposures and dependent variables were evaluated for normality, and continuous variables with skewed distributions were log-transformed (ALT and AST).

The association between the the exposure variables and outcome measures was assessed using univariable logistic and linear regression as appropriate. Unadjusted and multivariable sex-, age-, type II diabetes mellitus (DM)-adjusted models were evaluated. Age, sex and DM were chosen for multivariable adjustment based on their established association with the outcomes and potential to be differentially expressed by overweight years. The effect per 5-year change in overweight-years was assessed in adjusted multivariable models. A polygenic risk score was created by summing together the number risk variants of liver fat (*PNPLA3*, *TM6SF2*, *GCKR*) and liver fibrosis (*PNPLA3*, *TM6SF2*) and subtracting protective alleles (*HSD17B13* for liver fibrosis). Participants were dichotomized into high- and low-risk based on the median value of the polygenic risk score. The association between overweight-years as a continuous variable and genetic risk on the outcomes was assessed in linear and logistic regression models adjusted for age, sex and an interaction term for polygenic risk and overweight years.

Assuming a baseline risk of NAFLD of 30% and a risk in those with higher dichotomized polygenic risk and higher dichotomized overweight years of 45% a sample size of 352 participants would have 80% power with a two-tailed alpha threshold of 0.05. The sample size of 2478 was adequately powered for this outcome.

All the statistical analyses were performed using R v3.5.3, and a two-tailed $p < 0.05$ was considered statistically significant.

3 | RESULTS

3.1 | Characteristics of the study population

Two thousand four hundred and seventy-eight individuals were included. At their baseline visit, participants had a mean age of 40.2 (±8.5) years and were predominantly female (54.1%). The mean BMI was 26.5 (±5.1) kg/m^2. The mean follow-up time was 14 (±0.9) years, and each participant underwent three study visits. At the last follow-up visit, the mean BMI was 28.3 (±5.6) kg/m^2, 32.1% were on a hypertensive agent and 7.6% had DM. The median (IQR) overweight years was 41.0 (93). The prevalence of NAFLD was 28%, 8.4% had clinically significant fibrosis (VCTE≥ 8.2 kPa), and 1.6% had cirrhosis (VCTE> 13.6 kPa) (Table 1). The median (IQR) liver fat polygenic risk score was 1.1 (1) and the median (IQR) liver fibrosis polygenic risk score was 0 (1.5).

3.2 | Factors associated with liver fat

The mean (±SD) CAP value was 259.3 (±55.9), and 700 (28%) of participants had NAFLD. Age, DM, male sex, ALT, AST, body mass index and overweight years were associated with higher odds of NAFLD (Table 2). Overweight years was associated with an increased odds of NAFLD, OR = 3.85 (95% CI: 3.39–4.37). Each 5-year increase in overweight years was associated with a dose-dependent increase in the odds of NAFLD; 5 years OR = 1.09

(95% CI: 1.09–1.10), 10 years OR = 1.20 (95% CI: 1.18–1.22), 15 years OR 1.31 (95% CI: 1.28–1.35), 20 years OR = 1.44 (95% CI: 1.39–1.49) (Figure 1).

Only the risk variant in GCKR was significantly associated with the odds of NAFLD; however, each other NAFLD risk variant was associated with higher odds of NAFLD (*PNPLA3*, *TM6SF2*) that was not statistically significant. Similarly, age, DM, male sex, ALT, AST, body mass index and overweight years were associated with higher CAP values. BMI at last follow-up and overweight years were associated with a similar magnitude of increase in CAP, 34.8 (95% CI: 33.1–36.5, $p < 0.001$) and 32.0 (95% CI: 30.2–33.8, $p < 0.001$), respectively. Risk variants in *GCKR* (3.26 [95% CI: 0.04–6.48 $p = 0.048$]), *PNPLA3* (3.63 [95% CI: −0.55 to 7.80, $p = 0.089$]) and *TM6SF2* (5.04 [95% CI: −2.74 to 12.82, $p = 0.204$]) were associated with higher CAP values, however, only *GCKR* was statistically significant.

3.3 | Factors associated with liver fibrosis

The mean (±SD) VCTE value was 5.6 (±3.1) kPa, and 207 (8.4%) participants had significant fibrosis. Age, male sex, ALT, AST, body mass index and overweight-years were associated with higher odds of significant fibrosis (Table 3). Overweight years was associated with an increased odds of clinically significant fibrosis, OR = 1.83 (95% CI: 1.62–2.08). Each 5-year increase in overweight years was associated with a dose-dependent increase in the odds of clinically significant fibrosis; 5 years OR = 1.04 (95% CI: 1.03–1.05), 10 years OR = 1.08 (95% CI: 1.07–1.10), 15 years OR 1.13 (95% CI: 1.10–1.16), 20 years OR = 1.18 (95% CI: 1.14–1.22) (Figure 1), BMI at last follow-up was associated with a similar magnitude of increased odds of significant fibrosis, OR = 1.85 (95% CI: 1.63–2.11).

Fibrosis risk variants in *PNPLA3* and *TM6SF2* and the protective variant in *HSD17B13* had the expected direction of effect on significant fibrosis but were not statistically significant. Similarly, age, DM, male sex, ALT, AST, body mass index and overweight-years were associated with higher VCTE values.

Each 5-year increase in overweight years was also associated with a dose-dependent increase in the odds of cirrhosis; 5 years OR = 1.06 (95% CI: 1.04–1.07), 10 years OR = 1.11 (95% CI: 1.08–1.15), 15 years OR 1.18 (95% CI: 1.12–1.23), 20 years OR = 1.24 (95% CI: 1.17–1.32) (Figure 1).

3.4 | Polygenic risk, overweight years and the association with liver fat and fibrosis

In multivariable models adjusted for age, DM and sex, higher NAFLD polygenic risk was associated with a higher CAP score, 3.05 dB/m (95% CI: 0.77–5.32, $p = 0.009$). Similarly, overweight-years were associated with higher CAP per 5-year interval. (Figure 2A) and participants with higher polygenic risk had higher CAP at each overweight years threshold. However, the interaction term was not statistically significant ($p = 0.35$).

In multivariable models adjusted for age, DM and sex, higher polygenic risk of fibrosis was not associated with significantly higher liver stiffness on VCTE. Higher polygenic risk of fibrosis was associated with higher unadjusted odds of clinically significant fibrosis OR 1.20

(95% CI: 1.01–1.42, $p = 0.036$), however, this association was attenuated on adjustment for age, DM and sex OR 1.18 (95% CI: 0.99–1.40, $p = 0.068$). Higher genetic risk was not associated with statistically significantly higher risk of clinically significant fibrosis at each overweight year threshold (Figure 2B), and the interaction term was not stastically significant ($p = 0.27$).

4 | DISCUSSION

Using a well-phenotyped cohort of participants with longitudinal assessment of body weight and NAFLD genetic risk, we demonstrate the combination of intensity and duration of excess weight, overweight-years, has a strong association with NAFLD, fibrosis and cirrhosis. A longer duration of overweight years results in dose-dependent higher the odds of NAFLD, fibrosis and cirrhosis. Clinicians should consider duration of obesity/overweight when considering an individuals risk for clinically significant NAFLD. Furthermore, high-genetic risk increases the risk associated with overweight-years but did not have a significant interaction for liver fat or fibrosis. These data suggest that the clinical evaluation of patients at risk for NAFLD should consider evaluating the duration and intensity of excess weight over time and genetic risk, which independently contribute to the risk for NAFLD and clinically significant fibrosis.

5 | IN CONTEXT WITH PUBLISHED LITERATURE

The prevalence of obesity among patients with NAFLD and NASH are high at 50% and 80%, respectively.[5] Furthermore, approximately 80%–90% of patients undergoing bariatric surgery have NAFLD.[23] Stender and colleagues demonstrated an interaction between risk variants in PNPLA3, TM6SF2 and GCKR with BMI that amplified the risk of higher liver fat and liver tests. In a subset of patients, they also demonstrated an interaction between PNPLA3 risk variants, BMI and the odds of cirrhosis. Our study evaluated the impact of a metric that combines the longitudinal assessment of intensity and duration of excess weight, overweight-years, and found a significant dose-dependent association with NAFLD, significant fibrosis and cirrhosis. High-genetic risk was also associated with NAFLD and clinically significant fibrosis and the risk of these outcomes increased per 5 overweight-years.

Together, these studies highlight the importance of combining environmental and genetic risk when assessing the overall risk of disease progression in NAFLD. Emdin and colleagues, clearly demonstrated an interaction between genetic risk, alcohol use and obesity on the risk of cirrhosis,[11] where the risk of cirrhosis in those with the top 1% of polygenic risk could be mitigated by maintaining a normal BMI and avoiding significant alcohol intake. Our findings corroborate this concept in a well-phenoptyped cohort from the Framingham Heart Study. To date, most genetic studies have occurred in cohorts with less extensive phenotyping and relied on diagnosis codes, which often under-represent[24] or misclassify disease. Limited genetic studies of NAFLD have occurred in extensively well-phenotyped, longitudinally assessed cohorts. Importantly, this study also evaluates the interplay between genetics and a longitudinal assessment of excess body weight to elucidate significant independent effects.

6 | STRENGTHS AND LIMITATIONS

This study has many strengths including 14 years of follow up with the assessment of BMI at multiple time points. However, BMI variation in early life was not captured in this study. Furthermore, despite the clear dose dependent impact of overweight-years, it is not clear that this metric supersedes the most recent BMI in predicting the risk of NAFLD and fibrosis. Our study cohort had limited racial or ethnic diversity and was potentially underpowered to evaluate each common variants impact on NAFLD and fibrosis. However, we only included well-established common variants in this analysis and validation of their association with NAFLD was not an objective of this study. While this cohort is large for a well phenotyped cohort, typically discovery cohorts require a significantly larger sample size, particularly for new discovery. The lack of weighting for beta coefficients associated with genetic risk is a limitation based on limited data on the impact of each SNP on liver fat and stiffness. However, the beta coefficients from this study will help inform future studies. Finally, fat distribution may be more informative than BMI,[25] but BMI is often used and easily obtained in clinical practice, making it a relevant metric.

7 | IMPLICATIONS FOR FUTURE RESEARCH

Findings from our study demonstrate the clear impact of the longitudinal assessment of duration and intensity of body weight and polygenic risk of NAFLD and significant fibrosis. The clinical utility of genotyping will likely focus on the disease trajectory rather than NAFLD diagnosis and staging. Therefore, the finding that high-polygenic risk and overweight years were each associated with clinically significant fibrosis and contributed independently is a key finding with implications for clinical practice. Future studies with repeated assessment of liver fat and fibrosis over time will be needed to better characterise the impact of overweight-years and polygenic risk on NAFLD trajectory. In conclusion, the cumulative exposure to excess body weight defined as overweight-years is strongly associated with NAFLD, significant fibrosis and cirrhosis and when combined with polygenic risk provides a more detailed risk assessment in NAFLD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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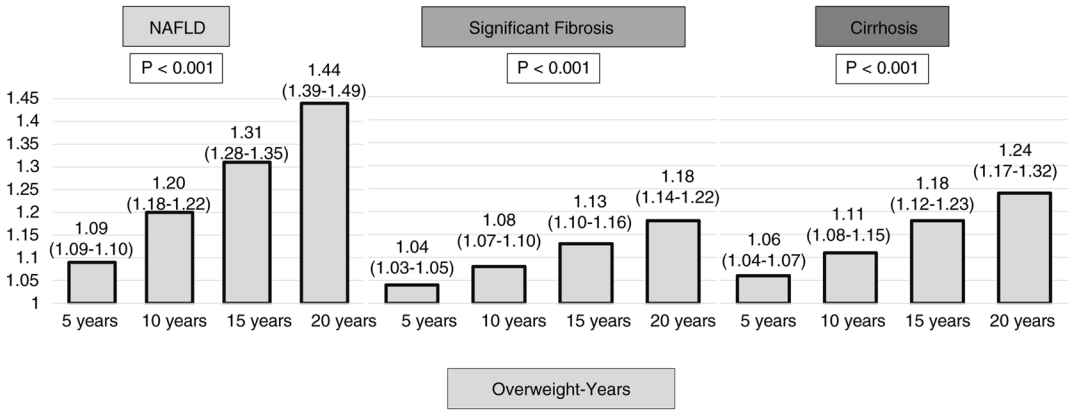

FIGURE 1.
Odds of NAFLD, significant fibrosis and cirrhosis by overweight years.

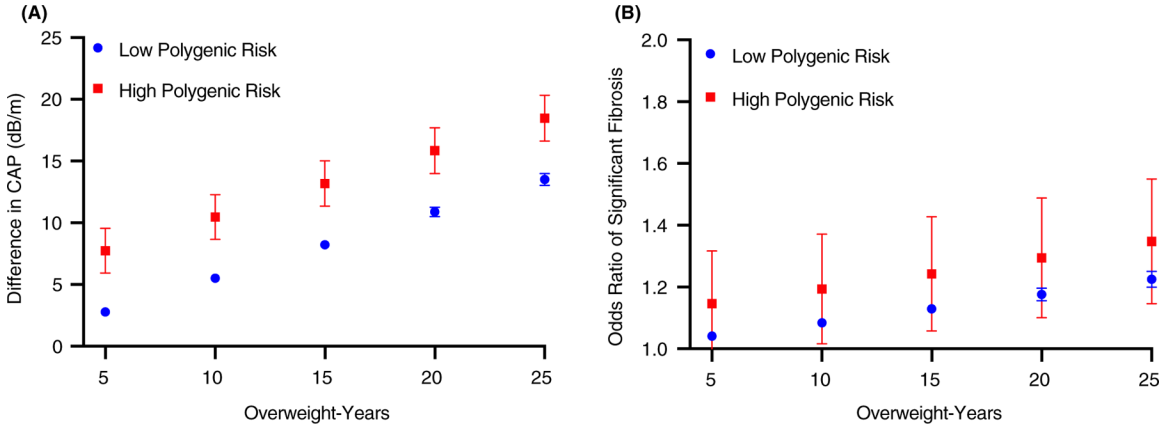

FIGURE 2.

Difference in (A) CAP and (B) odds of significant fibrosis by overweight-years and genetic risk.

TABLE 1

Clinical, demographic and imaging characteristics at baseline and follow-up.

Variable	Baseline (n = 2478)	Exam 3 (*n* = 2478)
Age, mean ± SD, years	40.2 ± 8.5	54.2 ± 8.4
Women, *n* (%)	1341 (54.1%)	1341 (54.1%)
BMI, mean ± SD, kg/m^2,	26.5 ± 5.1	28.3 ± 5.6
Overweight years, mean ± SD		52.8 ± 76.6
Hypertension, *n* (%)	327 (13.3%)	795 (32.1%)
ALT, mean ± SD, U/L	24.8 ± 17.5	24.7 ± 14.5
AST, mean ± SD, U/L	21.4 ± 9.6	23.1 ± 9.4
Diabetes, *n* (%)	52 (2.1%)	187 (7.6%)
Liver stiffness measurement, mean ± SD, kPa		5.6 ± 3.1
Significant fibrosis (≥8.2 kPa), *n* (%)		207 (8.4%)
Cirrhosis (≥13.6 kPa), n (%)		39 (1.6%)
Controlled attenuation parameter, mean SD, dB/m		259.3 55.9
NAFLD (CAP ≥ 290 dB/m) n (%)		700 (28.3%)
Polygenic risk liver fat, median (IQR)	1.1 (1)	
Polygenic risk liver fibrosis, median (IQR)	0 (1.5)	

TABLE 2

Factors associated with NAFLD on unadjusted and age, sex, DM-adjusted logistic regression.

	Unadjusted		Age, sex, DM-adjusted	
Exposures	**Odds ratio (95% CI)**	***p*-value**	**Odds ratio (95% CI)**	***p*-value**
Age[a]	1.26 (1.15–1.37)	<0.0001	1.16 (1.06–1.27)	0.0018
Women	0.53 (0.44–0.63)	<0.0001	0.57 (0.47–0.68)	<0.0001
DM	6.21 (4.51–8.55)	<0.0001	5.29 (3.81–7.33)	<0.0001
Physical activitya	1.02 (0.94–1.11)	0.6350	0.96 (0.881.05)	0.4005
ALT[a]	2.08 (1.89–2.29)	<0.0001	2.00 (1.792.22)	<0.0001
AST[a]	1.28 (1.181.40)	<0.0001	1.20 (1.101.32)	0.0001
BMI at last follow up[a]	4.48 (3.925.13)	<0.0001	4.21 (3.674.83)	<0.0001
Overweight years[a]	3.85 (3.394.37)	<0.0001	3.53 (3.104.02)	<0.0001
HSD17B13	0.97 (0.841.12)	0.6873	0.98 (0.841.14)	0.7603
PNPLA3	1.14 (0.971.34)	0.1232	1.11 (0.941.32)	0.2242
GCKR	1.14 (1.00–1.29)	0.0480	1.15 (1.00–1.31)	0.0455
TM6SF2	1.26 (0.94–1.70)	0.1250	1.24 (0.91–1.70)	0.1774
Polygenic risk fat	1.15 (1.04–1.27)	0.0043	1.14 (1.03–1.26)	0.0088

[a]Odds ratio per standard deviation presented.

TABLE 3

Factors associated with clinically significant fibrosis on unadjusted and age-, sex- and DM-adjusted logistic regression.

	Unadjusted		Age, sex and DM-adjusted	
Exposures	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Age[a]	1.27 (1.10–1.47)	0.0015	1.12 (0.96–1.30)	0.1439
Women	0.70 (0.52–0.93)	0.0135	0.80 (0.60–1.08)	0.1437
DM	5.51 (3.85–7.88)	<0.0001	4.95 (3.41–7.18)	<0.0001
Physical activity[a]	1.13 (0.99–1.28)	0.0737	1.11 (0.97–1.27)	0.1181
ALT[a]	1.69 (1.48–1.92)	<0.0001	1.61 (1.39–1.86)	<0.0001
AST[a]	1.62 (1.43–1.84)	<0.0001	1.57 (1.38–1.78)	<0.0001
BMI at last follow up[a]	1.85 (1.63–2.11)	<0.0001	1.65 (1.43–1.89)	<0.0001
Overweight years[a]	1.83 (1.62–2.08)	<0.0001	1.60 (1.40–1.84)	<0.0001
HSD17B13	0.84 (0.66–1.07)	0.1633	0.86 (0.67–1.10)	0.2218
PNPLA3	1.11 (0.85–1.44)	0.4437	1.07 (0.81–1.40)	0.6399
TM6SF2	1.52 (0.98–2.36)	0.0639	1.58 (1.00–2.49)	0.0500
Polygenic risk fibrosis	1.20 (1.01–1.42)	0.0359	1.18 (0.99–1.40)	0.0683

[a]Odds ratio per standard deviation presented.