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25-Year Trajectories of Insulin Resistance and Pancreatic β-Cell Response and Diabetes Risk in Nonalcoholic Fatty Liver Disease

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Abstract

Background & Aims: Insulin resistance (IR) is a risk marker for nonalcoholic fatty liver disease (NAFLD), and a risk factor for liver disease progression. We assessed temporal trajectories of IR and β-cell response to serum glucose concentration throughout adulthood and their association with diabetes risk in NAFLD.

Methods: 3,060 participants from CARDIA, a prospective bi-racial cohort of adults age 18–30 years at baseline (1985–1986; Y0) who completed up to five exams over 25 years and had fasting insulin and glucose measurement were included. At Y25 (2010–2011), NAFLD was assessed by noncontrast CT after exclusion of other liver fat causes. Latent mixture modeling identified 25-year trajectories in homeostatic model assessment IR (HOMA-IR) and β-cell response (HOMA-β).

Results: Three distinct trajectories were identified, separately, for HOMA-IR [low-stable (47%); moderate-increasing (42%); and high-increasing (12%)] and HOMA-β [low-decreasing (16%);

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moderate-decreasing (63%); and high-decreasing (21%)]. Y25 NAFLD prevalence was 24.5%. Among NAFLD, high-increasing HOMA-IR (referent: low-stable) was associated with greater prevalent (OR 95% CI=8.0, 2.0–31.9) and incident (OR=10.5, 2.6–32.8) diabetes after multivariable adjustment including Y0 or Y25 HOMA-IR. In contrast, NAFLD participants with low-decreasing HOMA-β (referent: high-decreasing) had the highest odds of prevalent (OR=14.1, 3.9–50.9) and incident (OR=10.3, 2.7–39.3) diabetes.

Conclusion: Trajectories of IR and β-cell response during young and middle adulthood are robustly associated with diabetes risk in NAFLD. Thus, how persons with NAFLD develop resistance to insulin provides important information about risk of diabetes in midlife above and beyond degree of IR at the time of NAFLD assessment.

LAY SUMMARY

- In NAFLD, presence of diabetes increases risk for liver disease progression

- Early identification of risk factors for diabetes is an important strategy to improve outcomes in NAFLD

- Increasing insulin resistance from young adulthood into middle age is associated with greatest risk of NAFLD and subsequent diabetes

- Thus, *how* insulin resistance develops in NAFLD provides important information about risk of diabetes independent of degree of insulin resistance in middle age

Keywords

obesity; NASH; NAFLD; CARDIA

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is considered the hepatic manifestation of the metabolic syndrome with a well-established association with insulin resistance (IR). NAFLD prevalence approaches 70% among persons with type 2 diabetes mellitus (T2DM).[1] However, NAFLD also occurs among persons without T2DM and may precede the development of T2DM.[2,3] Once established, T2DM promotes liver disease progression and is an independent risk factor for liver cancer.[2] There are multiple potential common pathogenic mechanisms in NAFLD and T2DM. The cascade of IR leading to hyperinsulinemia and then pancreatic β-cell dysfunction coupled with defective lipid metabolism and ensuing hepatic triglyceride accumulation are described in both NAFLD and T2DM.[4] Thus, multiple studies have evaluated the role of insulin-sensitizing agents as treatment for NAFLD.[5] However, improving IR alone does not appear sufficient to resolve NAFLD.[6,7] One speculative explanation for these findings might be that despite improvement in insulin sensitivity, pancreatic β-cell function continues to deteriorate and thus targeting insulin sensitivity alone has a null effect. Recent data demonstrate that biopsy-proven NAFLD is associated with an exaggerated pancreatic β-cell response.[8] However, clinical imaging-based NAFLD studies have failed to demonstrate a relationship between NAFLD and pancreatic β-cell dysfunction.[9,10] There are a lack of population-level studies

examining changes in pancreatic β-cell response to blood glucose concentration throughout adulthood in relation to changes in IR on NAFLD and T2DM.

Surrogate indicators for IR, as well as pancreatic β-cell response to glucose concentration, can be extrapolated from fasting blood glucose and insulin levels that are commonly included in population-based studies. The homeostatic model assessments (HOMA) are simple methods for estimating β-cell response to glucose concentration and how well insulin is utilized by its target cell populations.[11] Specifically, HOMA-IR is a measure for whole body IR and HOMA-β is a measure of pancreatic β-cell response to glucose concentration.[11] High HOMA-IR equates to high levels of tissue IR and high HOMA-β equates to high β-cell response. We sought to characterize temporal trends in HOMA-IR and HOMA-β during young adulthood in relation to prevalent NAFLD in middle adulthood and subsequent risk of T2DM among persons with NAFLD.

METHODS

Study Sample

The Coronary Artery Risk Development in Young Adults (CARDIA) study is an ongoing longitudinal cohort study that enrolled 5,115 black and white men and women 18 to 30 years of age from four U.S. field centers. The baseline exam (1985–1986; year 0, Y0) and follow-up exams at 2, 5, 7, 10, 15, 20, and 25 years after baseline included extensive collection of detailed clinical data, including non-contrast computed tomography (CT) measurement of liver fat at Y25. Retention rates among survivors have been high throughout the study with > 90% of the surviving cohort maintaining contact.[12] Participants provided written informed consent at each examination, and institutional review boards from each field center (University of Alabama at Birmingham, Birmingham, Alabama; Northwestern University, Chicago, Illinois; University of Minnesota, Minneapolis, Minnesota; and Kaiser Permanente, Oakland, California) approved the study annually.

Fasting glucose and insulin were measured at Y0, Y7, Y10, Y15, Y20, and Y25. Measures at examinations when the participant was pregnant were excluded (n=192). Measures at examinations when the participant reported taking exogenous insulin were excluded for calculation of HOMA-β (n=29).[11,13] Of 3,060 participants with fasting measures at Y0 and at three or more follow up examinations, 2,455 had liver fat assessed at Y25. Participants were then excluded if they had a self-reported history of cirrhosis, hepatitis (n=38), a risk factor for chronic liver disease (e.g. intravenous drug use, n=52) or secondary hepatic steatosis: alcohol consumption > 14 standard drinks/week in women and > 21 standard drinks/week in men (n=225),[7] human immunodeficiency virus (n=14), and medications (e.g. valproic acid, methotrexate, tamoxifen and/or amiodarone) (n=22). The remaining 2,104 participants formed the NAFLD-eligible sample population for the HOMA-IR analyses. For HOMA-β analyses, the sample was 2,089 due to 15 participants who had reported exogenous insulin use that resulted in less than three repeated fasting insulin measures over time (Supplemental Figure 1).

Measurements

Standardized protocols for data collection were used across study centers and have previously been described.[12,14] Blood was drawn after a 12-hour fast in the seated position, separated and plasma frozen to −70°C prior to analysis in a central laboratory.[12] Glucose was assayed at Y0 with the hexokinase UV method by American Bio-Science Laboratories (Van Nuys, California) and by hexokinase coupled to glucose-6-phosphate dehydrogenase (Merck Millipore, Billerica, Massachusetts) at Y7, Y10, Y15, Y20, and Y25. Insulin measurements were determined by radioimmunoassay (Linco Research, St. Charles, Missouri) at Y0, Y7, Y10, Y15, and Y20, as well as by an Elecsys sandwich immunoassay (Roche Diagnostics, Rotkreuz, Switzerland) at Y25. HOMA-IR, HOMA-β were calculated as:

$$\text{HOMA-IR} \quad = \quad (\text{FPI X FPG})/22.5$$

$$\text{HOMA-}\beta \quad = \quad (20 \text{ X FPI})/(\text{FPG} - 3.5)$$

where FPI is fasting plasma insulin concentration (uU/L) and FPG is fasting plasma glucose (mmol/l).[11,13]

The presence of T2DM was assessed at each examination based on a combination of medication use for T2DM (every examination), FPG 126 mg/dl (Y0, Y7, Y10, Y15, Y20, and Y25), 2-h glucose 200 mg/dl (Y10, Y20, and Y25) by OGTT, or hemoglobin A_{1c} (HbA$_{1c}$) 6.5% (Y20 and Y25). Prevalent T2DM was defined as meeting T2DM criteria at Y25 only and incident T2DM was defined as meeting T2DM criteria at any exam year (0, 7, 10, 15, 20 or 25), thus incidence is greater than prevalence.

The CT protocol included the heart and abdomen using a non-contrast CT scan performed using GE (GE 750HD 64 and GE LightSpeed VCT 64, Birmingham and Oakland Centers, respectively; GE Healthcare, Waukesha, WI) or Siemens (Sensation 64, Chicago and Minneapolis Centers; Siemens Medical Solutions, Erlangen, Germany) multi-detector CT scanners and has been described previously.[15] Quality control and image analysis was performed at a core reading center (Wake Forest University Health Sciences, Winston-Salem, NC). Any (e.g., Mild-Moderate-Severe) NAFLD was defined as liver attenuation (LA) < 51 Hounsfield Units (HU, equivalent to a liver/spleen ratio <1)[16] and moderate-severe NAFLD as a LA 40 HU (equivalent to 30% liver fat) after exclusion of other liver fat causes.[15]

Statistical Analysis

Group-based trajectory modeling was used to identify and categorize participants based on patterns of longitudinal change in HOMA-IR or HOMA-β during the 25 years of follow-up (N=3,060 for HOMA-IR, N=3,031 for HOMA-β).[18] HOMA-IR and HOMA-β were logarithmically transformed to approximate normality. Models were fit using SAS Proc traj. [17] Group-based trajectory analysis is designed to identify clusters of individuals with similar patterns of change over time. The optimal number of trajectory classes was determined using

the Bayesian information criterion such that no group included less than 5% of participants. Participants were assigned to the trajectory group for which they had the greatest posterior predictive probability.[18] Trajectory groups were then qualitatively examined and named to describe the visual pattern of change. To estimate the association of trajectory group with prevalent NAFLD or T2DM in NAFLD, trajectory group was included as an independent variable in a logistic regression model examining predictors of continuous LA or any NAFLD or moderate-severe NAFLD or T2DM in NAFLD at Y25. Models were sequentially adjusted *a priori* for demographics (age, sex, race, education, center), cumulative burden of metabolic risk factors (pack-years of smoking, physical activity (exercise units per year), alcohol use (drinks/week), systolic blood pressure (SBP), total/high density lipoprotein cholesterol (HDL-C) ratio, and number of visits with blood pressure or lipid-lowering medications)), percent change in BMI relative to baseline, and HOMA-IR or HOMA-β at Y0 or Y25. Cumulative SBP, alcoholic beverages, physical activity, and total-HDL-C ratio were calculated by summing the product of the average SBP (alcohol or physical activity or BMI or total/HDL-C ratio) and the time interval (in years) between 2 consecutive examinations over the 25 years. To account for hypoglycemic medication use over time, T2DM medication was included in the final model (Model 3) as a dichotomous variable at each exam year. Sensitivity analysis was also performed excluding measures from participants on any T2DM medications at any exam year. Interaction terms were assessed between trajectory group membership and race and sex. In addition, as a comparator group we assessed the relationship between HOMA-IR or HOMA-β trajectory groups and prevalent/incident T2DM among the 1593 NAFLD-eligible participants with CT liver attenuation > 51 HU (e.g., non-NAFLD) in CARDIA (Supplemental Figure 1).

Finally, three mutually exclusive clusters were defined based on hypothesized β-cell response and IR dynamics using observed HOMA-IR and HOMA-β trajectory group membership pair (e.g., increasing IR promotes β-cell demise and inhibits β-cell compensation, Supplemental Table 2). Adjusting for the same set of covariates, logistic regression analyses were used to model the odds of having NAFLD or prevalent/incident T2DM among NAFLD participants at Y25 for each cluster in separate models. All analyses were completed using SAS software version 9.4 (SAS Institute Inc., Chicago, IL). Two-sided P<0.05 was considered statistically significant.

RESULTS

HOMA-IR and HOMA-β Trajectories

Three discrete trajectories in HOMA-IR and HOMA-β from young adulthood to middle age were identified (Figure 1). Both HOMA-IR (Figure 1A) and HOMA-β (Figure 1B) tracked over time among participants. For IR, nearly half of the cohort (n=1429, 47%) maintained fairly stable low IR throughout follow-up (low-stable) whereas 42% (n=1285) had moderate increase in IR (moderate-increasing) and 12% (n=346) had high increase in IR (high-increasing). For HOMA-β, all trajectory groups demonstrated a decrease in HOMA-β after age 45 (Figure 1B). However, the majority of participants maintained fairly HOMA-β throughout most of young adulthood: 21% (n=626) had high-decreasing HOMA-β and 63% (n=1917) had moderate-decreasing HOMA-β. Only 16% (n=488) of participants

demonstrated a notable early and sustained decrease in HOMA-β throughout young adulthood (e.g., low-decreasing).

Participant characteristics at Y0 according to HOMA trajectory group are presented in Table 1. Individuals with high-decreasing HOMA-β were older and predominantly women and black. Individuals with high-decreasing HOMA-β were more likely to be overweight or obese compared to individuals with moderate-decreasing and low-decreasing HOMA-β. Similarly, individuals with high-increasing HOMA-IR were predominantly women, black and had higher baseline BMI compared to the low-stable IR group. At Y25, participants with moderate-decreasing and high-decreasing HOMA-β were more likely to display features of the metabolic syndrome compared to participants in the low-decreasing group (Table 2). Similar trends were seen in participants with moderate-increasing or high-increasing IR throughout adulthood compared to participants with low-stable IR (Table 2).

HOMA Trajectories and NAFLD

NAFLD prevalence in CARDIA was 24.5% and was higher with increasing HOMA-IR group. Any NAFLD (e.g., LA < 51 HU) was present in 7.4%, 32.5%, and 63.6% in the low-stable, moderate-increasing and high-increasing HOMA-IR groups, respectively (p for trend <0.0001, Figure 2A). Within each HOMA-IR group, NAFLD was greater in whites compared to blacks and in men compared to women, with the exception of the high-increasing HOMA-IR group in which white women had the highest NAFLD prevalence (Supplemental Figure 2A). There was no significant interaction by race or sex in all models and thus pooled results are shown.

Table 3 demonstrates the association between HOMA-IR or HOMA-β trajectory group and continuous LA or NAFLD. For HOMA-IR, those in trajectory groups with patterns of increasingly severe IR (referent: low-stable) had progressively greater odds of having any NAFLD after adjustment for demographic characteristics and education (Table 3). These associations were moderately attenuated when adjusted for demographics, cumulative burden of metabolic risk factors and Y0 HOMA-IR. Associations were attenuated more substantially, but remained statistically significant when adjusted for Y25 HOMA-IR. The association between HOMA-IR trajectory group and moderate-severe NAFLD (n events=224) was similar in direction and magnitude (Table 3). Findings were also similar for continuous LA.

NAFLD prevalence at Y25 was also higher with increasing HOMA-β group, with NAFLD present in 14.3%, 21.3%, and 40.8% of individuals in the low-decreasing, moderate-decreasing and high-decreasing groups, respectively (p for trend <0.0001, Figure 2B). NAFLD prevalence increased with increasing HOMA-β trajectory in all race sex groups with the exception of black women where NAFLD prevalence was 24.5%, 13.6% and 29.3% in the low, moderate and high HOMA-β trajectory groups, respectively (Supplemental Figure 2B).

In comparison with individuals in the low-decreasing group, those in trajectory groups with higher HOMA-β had progressively greater odds of NAFLD even after adjustment for demographics (Table 3). These associations were moderately attenuated when adjusted for

cumulative NAFLD risk factors, including Y0 HOMA-β. Associations were attenuated more substantially, but remained statistically significant when adjusted for Y25 HOMA-β. The association between HOMA-β trajectory and continuous LA and moderate-severe NAFLD (n events=224) was similar in direction and magnitude (Table 3). In sensitivity analyses excluding those participants who were taking T2DM medications at any time point, all associations were unchanged (data not shown).

HOMA Trajectories and T2DM Among NAFLD Participants

Among participants with any NAFLD (n=511), both prevalent and incident T2DM at Y25 was higher with increasing HOMA-IR (p <0.0001, Figure 3A). In contrast, participants with low-decreasing HOMA-β trajectory had the highest prevalence of T2DM (p<0.0001, Figure 3B). In multivariable analysis, low-decreasing HOMA-β (referent: high-decreasing) trajectory was associated with higher odds of prevalent (OR=11.8 [4.3,32.4]) and incident (OR=9.1 [3.4,24.3]) T2DM independent of cumulative T2DM risk factors and Y25 HOMA-IR (Table 4). In contrast, high-increasing HOMA-IR (referent: low-stable) trajectory was associated with greater prevalent (OR=4.6 [1.1,18.9]) and incident (OR=7.2 [1.8,29.2]) T2DM (Table 4). Findings were similar in direction though somewhat stronger in magnitude in both unadjusted and adjusted analyses among non-NAFLD CARDIA participants who were excluded from the primary analyses (n=1593, Supplemental Table 1).

HOMA-IR and HOMA-β Trajectory Group Clusters

The prevalence of CARDIA participants in each HOMA-IR/HOMA-β trajectory group cluster are shown in Supplemental Table 2. The low HOMA IR-low HOMA β cluster and high HOMA IR-high HOMA β cluster contained 45.7% and 21.1% of participants, respectively. The remaining participants formed the referent cluster (n=1008, 33.2%). Participants in the high HOMA IR-high HOMA β cluster were predominantly black (61.4%) and women (63.8%), and participants with low HOMA IR-low HOMA β cluster were predominantly white (67.2%) and women (57.5%). Notably, participants in the high HOMA IR-high HOMA β cluster had the lowest education and physical activity level, and less favorable levels for components of the metabolic syndrome at Y0 (Supplemental Table 3) and at Y25 (Supplemental Table 4).

Table 5 displays the odds of NAFLD or T2DM among NAFLD participants at Y25 for the three HOMA IR-HOMA β trajectory group clusters. The odds of NAFLD were significantly higher in the high HOMA IR-high HOMA β cluster than the referent cluster in all models. When IR and β-cell response trajectories were both high, the odds of developing NAFLD were significantly higher than the referent. In contrast, participants in the low HOMA IR-low HOMA β cluster had significantly lower odds of NAFLD compared to the referent. In terms of T2DM risk, NAFLD participants in the high HOMA IR-high HOMA β cluster had significantly higher odds of both prevalent and incident T2DM in the base model, but associations were attenuated and no longer significant in the fully adjusted model.

DISCUSSION

In this population-based prospective study of black and white adults followed for 25 years, we identified three distinct trajectories of IR and pancreatic β-cell response to glucose, separately. These trajectories were independently associated with prevalent NAFLD and T2DM among individuals with NAFLD in midlife. We found that those groups with greater IR increase from young adulthood into middle age have the greatest odds of having NAFLD and subsequent T2DM, regardless of demographics, cumulative burden of metabolic covariates, and degree of IR at Y0 or concurrently at Y25. Higher β-cell response, was also related to higher odds of NAFLD, however lower β-cell response, was related to higher odds of T2DM. When taken collectively, persons with high β-cell response, in relation to high IR had the highest odds of prevalent NAFLD and T2DM in midlife independent of cumulative metabolic confounders. These findings highlight early identification of increasing IR and pancreatic β-cell response to glucose, as potential targets for primary prevention of NAFLD and T2DM in NAFLD.

Multiple studies have demonstrated hyperinsulinemia, and thus elevated HOMA-IR, in NAFLD.[19] IR is inadequate response by tissues to the physiological effects of insulin. IR is thus <u>tissue-specific</u>. HOMA-IR typically reflects hepatic IR.[20] However, the liver is also the primary site of insulin clearance in humans.[21] Several studies have shown that HOMA-IR elevation in NAFLD is primarily related to impaired hepatic insulin clearance rather than impaired insulin suppression of hepatic glucose production.[1,22] Thus, HOMA-IR may be a poor overall marker of hepatic IR in NAFLD and the relationship between glucose and insulin is impaired in these patients. In contrast, adipose IR may be an important driver of NAFLD pathogenesis: dysfunctional adipose tissue $\rightarrow$ increase in circulating free fatty acids $\rightarrow$ hepatic steatosis (e.g., lipotoxicity).[22,23] Therefore, in NAFLD, HOMA-IR may be a *risk marker* for underlying dysfunctional adipose tissue and may not necessarily correlate with hepatic IR. Direct measures of adipose tissue IR would add strength to our study but are not available.

We also demonstrate that high pancreatic β-cell response to glucose throughout adulthood is a marker of NAFLD independent of metabolic risk factors. Previous studies likewise demonstrate that liver fat is associated with absolute increases in insulin secretion from the β-cell, in order to compensate for IR and maintain euglycemia.[24] It has also been demonstrated that NAFLD is associated with pancreatic β-cell dysfunction in non-diabetic obese subjects.[8,9] NAFLD individuals have an exaggerated β-cell insulin secretory response to an oral glucose load independent of BMI, age and sex; and a decline in β-cell index, which reflects pancreatic β-cell function, in the setting of underlying IR.[8,23] Our current findings add to the epidemiologic evidence that increasing IR and pancreatic β-cell response to glucose are markers of underlying metabolic disarray that predisposes to risk for T2DM in persons with both NAFLD and non-NAFLD. However, it is important to note that similar to HOMA-IR, HOMA-β is also affected by degree of hepatic insulin clearance, which is proportional to hepatic fat content. Thus, HOMA-β may be a poor overall marker of pancreatic β-cell function in NAFLD. Prospective studies that assess rate of change in hepatic insulin clearance over time are needed to fully understand the role of IR and pancreatic β-cell response during NAFLD development.

Progression to diabetes is a complex interplay between IR, insulin sensitivity, and pancreatic β-cell function. A decrease in sensitivity to insulin demands compensation through a proportionate adjustment in insulin secretion by pancreatic β-cells to maintain glucose homeostasis.[25] On a population-level, T2DM risk is driven by multiple factors. We have now demonstrated among persons with both NAFLD and non-NAFLD that increasing level of IR over time is an important driver in the risk of subsequent T2DM. In addition, we found that high IR and high β-cell response in participants with NAFLD increased odds of incident T2DM by 30% compared to participants with NAFLD and high IR and low β-cell response. In contrast, low IR despite low pancreatic β-cell response was associated with a 36% decreased odds of T2DM suggesting that IR is the primary driver of T2DM in NAFLD. Once established, T2DM may promote progression to NASH, cirrhosis, and hepatocellular carcinoma.[2] Thus, improved understanding of risk factors for development of T2DM in NAFLD is critical in order to target prevention of liver disease progression.

Several limitations should also be considered when interpreting our results. CT is a relatively insensitive measure of hepatic fat when compared with magnetic resonance imaging,[16,26] which may bias our results toward the null and underestimate the strength of the observed association. NAFLD was also not assessed in CARDIA prior to the Y25 follow up examination and thus, we cannot establish temporality of our HOMA-IR and HOMA-β trajectories or incident diabetes in relation to NAFLD onset. However, since NAFLD is primarily an asymptomatic disease, detection in midlife mirrors clinical practice when NAFLD is commonly incidentally found on imaging performed for other reasons.[27] It is also possible that some CARDIA participants had undiagnosed NAFLD at Y0. However, 62% of NAFLD participants were normal weight at Y0 and only 10% had obesity. Since undiagnosed NAFLD may have been present early in follow up, we also cannot rule out the possibility of reverse causality (e.g. NAFLD causing an increase in IR, rather than vice versa). CARDIA only included whites and blacks and did not specifically ask about ethnicity. Thus, we cannot generalize our findings to the Hispanic population wherein NAFLD and T2DM are exceedingly high. The assays for glucose and insulin changed during the 25-year follow-up due to technological advances. However, 83% of the measurements were assessed using the same method. Finally, we employed surrogate markers of IR and β-cell response and did not use repeated OGTT or frequent sampling of intravenous glucose tolerance test or c-peptide levels to measure IR or pancreatic β-cell function. Thus, we cannot directly relate insulin resistance to insulin secretion within an individual. We are also unable to assess effect of degree of hepatic insulin clearance on absolute levels of HOMA-IR or HOMA-β. However, HOMA models can be easily calculated in clinical practice and thus temporal trends (rather than absolute levels) may be useful for detection of NAFLD individuals at high risk for T2DM.

POTENTIAL CLINICAL IMPLICATIONS

Higher IR is a well-known risk factor for the development of NAFLD and T2DM and β-cell failure is a known requirement for the development of T2DM in IR patients. However, our findings suggest than an individual's long-term pattern of change in insulin sensitivity and secretion starting in early adulthood provides additional information about their risk for the development of NAFLD and T2DM in midlife independent of absolute level of insulin

resistance or β-cell response in early adulthood or in midlife. In the age of the electronic medical record, repeated measures of insulin sensitivity and secretion throughout adulthood can be readily graphed allowing clinicians to recognize at-risk patterns (e.g., rapidly rising IR) early in adulthood. Early identification of young adults with high HOMA-IR trajectory may lead to treatments that target prevention of adipose tissue overload (e.g., weight maintenance, physical activity) and prevention of adipose tissue insulin signaling inactivation (e.g., pioglitazone) for primary prevention of NAFLD. The potential clinical implications of our findings require further prospective study.

CONCLUSION

Trajectories of IR and pancreatic β-cell response to glucose concentration throughout early adulthood to middle age—independent of baseline and concurrent IR and β-cell response— may provide additional information about the cumulative burden of IR and risk of prevalent NAFLD and T2DM in midlife. These associations were independent of key comorbidities and metabolic risk factors. This novel characterization of the relationship between IR and β-cell response trajectories across young adulthood highlights this age period as an important time to target behavior and lifestyle interventions for primordial prevention of NAFLD and subsequent T2DM.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations.

IR	insulin resistance
NAFLD	non-alcoholic fatty liver disease
CARDIA	Coronary Artery Risk Development in Young Adults
Y0	year 0
HOMA	homeostatic model assessment
IR	insulin resistance
OR	odds ratio
CI	confidence interval
T2DM	type 2 diabetes mellitus

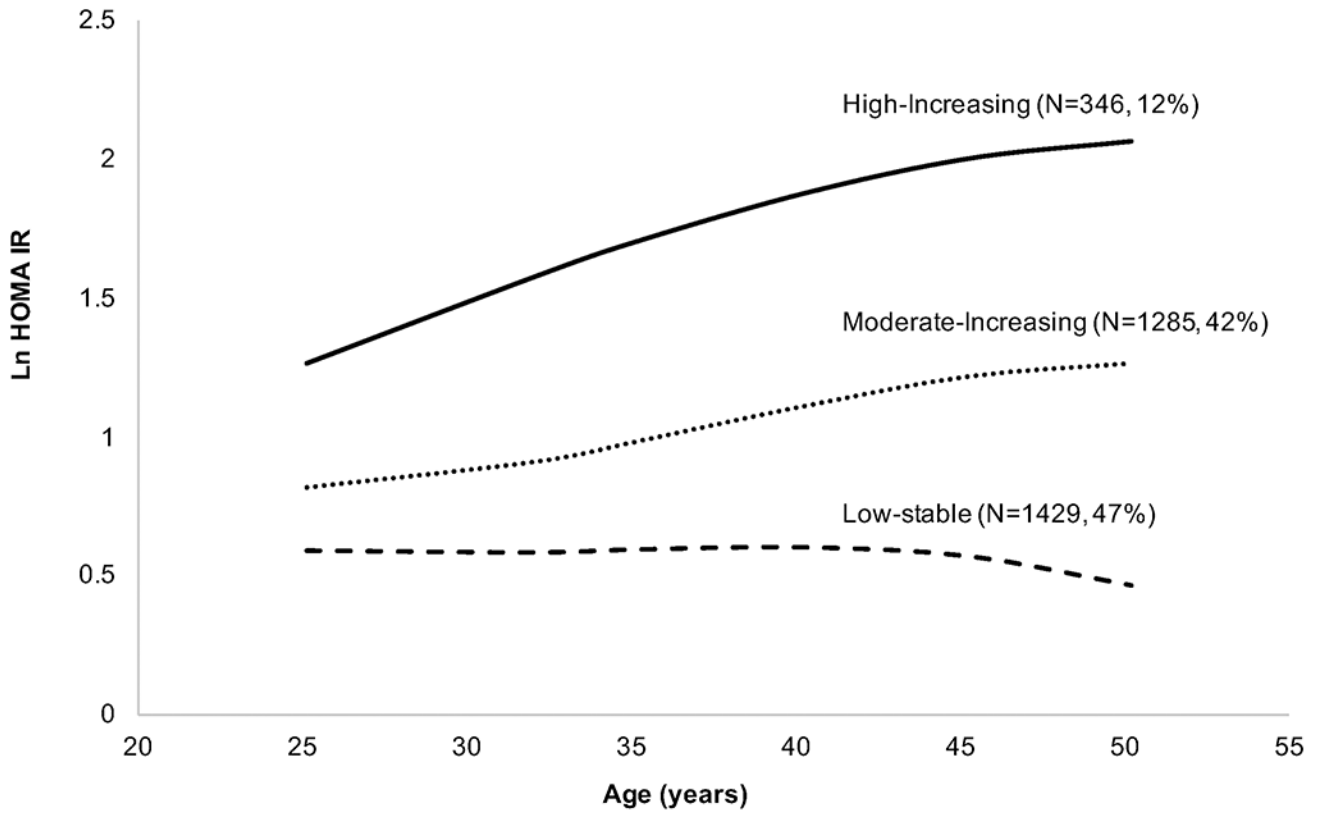| CT	computed tomography
EU	exercise units
FPI	fasting plasma insulin
FPG	fasting plasma glucose
HU	Hounsfield units
LA	liver attenuation
BMI	body mass index
SBP	systolic blood pressure
HDL-C	high density lipoprotein cholesterol

REFERENCES

1. Gaggini M, Morelli M, Buzzigoli E, DeFronzo RA, Bugianesi E, Gastaldelli A. Non-alcoholic fatty liver disease (NAFLD) and its connection with insulin resistance, dyslipidemia, atherosclerosis and coronary heart disease. Nutrients. 2013;5(5):1544–1560. [PubMed: 23666091]

2. Anstee QM, Targher G, Day CP. Progression of NAFLD to diabetes mellitus, cardiovascular disease or cirrhosis. Nat Rev Gastroenterol Hepatol. 2013;10(6):330–344. [PubMed: 23507799]

3. Byrne CD, Targher G. NAFLD: a multisystem disease. J Hepatol. 2015;62(1 Suppl):S47–64. [PubMed: 25920090]

4. Marchesini G, Marzocchi R. Metabolic syndrome and NASH. Clin Liver Dis. 2007;11(1):105–117, ix. [PubMed: 17544974]

5. Rakoski MO, Singal AG, Rogers MA, Conjeevaram H. Meta-analysis: insulin sensitizers for the treatment of non-alcoholic steatohepatitis. Aliment Pharmacol Ther. 2010;32(10):1211–1221. [PubMed: 20955440]

6. Mazzotti A, Caletti MT, Marchignoli F, Forlani G, Marchesini G. Which treatment for type 2 diabetes associated with non-alcoholic fatty liver disease? Dig Liver Dis. 2017;49(3):235–240. [PubMed: 28089623]

7. EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol. 2016;64(6):1388–1402. [PubMed: 27062661]

8. Siddiqui MS, Cheang KL, Luketic VA, et al. Nonalcoholic Steatohepatitis (NASH) Is Associated with a Decline in Pancreatic Beta Cell (beta-Cell) Function. Dig Dis Sci. 2015;60(8):2529–2537. [PubMed: 25784075]

9. Bedogni G, Gastaldelli A, Tiribelli C, et al. Relationship between glucose metabolism and non-alcoholic fatty liver disease severity in morbidly obese women. J Endocrinol Invest. 2014;37(8): 739–744. [PubMed: 24906975]

10. Rijkelijkhuizen JM, Doesburg T, Girman CJ, et al. Hepatic fat is not associated with beta-cell function or postprandial free fatty acid response. Metabolism. 2009;58(2):196–203. [PubMed: 19154952]

11. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. Diabetes Care. 2004;27(6):1487–1495. [PubMed: 15161807]

12. Friedman GD, Cutter GR, Donahue RP, et al. CARDIA: study design, recruitment, and some characteristics of the examined subjects. J Clin Epidemiol. 1988;41(11):1105–1116. [PubMed: 3204420]

13. Bergman RN, Ader M, Huecking K, Van Citters G. Accurate assessment of beta-cell function: the hyperbolic correction. Diabetes. 2002;51 Suppl 1:S212–220. [PubMed: 11815482]

14. Parker ED, Schmitz KH, Jacobs DR, Dengel DR, Schreiner PJ. Physical activity in young adults and incident hypertension over 15 years of follow-up: the CARDIA study. American journal of public health. 2007;97(4):703–709. [PubMed: 17329668]

15. VanWagner LB, Ning H, Lewis CE, et al. Associations between nonalcoholic fatty liver disease and subclinical atherosclerosis in middle-aged adults: The Coronary Artery Risk Development in Young Adults Study. Atherosclerosis. 2014;235(2):599–605. [PubMed: 24956534]

16. Kodama Y, Ng CS, Wu TT, et al. Comparison of CT methods for determining the fat content of the liver. AJR Am J Roentgenol. 2007;188(5):1307–1312. [PubMed: 17449775]

17. Nagin DS, Odgers CL. Group-Based Trajectory Modeling (Nearly) Two Decades Later. Journal of quantitative criminology. 2010;26(4):445–453. [PubMed: 21132047]

18. Allen NB, Siddique J, Wilkins JT, et al. Blood pressure trajectories in early adulthood and subclinical atherosclerosis in middle age. Jama. 2014;311(5):490–497. [PubMed: 24496536]

19. Gutierrez-Buey G, Nunez-Cordoba JM, Llavero-Valero M, Gargallo J, Salvador J, Escalada J. Is HOMA-IR a potential screening test for non-alcoholic fatty liver disease in adults with type 2 diabetes? Eur J Intern Med. 2017;41:74–78. [PubMed: 28283346]

20. Tripathy D, Almgren P, Tuomi T, Groop L. Contribution of insulin-stimulated glucose uptake and basal hepatic insulin sensitivity to surrogate measures of insulin sensitivity. Diabetes Care. 2004;27(9):2204–2210. [PubMed: 15333485]

21. Duckworth WC, Kitabchi AE. Insulin metabolism and degradation. Endocr Rev. 1981;2(2):210–233. [PubMed: 7028472]

22. Bril F, Barb D, Portillo-Sanchez P, et al. Metabolic and histological implications of intrahepatic triglyceride content in nonalcoholic fatty liver disease. Hepatology. 2017;65(4):1132–1144. [PubMed: 27981615]

23. Fabbrini E, Magkos F. Hepatic Steatosis as a Marker of Metabolic Dysfunction. Nutrients. 2015;7(6):4995–5019. [PubMed: 26102213]

24. Pagano G, Pacini G, Musso G, et al. Nonalcoholic steatohepatitis, insulin resistance, and metabolic syndrome: further evidence for an etiologic association. Hepatology. 2002;35(2):367–372. [PubMed: 11826410]

25. Kahn SE. The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of Type 2 diabetes. Diabetologia. 2003;46(1):3–19. [PubMed: 12637977]

26. Musso G, Gambino R, Cassader M, Pagano G. Meta-analysis: natural history of non-alcoholic fatty liver disease (NAFLD) and diagnostic accuracy of non-invasive tests for liver disease severity. Ann Med. 2011;43(8):617–649. [PubMed: 21039302]

27. Blais P, Husain N, Kramer JR, Kowalkowski M, El-Serag H, Kanwal F. Nonalcoholic fatty liver disease is underrecognized in the primary care setting. Am J Gastroenterol. 2015;110(1):10–14. [PubMed: 24890441]

A

HOMA-IR Trajectories
Total N=3060

High-Increasing (N=346, 12%)

Moderate-Increasing (N=1285, 42%)

Low-stable (N=1429, 47%)

Ln HOMA IR

Age (years)

B

HOMA-β Trajectories
Total N=3031

High-Decreasing (N=626, 21%)

Moderate-Decreasin (N=1917, 63%)

Low-decreasing (N=488, 16%)

Ln HOMA-β

Ages (years)
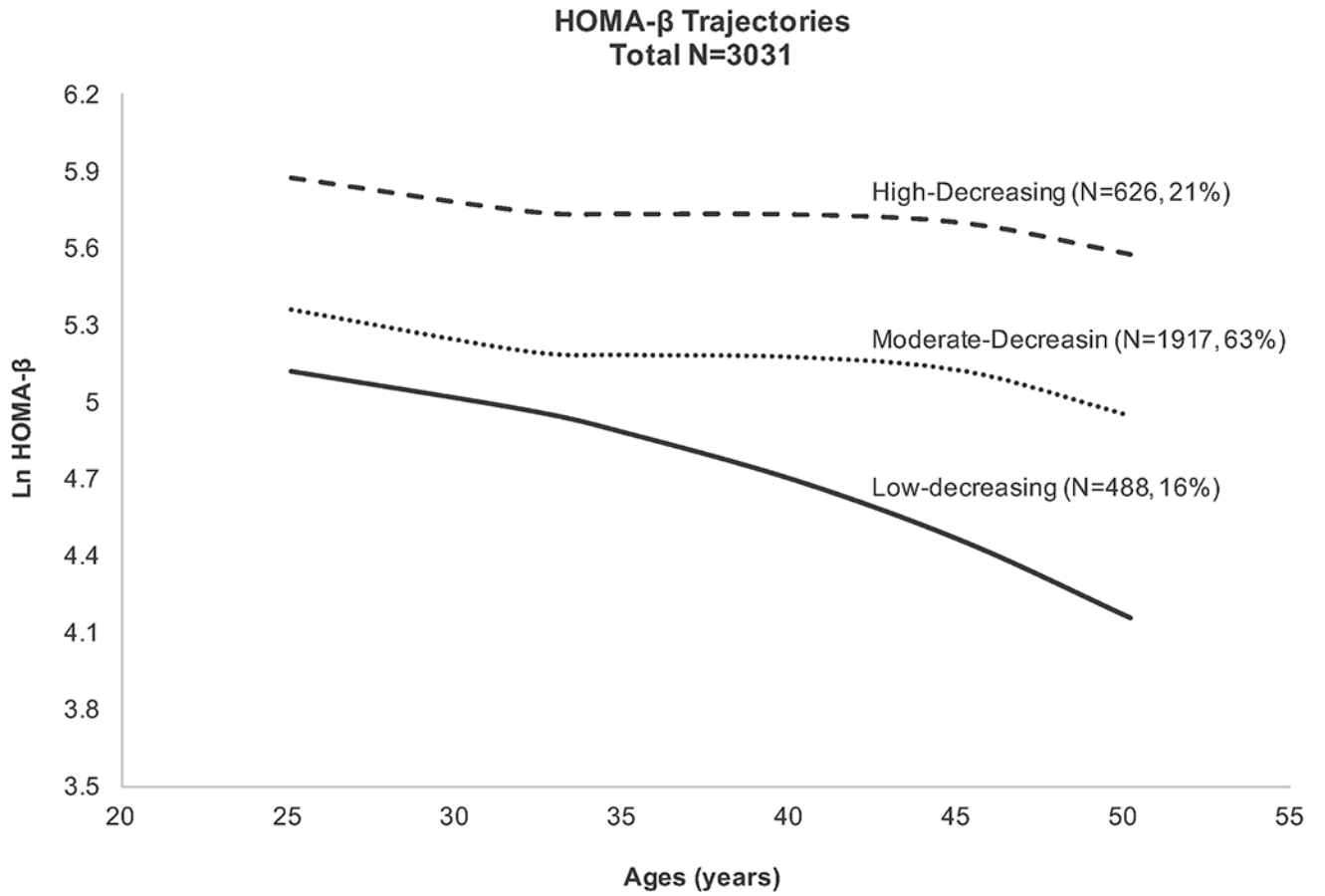
Figure 1.
Trajectories by Age in the Coronary Artery Risk Development in Young Adults (CARDIA)
Study of (A) HOMA-IR and (B) HOMA-β.

A
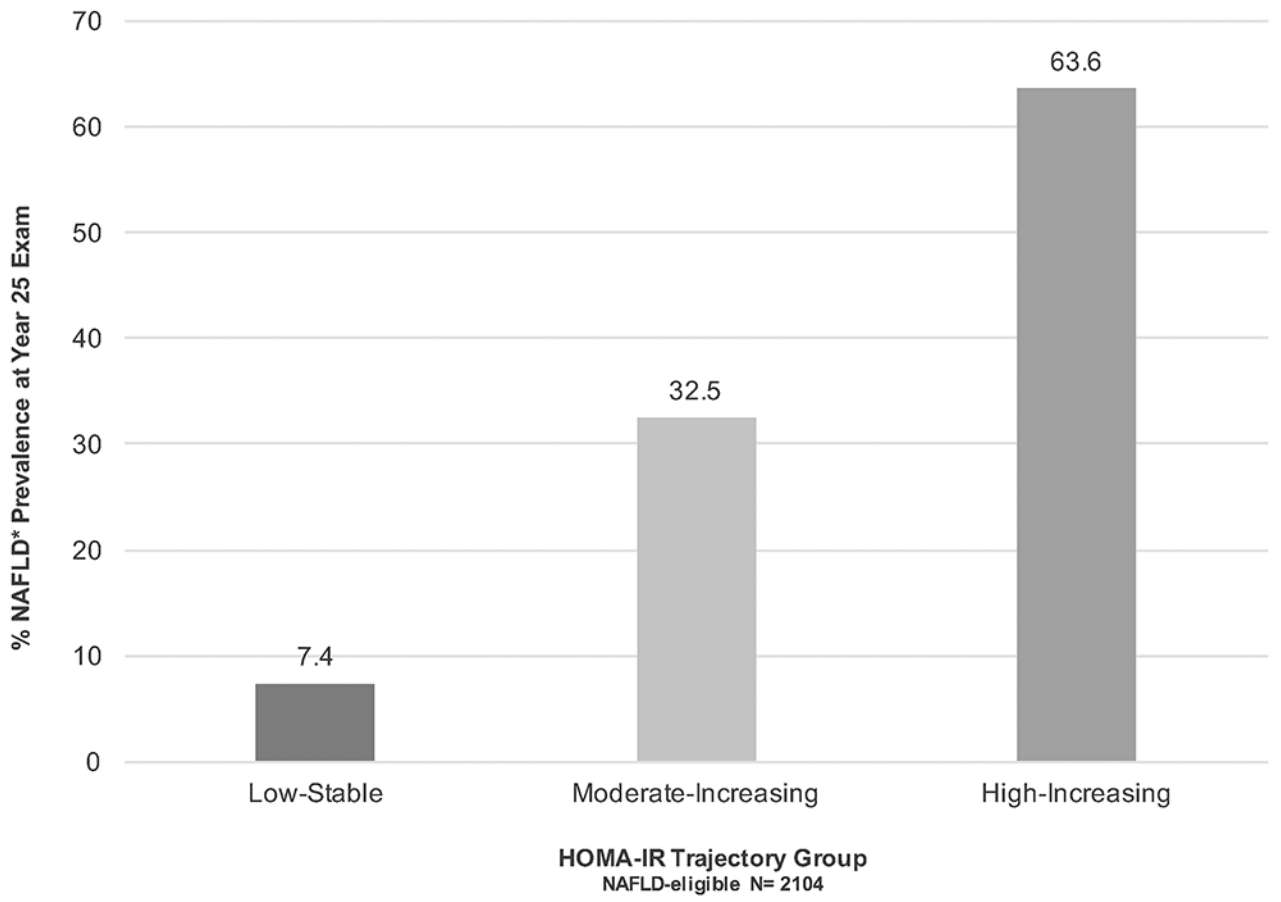
B
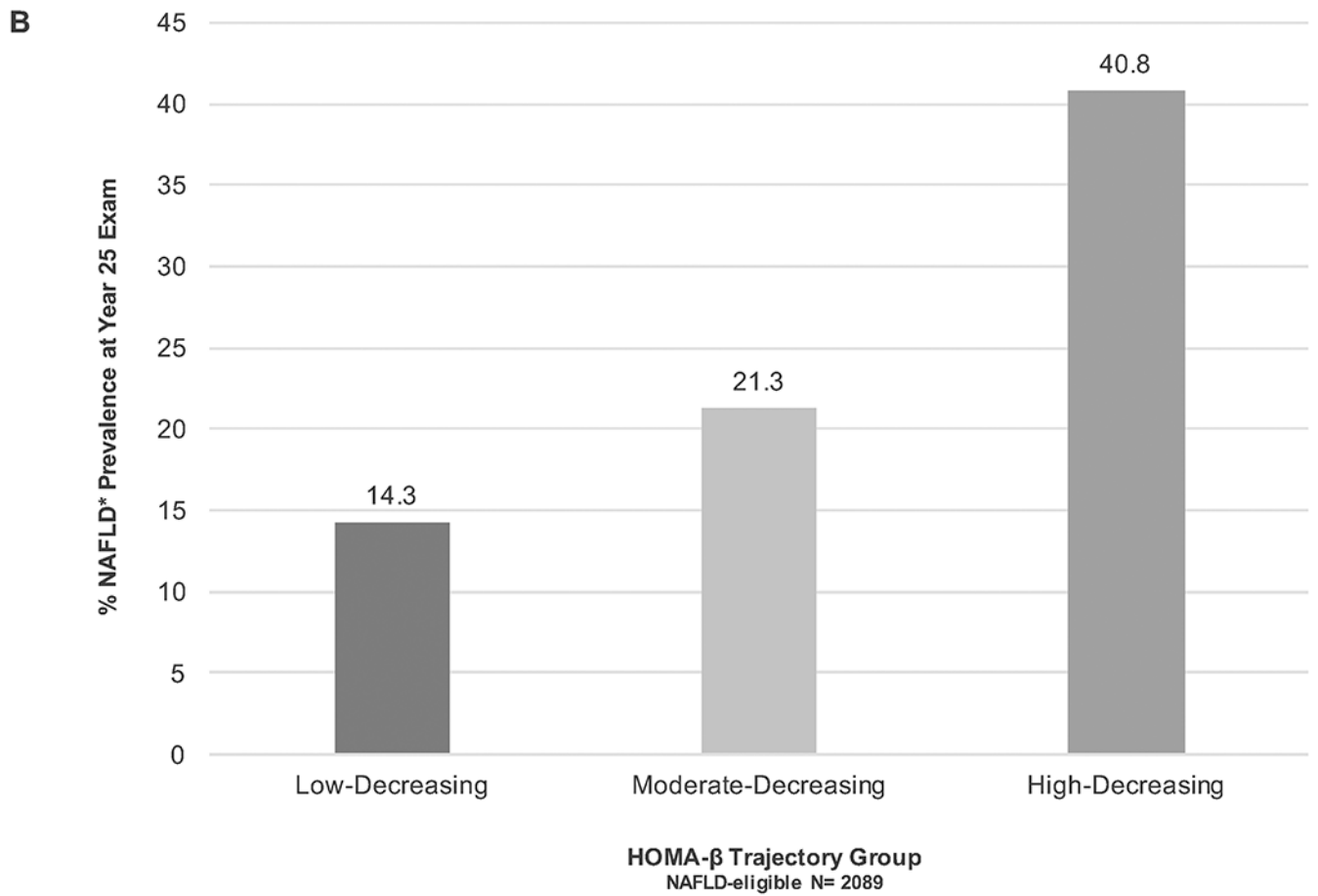
Figure 2. Year 25 NAFLD* Prevalence stratified by A) HOMA-IR and B) HOMA-β Trajectory Group.

Chi-square P <0.0001 for trajectory group membership for both HOMA assessments.

*NAFLD defined as CT liver attenuation < 51 HU after exclusions for other causes of liver fat.

A

HOMA-IR Trajectory Group
N with Y25 NAFLD*= 511

B

Figure 3. Year 25 Prevalent and Incident Diabetes among persons with NAFLD* stratified by (A) HOMA-IR and (B) HOMA-β Trajectory Group.

Chi-square P <0.0001 for trajectory group membership for both HOMA assessments.

*NAFLD defined as CT liver attenuation < 51 HU after exclusions for other causes of liver fat. Estimates are for participants with diabetes by Y25 follow up, not at Y25 follow up, thus incidence is > prevalence.

TABLE 1.

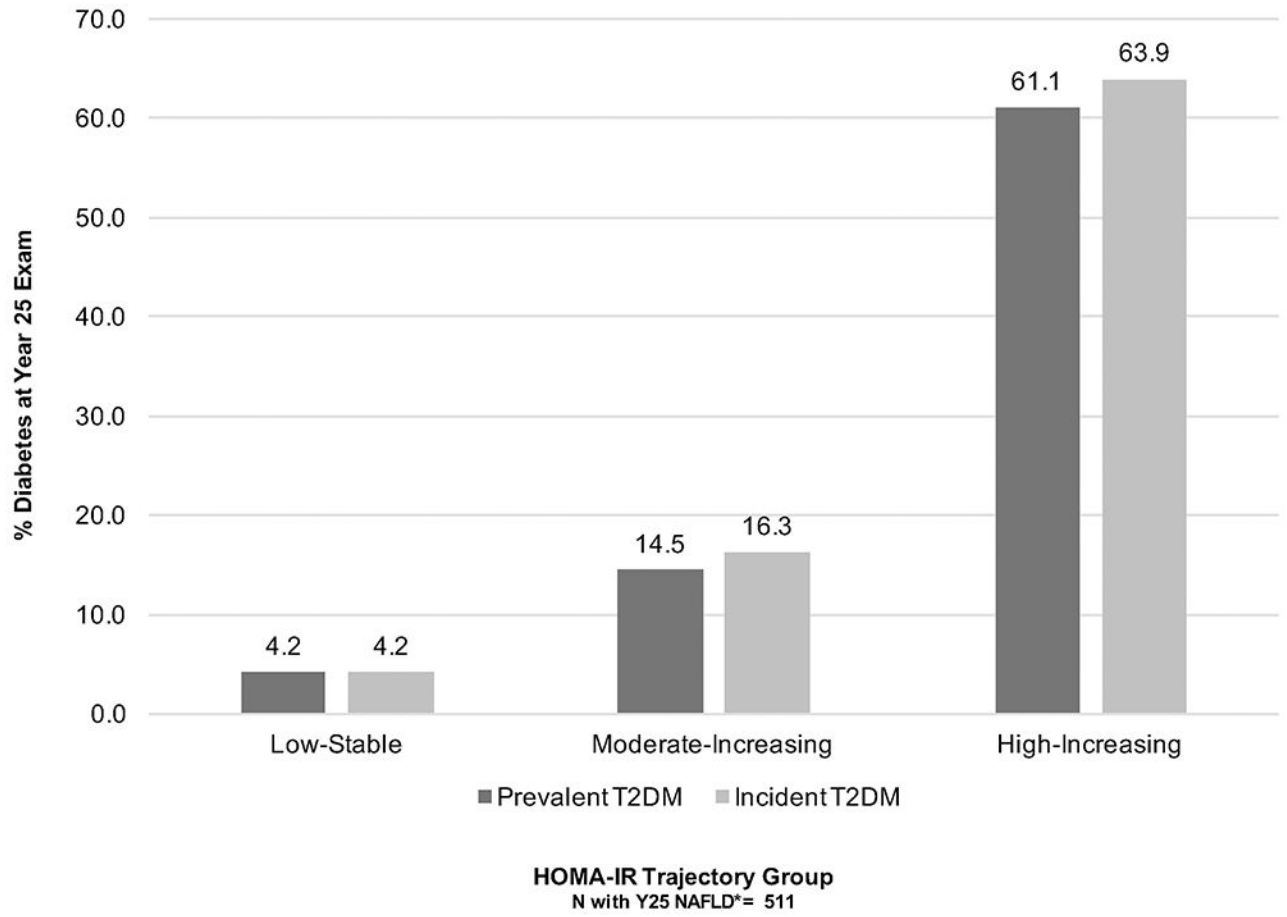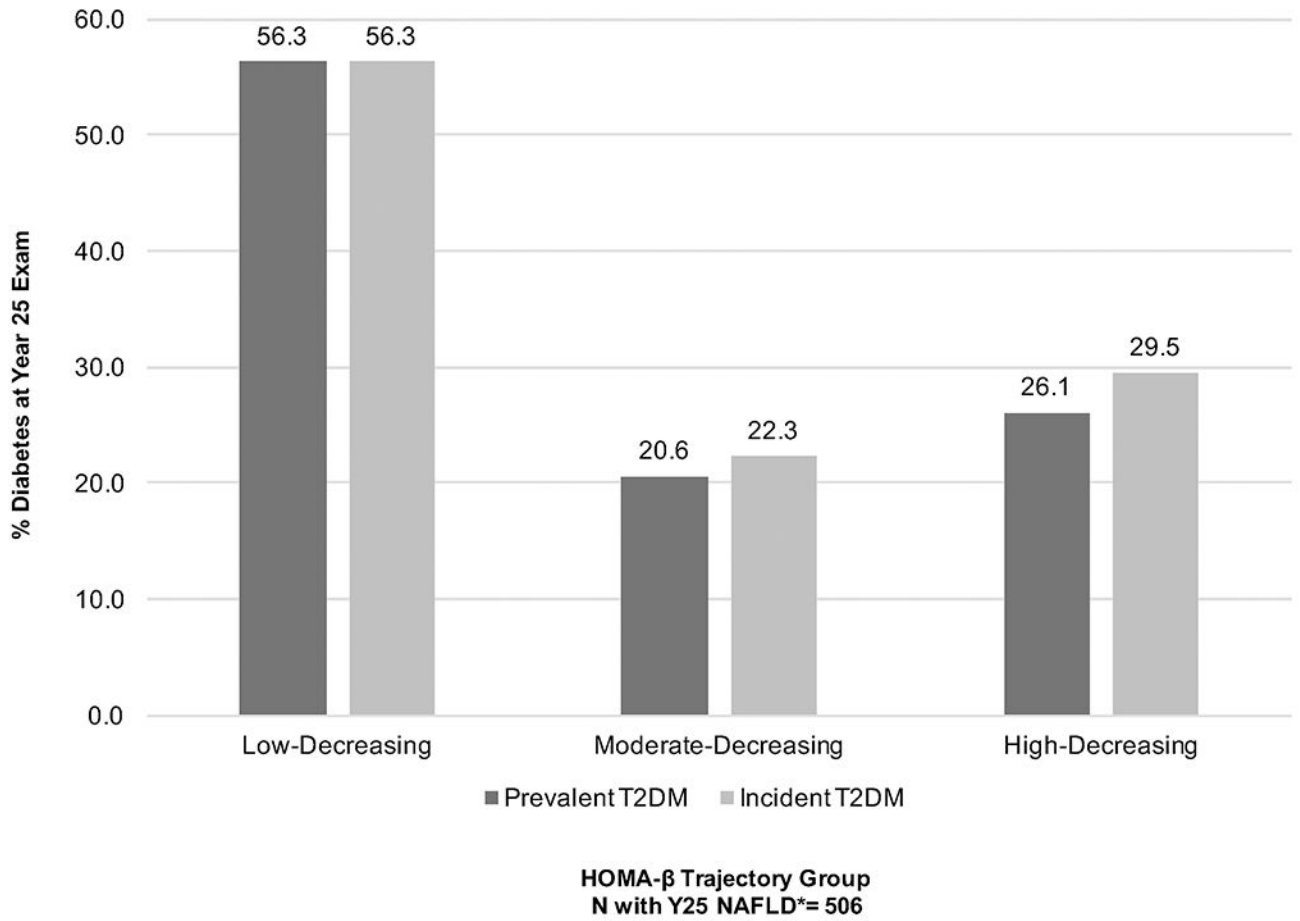Baseline (Year 0) Characteristics by HOMA-β or HOMA-IR Trajectory Group

Characteristics	HOMA-β Trajectory**				HOMA-IR Trajectory			
	Low-decreasing N=488	Moderate-decreasing N=1917	High-decreasing N=626	P value*	Low-stable N=1429	Moderate-increasing N=1285	High-increasing N=346	P value*
Age, years	24.1±3.3	25.2±3.5	25.5±3.7	<.0001	25.1±3.5	25.2±3.6	24.7±3.9	.07
Race, n (%)				<.0001				<.0001
Blacks	163(33.4)	763(39.8)	394(62.9)		486(34.0)	635(49.4)	216(62.4)	
Whites	325(66.6)	1154(60.2)	232(37.1)		943(66.0)	650(50.6)	130(37.6)	
Sex				<.0001				<.0001
Women	197(40.4)	1048(54.7)	433(69.2)		862(60.3)	658(51.2)	175(50.6)	
Men	291(59.6)	869(45.3)	193(30.8)		567(39.7)	627(48.8)	171(49.4)	
Education, years	14.0±2.3	14.2±2.3	13.8±2.2	<.0001	14.4±2.3	13.9±2.3	13.5±2.0	<.0001
Current smoker	141(29.0)	484(25.3)	153(24.7)	.32	377(26.4)	327(25.6)	84(24.6)	.41
Physical activity, exercise unit†	505.0±320.2	433.4±302.2	334.1±250.8	<.0001	450.6±296.9	412.4±307.0	358.3±271.9	<.0001
Alcohol drinkers	338(69.6)	1228(64.4)	286(46.0)	<.0001	950(66.9)	754(58.9)	168(48.8)	<.0001
Alcohol use, g/day	17.1±31.1	11.9±19.8	7.4±14.8	<.0001	15.3±20.0	15.6±19.0	14.4±19.3	.76
Weight, lbs	153.8±32.7	153.9±32.3	167.0±41.4	<.0001	165.7±33.1	210.4±44.1	244.2±51.8	<.0001
Height, cm	172.2±9.4	170.7±9.4	168.2±9.4	<.0001	169.9±9.3	170.8±9.7	171.2±9.8	.02
BMI, kg/m²	23.5±4.1	23.9±4.4	26.7±5.8	<.0001	22.5±3.5	25.3±4.6	29.5±5.8	<.0001
Normal weight	371(76.0)	1337(70.0)	282(45.2)	<.0001	1194(83.8)	737(57.6)	73(21.1)	<.0001
Overweight	82(16.8)	423(22.2)	198(31.7)		192(13.5)	383(29.9)	131(37.9)	
Obese	35(7.2)	149(7.8)	144(23.1)		39(2.7)	160(12.5)	142(41.0)	
Waist circumference, cm	76.4±10.4	76.7±10.3	81.6±13.1	<.0001	72.9±8.3	79.8±10.3	89.6±13.4	<.0001
Waist-to-hip ratio	0.78±0.07	0.77±0.07	0.78±0.07	.01	0.76±0.06	0.78±0.07	0.82±0.08	<.0001
Systolic BP, mm Hg	111.3±11.8	109.9±10.6	110.4±10.2	.04	108.2±10.5	111.3±10.2	114.8±12.1	<.0001

Characteristics	HOMA-β Trajectory**				HOMA-IR Trajectory			
	Low-decreasing N=488	Moderate-decreasing N=1917	High-decreasing N=626	P value*	Low-stable N=1429	Moderate-increasing N=1285	High-increasing N=346	P value*
Diastolic BP, mm Hg	68.3±9.2	68.3±9.2	69.3±9.6	.049	67.5±9.3	69.1±9.2	71.4±10.7	<.0001
Hypertension	21(4.3)	55(2.9)	29(4.6)	.06	36(2.5)	41(3.2)	33(9.5)	<.0001
Total cholesterol, mg/dl	174.7±32.5	176.6±32.2	180.9±33.5	.003	174.4±31.6	178.9±33.3	182.5±33.1	<.0001
HDL cholesterol, mg/dl	54.2±12.4	53.5±12.9	51.2±12.6	<.0001	56.3±15.6	51.3±12.2	46.4±11.9	<.0001
LDL cholesterol, mg/dl	106.4±30.2	109.0±29.6	114.4±32.7	<.0001	105.4±29.4	112.6±31.0	116.7±30.5	<.0001
Triglyceride, mg/dl	70.8±49.1	70.8±45.2	77.1±46.6	.009	65.5±36.8	75.0±43.4	99.0±77.4	<.0001
Fasting glucose, mmol/L	4.8±0.56	4.5±0.46	4.4±0.42	<.0001	4.5±0.45	4.6±0.52	4.9±1.1	<.0001
Fasting insulin, uU/mL	9.8±5.0	10.6±4.3	14.7±7.2	<.0001	9.2±3.1	11.8±4.1	19.1±10.8	<.0001
HOMA-IR score	2.1±1.3	2.2±1.0	2.9±1.6	<.0001	1.8±0.73	2.4±0.96	4.2±3.3	<.0001
HOMA-β score	166.5±101.9	214.4±216.4	432.8±469.4	<.0001	230.0±280.9	254.0±313.8	331.8±231.5	<.0001

*
Chi square test for categorical variables and ANOVA for continuous variables within HOMA-β or HOMA-IR trajectory groups

**
total n for HOMA-β = 3031; 29 participants were excluded due to < 3 repeated measures of fasting insulin/glucose as a result of exogenous insulin use

†
Physical activity was assessed using a standard self-report instrument; energy expenditure for moderate and vigorous activities was calculated in exercise units.

Abbreviations: NAFLD, nonalcoholic fatty liver disease; BMI, body mass index; BP, blood pressure; HU, Hounsfield Units; LDL, low density lipoprotein; HDL, high density lipoprotein; HOMA, homeostatic model assessment; IR, insulin resistance

TABLE 2.

Diabetes Risk Factors at Year 25 by HOMA-β or HOMA-IR trajectory group

Characteristics	HOMA-β Trajectory**				HOMA-IR Trajectory			
	Low-decreasing N=449	Moderate-decreasing N=1685	High-decreasing N=539	P value*	Low-stable N=1277	Moderate-increasing N=1116	High-increasing N=285	P value*
Age, years	49.2±3.3	50.4±3.6	50.7±3.7	<.0001	50.3±3.5	50.3±3.6	49.7±3.9	.03
Current smoker	88(19.8)	235(14.1)	83(15.8)	.054	201(15.9)	173(15.6)	33(11.9)	.20
Physical activity, exercise unit†	406.4±286.4	350.4±273.9	250.2±230.7	<.0001	386.8±283.1	307.6±262.3	250.7±215.4	<.0001
Alcohol drinkers	319(72.0)	973(58.2)	204(38.3)	<.0001	836(65.8)	575(51.7)	94(33.2)	<.0001
Alcohol use, g/day	18.0±31.8	11.8±19.5	6.7±24.0	<.0001	14.7±26.7	9.9±19.4	6.1±16.4	<.0001
Weight, lbs	173.5±39.5	189.5±45.5	218.5±55.2	<.0001	165.7±33.1	210.4±44.1	244.2±51.8	<.0001
Height, cm	172.3±9.4	170.7±9.4	168.3±9.5	<.0001	169.9±9.2	170.9±9.8	171.4±9.3	.006
BMI, kg/m²	26.4±5.2	29.5±6.6	35.0±8.0	<.0001	26.1±4.6	32.8±6.7	37.8±7.5	<.0001
Normal weight	204(45.6)	434(25.8)	42(7.8)	<.0001	605(47.4)	70(6.3)	5(1.8)	<.0001
Overweight	153(34.2)	567(33.7)	107(19.9)		452(35.4)	344(30.9)	31(11.2)	
Obese	90(20.1)	681(40.5)	388(72.3)		219(17.2)	699(62.8)	241(87.0)	
Waist circumference, cm	87.2±13.6	93.3±15.0	103.5±16.8	<.0001	84.3±11.1	101.1±12.8	113.2±15.0	<.0001
Waist-to-hip ratio	0.84±0.08	0.85±0.09	0.87±0.09	<.0001	0.81±.08	0.88±.08	0.92±0.09	<.0001
Systolic BP, mm Hg	117.8±15.6	118.9±15.8	122.1±17.2	<.0001	115.5±14.8	121.8±15.8	126.7±18.3	<.0001
Diastolic BP, mm Hg	72.5±11.3	74.1±11.0	77.7±11.3	<.0001	71.1±10.6	77.2±10.8	79.7±11.1	<.0001
Hypertension	98(21.8)	497(29.5)	270(49.8)	<.0001	219(17.1)	453(40.4)	202(69.7)	<.0001
Total cholesterol, mg/dl	195.3±37.6	193.6±35.8	186.3±37.7	<.0001	193.7±34.4	193.7±37.5	180.8±40.7	<.0001
HDL cholesterol, mg/dl	62.0±17.7	58.2±18.4	53.2±16.1	<.0001	65.2±18.8	52.3±14.8	46.8±11.9	<.0001
Triglyceride, mg/dl	108.2±105.2	115.4±90.4	120.3±74.4	.11	88.4±44.6	133.1±101.7	164.8±143.9	<.0001

Characteristics	HOMA-β Trajectory**				HOMA-IR Trajectory			
	Low-decreasing N=449	Moderate-decreasing N=1685	High-decreasing N=539	P value*	Low-stable N=1277	Moderate-increasing N=1116	High-increasing N=285	P value*
LDL cholesterol, mg/dl	112.5±34.5	112.9±31.5	109.1±33.1	.06	110.8±30.8	115.5±33.1	102.9±34.2	<.0001
Fasting glucose, mmol/L	6.2±2.8	5.4±1.2	5.4±1.1	<.0001	5.0±.47	5.6±1.2	7.7±3.5	<.0001
Fasting insulin, uU/mL	5.5±3.4	10.1±9.1	19.4±11.3	<.0001	5.6±2.5	14.0±6.4	25.3±19.2	<.0001
HOMA-IR score	1.7±1.7	2.6±2.7	4.9±3.6	<.0001	1.3±.58	3.5±1.8	7.8±5.3	<.0001
HOMA-β score	49.6±47.5	109.1±143.6	217.2±259.9	<.0001	78.9±87.0	144.6±159.2	214.1±359.5	<.0001
Liver Attenuation, HU	57.3±9.7	55.8±11.6	51.1±13.7	<.0001	59.5±8.4	52.9±12.3	44.4±14.4	<.0001

*
Chi square test for categorical variables and ANOVA for continuous variables within HOMA-β or HOMA-IR trajectory groups

**
total n for HOMA-β = 2673; 15 participants were excluded due to < 3 repeated measures of fasting insulin/glucose as a result of exogenous insulin use

†
Physical activity was assessed using a standard self-report instrument; energy expenditure for moderate and vigorous activities was calculated in exercise units.

Abbreviations: NAFLD, nonalcoholic fatty liver disease; BMI, body mass index; HU, Hounsfield Units; LDL, low density lipoprotein; HDL, high density lipoprotein; HOMA, homeostatic model assessment; IR, insulin resistance

TABLE 3.

Multivariable Association of Prevalent NAFLD According to Trajectory of HOMA-β and HOMA-IR, the Coronary Artery Risk Development in Young Adults study (1985–1986 to 2010–2011)

N	Continuous Liver Attenuation β (SE) P value			Any NAFLD[a] N events/total N=515/2104** OR (95% CI)			Moderate-Severe NAFLD[b] N events/total N=224/2104** OR (95% CI)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
HOMA-IR trajectory[c]									
Low-stable	976	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Moderate-increasing	894	−7.5‡ (0.48)	−4.0‡ (0.58)	−3.1‡ (0.59)	6.7* (5.0, 8.9)	3.7‡ (2.7, 5.2)	3.1* (2.2, 4.5)	7.3* (4.6, 11.6)	3.8* (2.3, 6.3)	3.6* (2.1, 6.2)
High-increasing	234	−17.2‡ (0.76)	−10.8‡ (1.1)	−6.7‡ (1.1)	30.5‡ (20.6, 45.1)	11.9‡ (7.1, 20.0)	7.2‡ (4.1, 12.8)	30.2‡ (17.9, 51.0)	11.9‡ (6.1, 23.1)	6.1‡ (2.8, 12.9)
HOMA-β trajectory[d]									
Low-decreasing	349	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Moderate-decreasing	1685	−2.5§ (0.68)	−1.2* (0.68)	−0.33 (0.70)	2.0* (1.4, 2.9)	1.9* (1.2, 2.8)	1.5* (1.1, 2.2)	2.2* (1.3–3.7)	2.1* (1.1–3.9)	2.2 (0.85–2.6)
High-decreasing	639	−9.4‡ (0.84)	−5.7‡ (0.91)	−4.2‡ (0.92)	7.2‡ (4.9, 10.8)	5.0‡ (3.1, 8.1)	3.5‡ (2.2, 5.6)	6.3‡ (3.6–11.0)	4.3‡ (2.1–8.5)	2.6§ (1.3–4.9)

Results presented as beta (standard error) or Odds Ratio (95% Confidence Interval) for prevalent NAFLD versus no NAFLD

[a] Any NAFLD = liver attenuation < 51 HU after exclusion for secondary causes of liver fat

[b] Moderate-to-severe NAFLD= liver attenuation　40 HU after exclusion for secondary cause of liver fat

** total n for HOMA-β = 2089; 15 participants were excluded due to < 3 repeated measures of fasting insulin/glucose as a result of exogenous insulin use

‡ p < 0.001 compared with the referent group

§ p <0.01 compared with the referent group

* p <0.05

Model 1: Age, sex, race, field center, educational attainment

Model 2: Model 1 + pack-years smoking exposure, cumulative alcohol use (drinks/day), physical activity level (exercise units-year), cumulative TC/HDL ratio, diabetes medications (at each exam year), %change BMI and baseline HOMA-IR[c] HOMA-β[d]

Model 3: Model 1 + pack-years smoking exposure, cumulative alcohol use (drinks/day), physical activity level (exercise units-year), cumulative TC/HDL ratio, diabetes medications (at each exam year), %change BMI and Y25 HOMA-IR[c] HOMA-β[d]

Abbreviations: NAFLD, nonalcoholic fatty liver disease; Y25, year 25 follow-up exam; SE, standard error; OR, odds ratio; CI, confidence interval; TC, total cholesterol; HDL, high density lipoprotein; HOMA, homeostatic model assessment; IR, insulin resistance; BMI, body mass index

TABLE 4.

Prevalent or Incident Type 2 Diabetes Mellitus According to HOMA-β or HOMA-IR Trajectory Group Among 511 Participants with Prevalent NAFLD at the Year 25 Exam, the Coronary Artery Risk Development in Young Adults study (1985–1986 to 2010–2011)

	N	Prevalent Y25 T2DM N events/total N=136/511[a] OR (95% CI)			N	Incident Y25 T2DM N events/total N=144/508[b] OR (95% CI)		
		Model 1	Model 2	Model 3		Model 1	Model 2	Model 3
HOMA-IR trajectory[c]								
Low-stable	3/72		Reference		3/72		Reference	
Moderate-increasing	42/290	3.1 (0.91,10.3)	1.7 (0.48,6.2)	1.2 (0.32,4.4)	47/289	3.6* (1.1,12.0)	2.2 (0.62,8.1)	1.7 (0.46,6.2)
High-increasing	91/149	31.6‡ (9.3,107.3)	8.0‡ (2.0,31.9)	4.6* (1.1,18.9)	94/147	36.3‡ (10.7,123.4)	10.5‡ (2.6,42.8)	7.2§ (1.8,29.2)
HOMA-β trajectory[d]								
Low-decreasing	27/48	9.4‡ (4.1, 21.5)	14.1‡ (3.9, 50.9)	11.8‡ (4.3, 32.4)	27/48	7.2‡ (3.2, 16.2)	10.3‡ (2.7, 39.3)	9.1‡ (3.4, 24.3)
Moderate-decreasing	58/282	1.1 (0.70, 1.8)	1.6 (0.79, 3.2)	1.5 (0.92, 2.9)	63/282	1.0 (0.64, 1.6)	1.3 (0.62, 2.6)	1.7 (0.94, 2.9)
High-decreasing	46/176		Reference		52/176		Reference	

NAFLD = liver attenuation < 51 HU after exclusion for secondary cause of liver fat

[a] total N=506 for analyses with HOMA-β after exclusion of participants with exogenous insulin use

[b] total N= 506 for analyses with HOMA-β after exclusion of participants with exogenous insulin use

‡ $p < 0.001$ compared with the referent group

§ $p < 0.01$ compared with the referent group

* $p < 0.05$ compared to Low group

** number of participants with diabetes over the total number of NAFLD participants in each trajectory group

Results presented as Odds Ratio (95% Confidence Interval)

Model 1: Age, sex, race, field center, educational attainment

Model 2: Model 1 + pack-years smoking exposure, cumulative alcohol use (drinks/day), physical activity level (exercise units-year), cumulative systolic blood pressure (mm Hg-years), number of years with blood pressure or lipid-lowering medications, cumulative TC/HDL ratio, diabetes medications (at each exam year), %change BMI and baseline HOMA-IR[c] HOMA-β[d]

Model 3: Model 1 + pack-years smoking exposure, cumulative alcohol use (drinks/day), physical activity level (exercise units-year), cumulative systolic blood pressure (mm Hg-years), number of years with blood pressure or lipid-lowering medications, cumulative TC/HDL ratio, diabetes medications (at each exam year), %change BMI and Y25 HOMA-IR[c] HOMA-β[d]

Abbreviations: T2DM, type 2 diabetes mellitus; NAFLD, nonalcoholic fatty liver disease; Y25, year 25 follow-up exam; OR, odds ratio; CI, confidence interval; TC, total cholesterol; HDL, high density lipoprotein; HOMA, homeostatic model assessment; IR, insulin resistance; BMI, body mass index

TABLE 5.

Relationship between HOMA-β and HOMA-IR Trajectory Group Clusters in Relation to Risk of Y25 NAFLD[a] and Prevalent or Incident Type 2 Diabetes Among NAFLD Participants

		OR (95% CI)	
		Base model	Multivariable model
Prevalent NAFLD[a]	N[*]		
Referent Cluster[b]	209/685	1.00	1.00
High IR-High β Cluster[c]	215/445	3.44 (2.59, 4.6) [‡]	2.48 (1.81, 3.41) [‡]
Low IR-Low β Cluster[d]	82/959	0.18 (0.13, 0.24) [‡]	0.34 (0.25, 0.48) [‡]
Prevalent T2DM in NAFLD	N[**]		
Referent Cluster[b]	42/209	1.00	1.00
High IR-High β Cluster[c]	78/215	1.75 (1.09, 2.81) [§]	1.53 (0.66, 3.55)
Low IR-Low β Cluster[d]	11/82	0.79 (0.37, 1.68)	0.98 (0.55, 1.73)
Incident T2DM in NAFLD	N[**]		
Referent Cluster[b]	46/209	1.00	1.00
High IR-High β Cluster[c]	85/215	1.79 (1.12, 2.85) [§]	1.01 (0.58, 1.76)
Low IR-Low β Cluster[d]	11/82	0.72 (0.34, 1.53)	0.88 (0.44, 1.76)

[a]NAFLD = liver attenuation < 51 HU after exclusion for secondary cause of liver fat

[*] number of participants with NAFLD over the total number of NAFLD-eligible participants (n=2089) assessed at the year 25 follow-up exam in each trajectory group pair

[**] number of participants with T2DM over the total number of NAFLD participants (n=506) at the year 25 follow-up exam in each trajectory group pair

[b]Referent Cluster=high HOMA-IR and low HOMA-β, moderate HOMA-IR and moderate HOMA-β or low HOMA-IR and high HOMA-β

[c]High IR-High β cluster=high HOMA-IR and high HOMA-β, high HOMA-IR and moderate HOMA-β or moderate HOMA-IR and high HOMA-β

[d]Low IR-Low β cluster=low HOMA IR and low HOMA-β, low HOMA-IR and moderate HOMA-β, or moderate HOMA-IR and low HOMA-β

Base model: Age, sex, race, field center, educational attainment

Multivariable Model: Base model + pack-years smoking exposure, cumulative alcohol use (drinks/day), physical activity level (exercise units-year), cumulative systolic blood pressure (mm Hg-years), number of years with blood pressure or lipid-lowering medications, cumulative TC/HDL ratio, diabetes medications (at each exam year), %change BMI, Y25 HOMA-IR and Y25 HOMA-β

[‡]p < 0.001 compared with the referent group

[§]p <0.01 compared with the referent group

Abbreviations: T2DM, type 2 diabetes mellitus; NAFLD, nonalcoholic fatty liver disease; Y25, year 25 follow-up exam; OR, odds ratio; CI, confidence interval; TC, total cholesterol; HDL, high density lipoprotein; HOMA, homeostatic model assessment; IR, insulin resistance; BMI, body mass index