Height predict incident non-alcoholic fatty liver disease in a general adult population, independent of body mass index and metabolic syndrome

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Abstract

Background Early-life hormonal and nutritional factors can greatly influence the risk of non-alcoholic fatty liver disease (NAFLD). Adult height is a simple marker for these factors. We aimed to evaluate adult height as a predictor of NAFLD.

Methods We performed a prospective cohort study of 35, 994 participants recruited from 2010 to 2016 in Tianjin, China. NAFLD was diagnosed by ultrasound. Adjusted Cox proportional hazards regression models were conducted in 2019 to assess the gender-specific association between the quintiles of height and the incidence of NAFLD.

Results Participants were followed up for 5.5 years with a mean follow-up of 2.6 years. During the follow-up period, 6,245 of 35,994 participants developed NAFLD. The multiple-adjusted hazard ratios (95% confidence interval) of NAFLD for increasing quintiles of height were 1.00 (reference), 0.90 (0.81, 0.99), 0.97 (0.87, 1.07), 0.86 (0.78, 0.96), and 0.84 (0.75, 0.94) (P for trend < 0.01) in males and 1.00 (reference), 0.97 (0.86, 1.09), 0.98 (0.86, 1.11), 0.93 (0.81, 1.06), and 0.84 (0.73, 0.96) (P for trend = 0.02) in females, respectively.

Conclusions The study is the first to demonstrate adult height is a new, simple and inexpensive marker for ultra-early prediction of NAFLD.

Background

Non-alcoholic fatty liver disease (NAFLD) is defined as the presence of ≥ 5% of hepatic steatosis, in the absence of secondary causes of hepatic fat accumulation, such as chronic use of medications or significant alcohol intake(1). It is the most common chronic liver disease all over the world and its prevalence is constantly increasing(2). About 25% of world population was estimated to have NAFLD(3). Unhealthy lifestyles and dietary habits in addition to genetic predisposition have pose increased the prevalence of NAFLD in the Asia Pacific region(4).

Early life experiences, including nutrition and hormone, play an important role in influencing later susceptibility to chronic diseases by epigenetic mechanisms(5, 6). Accumulating evidence suggests that hormonal and nutritional experiences in early life may predispose high incidence of type 2 diabetes mellitus (T2DM) and insulin resistance in later life(7). Furthermore, there is sufficient evidence to demonstrate that T2DM, insulin resistance and NAFLD share many important metabolic risk factors and common pathogenetic mechanism(8). Several studies preliminarily suggested that growth hormone (GH) levels and insulin-like growth factor–1 (IGF–1) levels are negatively associated with NAFLD in adults(9, 10), and GH replacement therapy in GH-deficient patients can alleviate NAFLD and improve liver fibrosis(11). Moreover, suboptimal early life nutrition may increase the susceptibility, age on set, and severity of NAFLD(12).

Adult height is defined as the tallest height after height velocity had decreased to 1 cm or less over 6 months and relatively fixed as compared with child or youth height(13). Adult height greatly reflects differences in nutrition and hormone levels in early life(14, 15). It is well recognized that GH and IGF–1 are strongly and positively associated with growth in height, and GH therapy in children with short stature caused by several diseases augments adult height(16). Since early hormonal and nutritional experiences are major risk factors of final height, it is assumed that adult height may be a potentially useful predictor of incident NAFLD. To date, few studies have focused on the association between adult height and NAFLD.

In the present study, we designed a prospective cohort study to determine whether adult height was associated with the risk of NAFLD in the general Chinese adult population.

Methods

Study design and participants

Details of the Tianjin Chronic Low-Grade Systemic Inflammation and Health (TCLSIH) Cohort Study have been described elsewhere(17). Briefly, participants were randomly recruited between January 2010 and December 2016 from the general population in Tianjin, China. All participants received annual health examinations (including liver ultrasound examination, anthropometric measurements, and blood tests) and completed a structured questionnaire survey. Written informed consent was obtained from all participants. The protocol of this study was approved by the Institutional Review Board of Tianjin Medical University.

From 2010 to 2016, a total of 90,536 participants received health examinations. We excluded 170 participants who had missing data on alanine aminotransferase, 4,013 participants had excessive alcohol intake (>140 g/week in males and >70 g/week in females), and 28,935 participants who had NAFLD at baseline. Moreover, we excluded 767 participants with other liver diseases (including autoimmune liver diseases, chronic hepatitis B or C, cirrhotic or operation on liver), and those with a history of cardiovascular disease (n = 5,475) or cancer (n = 1,039), and those aged < 25 years (n = 3,996). Furthermore, participants were also excluded if they were recruited in 2016 (n = 4,894) or were lost in following up (n = 5,253). Finally, a total of 35,994 participants were available for analysis (follow-up rate: 87%; followed up for 1–5.5 y; mean duration of follow-up (standard deviation): 2.6 (1.6)).

Assessment of height

Height was measured to the nearest 0.1 cm using a standard protocol. In order to investigate how height level is associated with NAFLD, we divided males and female participants into 5 categories (quintiles) according to height level (cm, range) as follows: (1) Level 1 (148.5–167.7), Level 2 (167.8–171.2), Level 3 (171.3–174.3), Level 4 (174.4–178.1), and Level 5 (178.2–204.1) in males; (2) Level 1 (138.0–156.2),

Level 2 (156.3–159.5), Level 3 (159.6–162.1), Level 4 (162.2–165.4), and Level 5 (165.5–184.6) in females.

Diagnosis of NAFLD

Real-time ultrasonography performed by trained and certified technicians was used to diagnose NAFLD. Participants were considered to have NAFLD if (1) they had a self-reported alcohol intake of < 140 g/week and < 70 g/week for males and females, respectively; (2) and at least two of the following abnormal findings of abdominal ultrasound images: diffusely increased liver near field ultrasound echo; increased liver echotexture, compared to the kidneys; vascular blurring and the gradual attenuation of far field ultrasound echo(18).

Assessment of other variables

Waist circumference (WC) was measured using a nonelastic plastic anthropometric tape at the level of umbilicus with subjects standing and breathing normally.Participants rest for at least 5 minutes in a seated position prior to blood pressure measurements. Blood pressure was measured twice from participants' upper right arms using the TM–2655 device (A&D Company Ltd, Tokyo, Japan), and the blood pressure value was recorded in average. Fasting blood samples for the analysis of biochemical values were collected in siliconized vacuum plastic tubes. Fasting blood glucose, total cholesterol, triglycerides, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol were measured using appropriate kits on a Cobas 8000 analyzer (Roche, Mannheim, Germany). We defined metabolic syndrome (MetS) according to the American Heart Association scientific statements of 2009(19). Alanine aminotransferase was measured by IFCC method.

Body weight was measured by training nurses, with participants without heavy clothes. Body mass index (BMI) was calculated as weight (kg) divided by squared height (m^2). Information on family history of cardiovascular disease, family history of hypertension, family history of hyperlipidemia, and history of diabetes, was assessed at baseline using a structured questionnaire.

Statistical analysis

Baseline characteristics of participants were compared using analysis of variance for continuous variables and logistic regression analysis for categorical variables. Continuous variables were shown as geometric mean (95% confidence interval (CI)), and categorical variables were presented as percentage.

Because the interaction between sex and height was statistically significant (P <0.0001), we analyzed the association between height and NAFLD stratified by sex. We fitted four Cox proportional hazards regression models to evaluate the association between baseline height and incident NAFLD. The initial model was unadjusted model (crude model). Model 2 was adjusted for age and WC. In model 3, we

additionally adjusted for smoking status, alcohol drinking status, Mets, family history of cardiovascular disease, family history of family history of hypertension, family history of hyperlipidemia, and family history of diabetes. In model 4, we further adjusted for baseline BMI. All *P* values for linear trends were calculated using the median value for each quintile.

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc.). Two-tailed $P<0.05$ was considered as statistically significant.

Results

In this study, 41.3% of participants were males and 58.7% were females. Mean age (standard deviation) years was 42.2 (12.9) in males and 39.2 (11.3) in females, respectively. During the 5.5 years follow-up period between 2010 and 2016, 6,245 of 35,994 individuals (17.4%) developed NAFLD. The incidence of NAFLD was 65.8 per 1,000 person-years. In the 5 height quintiles, the respective rates of NAFLD were 110.1, 104.4, 113.2, 108.7 and 110.2 per 1000 person-years in males and 48.4, 43.1, 40.7, 35.9 and 31.7 per 1,000 person-years in females.

Characteristics of participants relative to NAFLD status for follow-up analysis are presented in *Table 1.* The mean age (95% CI) in non-NAFLD and NAFLD participants was 38.3 (38.2, 38.4) years and 41.4 (41.1, 41.7) years, respectively. Compared with participants without NAFLD, participants with NAFLD had older age, lower high-density lipoprotein cholesterol, but higher BMI, WC, total cholesterol, low-density lipoprotein cholesterol, triglycerides, fasting blood glucose, systolic blood pressure, diastolic blood pressure, and alanine aminotransferase (all $P< 0.0001$). Participants with NAFLD tended to be male, smoker, ex-smoker, everyday drinker, sometimes drinker, while those without NAFLD tended to be non-smoker and non-drinker (all $P< 0.0001$). In addition, a higher proportion of participants with NAFLD had MetS and a family history of cardiovascular disease, hypertension and diabetes (all $P< 0.0001$).

Table 2 and *Table 3* show the crude and adjusted associations between quintiles of height and NAFLD in male and female participants, respectively. In the third multivariate model which didn't adjust for BMI, the adjusted HRs (95% CI) for NAFLD across height quintiles were 1.00 (reference), 0.86 (0.78, 0.95), 0.90 (0.81, 0.99), 0.77 (0.70, 0.85) and 0.71 (0.64, 0.78) in males and 1.00 (reference), 0.92 (0.82, 1.04), 0.85 (0.75, 0.97), 0.78 (0.68, 0.89) and 0.65 (0.57, 0.74) in females (both *P* for trend < 0.0001). Similarly, in the final multivariate model which adjusted BMI, the adjusted HRs (95% CI) for NAFLD across height quintiles were 1.00 (reference), 0.90 (0.81, 0.99), 0.97 (0.87, 1.07), 0.86 (0.78, 0.96) and 0.84 (0.75, 0.94) in males (*P* for trend < 0.01) and 1.00 (reference), 0.97 (0.86, 1.09), 0.98 (0.86, 1.11), 0.93 (0.81, 1.06) and 0.84 (0.73, 0.96) in females (*P* for trend = 0.02).

Discussion

In this large-scale prospective cohort study, we found that higher level of adult height was inversely associated with the risk of NAFLD among males and females in China. The inverse association remained

even after controlling for potential confounding factors. To our knowledge, this is the first study to investigate the association between adult height and NAFLD.

We adjusted for multiple potentially confounding factors in our analysis. This study indicated that numerous factors (such as age, BMI, WC, smoking status, metabolic syndrome and family history of some diseases) correlated positively with NAFLD. We used crude model (model 1) first and results showed negative association between height and NAFLD in both males and females. It is well-recognized that NAFLD and height are related to age and WC(20, 21), so we adjusted for these two variables in model 2. Adjustment for age and WC made the associations in males more obvious compared with model 1; however, in females, this adjustment didn't significantly influence the associations in model 1, leading us to conclude that age and WC are major confounding factors in males but not in females. Since NAFLD was associated with WC, smoking status, drinking status, metabolic syndrome, family history of cardiovascular disease, hypertension, hyperlipidemia and diabetes(22, 23), we subsequently adjusted for these variables in model 3. After adjustments for these factors, the associations didn't change significantly in both males and females, implying these factors may not confound the association between height and NAFLD. In model 4, the present study adjusted BMI and variables in model 3 to confirm the role of BMI in association between height and NAFLD. This adjustment made the association less obvious in both males and females, suggesting that BMI play an important role in association between height and NAFLD.

To date, no studies have investigated the association between height and NAFLD. Several studies investigated the association between height and T2DM. Reports about the risk of T2DM and height have produced conflicting results(24, 25). A meta-analysis showed negative association between height and risk of T2DM in woman only(26), whereas a cohort study of Finnish men showed adult height is associated with decreased risk of T2DM (1). Since T2DM and NAFLD both result from metabolic dysregulation, these results are, to some extent, consistent with our novel findings that shorter people were associated with higher incidence of NAFLD. Compared to previous cohort studies using Chinese adults with overall incidence of NAFLD ranging from 15.2% to 24.8%(27),the overall incidence of NAFLD in our study is 17.4%, consistent with previous studies.

The mechanisms of association between adult height and NAFLD may involve epigenetic changes induced by early life adversity. Interacting with epigenetic mechanisms, hormonal and nutritional conditions in early life influence both attained height and later susceptibility to NAFLD. GH and IGF–1 play essential roles in linear growth as well as in the liver metabolism(28). Therefore, epigenetic modification of IGF–1 gene might play a critical role in the development of NAFLD and the growth in height. NAFLD-specific expression and methylation differences between healthy controls and morbidly obese patients with all stages of NAFLD were seen for the IGF–1 gene, one of the key drivers of the liver's phenotype(29). Furthermore, the methylation of the IGF–1 P2 promoter showed a strong negative association with serum IGF–1 levels and height as a child(30). In addition, data from animal models have indicated that nutritional perturbation of epigenetic regulation is a likely link between prenatal and early postnatal nutrition and health status in later life(31). A study in mice showed that exposure to

prenatal and post-weaning western-style diet predisposed male mouse offspring to the development of NAFLD in adulthood and induced alterations in DNA methylation in key metabolic genes(32). On the other hand, a recent study has demonstrated that height plays an important partial role in determining several aspects of a person's socioeconomic status(33). Since lower socioeconomic status is closely associated with increased levels of health impairment(34), socioeconomic status maybe an explanation for the association between height and NAFLD. Further research is warranted to validate the hypotheses.

The present study has several limitations. Firstly, NAFLD was diagnosed by abdominal ultrasound rather than liver biopsy, which is the gold standard for diagnosis of NAFLD. However, abdominal ultrasound is not invasive and widely used in large-scale population-based studies. Moreover, this noninvasive method has a sensitivity of 89% and a specificity of 93%(35). Second, although we adjusted for a considerable number of potential confounding factors in the present study, residual confounding cannot be excluded.

Conclusions

Adult height was negatively associated with incident NAFLD in males and female, independent of BMI and MetS. The present results indicate that adult height may be a useful predictor for NAFLD to identify high-risk populations and prevent NAFLD at an early age. Furthermore, this study provides clues to the mechanism of the link between early life experiences and NAFLD. Future studies are needed to elucidate the mechanism of association between adult height and the risk of NAFLD.

List Of Abbreviations

NAFLDNon-alcoholic fatty liver disease

T2DMType 2 diabetes mellitus

GHGrowth hormone

IGF–1Insulin-like growth factor–1

WCWaist circumference

TCLSIHTianjin Chronic Low-Grade Systemic Inflammation and Health

MetS Metabolic syndrome

BMIBody mass index

CIConfidence interval

HRHazard ratio

Declarations

Ethics approval and consent to participate

The protocol of this study was approved by the Institutional Review Board of the Tianjin Medical University and each participant gave written informed consent prior to participation in the study.

Consent for publication

Not applicable

Availability of data and materials

The datasets generated and analysed during the current study are not publicly available due [public availability would compromise participant privacy] but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Conception and design of the study: S.K., X.W., and K.N. Data collection and analysis: S.K., X.W., Y.G., Y.H., Q.Z., L.L., G.M., H.W., S.S., X.W., M.Z., Q.J., G.W., K.S., and K.N. Interpretation of data: S.K., X.W., and K.N. Drafting the manuscript: S.K., X.W., and K.N. All authors read and approved the final manuscript.

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Tables

Table 1. Baseline characteristics of participants by NAFLD status [a].

	NAFLD		*P* value [b]
	No	Yes	
No. of subjects	29,749	6,245	
Age (y) [c]	38.3 (38.2, 38.4)	41.4 (41.1, 41.7)	< 0.0001
Sex (males, %)	36.9	62.1	< 0.0001
BMI (kg/m^2)	22.2 (22.2, 22.3)	24.9 (24.8, 25.0)	< 0.0001
Waist circumference (cm)	75.4 (75.4, 75.5)	83.4 (83.1, 83.6)	< 0.0001
Metabolic syndromes (yes, %)	8.3	26.6	< 0.0001
TC	4.62 (4.62, 4.63)	4.83 (4.81, 4.86)	< 0.0001
LDL	2.65 (2.65, 2.66)	2.90 (2.88, 2.92)	< 0.0001
TG	0.87 (0.87, 0.88)	1.24 (1.22, 1.25)	< 0.0001
HDL	1.48 (1.48, 1.48)	1.28 (1.27, 1.28)	< 0.0001
FBG	4.78 (4.78, 4.78)	4.89 (4.88, 4.91)	< 0.0001
SBP	114.6 (114.6, 114.8)	120.4 (120.1, 120.8)	< 0.0001
DBP	72.1 (72.1, 72.2)	76.1 (75.9, 76.4)	< 0.0001
ALT (U/L)	15.2 (15.2, 15.3)	20.1 (19.8, 20.3)	< 0.0001
Smoking status (%)			–
Smoker	14.3	26.6	< 0.0001
Ex-smoker	2.0	4.3	< 0.0001
Non-smoker	83.7	69.2	< 0.0001
Drinker status (%)			
Everyday	1.6	2.4	< 0.0001
Sometime	37.3	47.4	< 0.0001
Ex-drinker	4.2	4.5	0.27
Non-drinker	56.9	45.7	< 0.0001
Family history of diseases (%)			

CVD	28.1	34.8	< 0.0001
Hypertension	48.0	55.3	< 0.0001
Hyperlipidemia	0.5	0.6	0.055
Diabetes	20.7	26.0	< 0.0001

[a] NAFLD, non-alcoholic fatty liver disease; BMI, body mass index; MS, metabolic syndromes; TC, total cholesterol; LDL, low-density lipoprotein cholesterol; TG, triglycerides; HDL, high-density lipoprotein cholesterol; FBG, fasting blood glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; ALT, alanine aminotransferase; CVD, cardiovascular disease.

[b] Analysis of variance or logistic regression analysis.

[c] Geometric mean (95% confidence interval) (all such values).

Table 2. Cohort analysis: adjusted associations of height quintiles with NAFLD [a] in males.

Cox proportional-hazard regression models	Quintiles of body height (cm, range)					*p* for trend [b]
	Level 1 (148.5-167.7) (n = 3021)	Level 2 (167.8-171.2) (n = 2957)	Level 3 (171.3-174.3) (n = 2852)	Level 4 (174.4-178.1) (n = 3049)	Level 5 (178.2-204.1) (n = 2978)	
Person-years of follow-up	7,018	7,235	6,778	7,315	7,179	
No. of NAFLD	773	755	767	795	791	
Model 1 [d]	1.00	0.94 (0.85, 1.04) [c]	1.02 (0.92, 1.13)	0.97 (0.88, 1.07)	0.99 (0.90, 1.10)	0.75
Model 2 [e]	1.00	0.87 (0.78, 0.96)	0.90 (0.82, 1.00)	0.77 (0.70, 0.86)	0.71 (0.64, 0.79)	<0.0001
Model 3 [f]	1.00	0.86 (0.78, 0.95)	0.90 (0.81, 0.99)	0.77 (0.70, 0.85)	0.71 (0.64, 0.78)	<0.0001
Model 4 [g]	1.00	0.90 (0.81, 0.99)	0.97 (0.87, 1.07)	0.86 (0.78, 0.96)	0.84 (0.75, 0.94)	<0.01

[a] NAFLD, non-alcoholic fatty liver disease.

[b] Analysis by Cox proportional hazards model.

[c] Adjusted hazard ratios (95% confidence interval) (all such values).

[d] Crude

[e] Adjusted for age and waist circumference.

[f] Adjusted for age, waist circumference, smoking status, drinking status, metabolic syndrome, and family history of cardiovascular disease, hypertension, hyperlipidemia, and diabetes.

[g] Adjusted for age, body mass index, waist circumference, smoking status, drinking status, metabolic syndrome, and family history of cardiovascular disease, hypertension, hyperlipidemia, and diabetes.

Table 3. Cohort analysis: adjusted associations of height quintiles with NAFLD [a] in females.

Cox proportional-hazard regression models	Quintiles of body height (cm, range)					*p* for trend [b]
	Level 1 (138.0-156.2) (n = 4223)	Level 2 (156.3-159.5) (n = 4442)	Level 3 (159.6-162.1) (n = 3947)	Level 4 (162.2-165.4) (n = 4145)	Level 5 (165.5-184.6) (n = 4370)	
Person-years of follow-up	11,318	12,593	11,153	11,576	12,736	
No. of NAFLD	548	543	454	416	404	
Model 1 [d]	1.00	0.88 (0.78, 0.99) [c]	0.83 (0.73, 0.94)	0.73 (0.64, 0.83)	0.64 (0.57, 0.73)	<0.0001
Model 2 [e]	1.00	0.91 (0.81, 1.02)	0.85 (0.75, 0.96)	0.75 (0.66, 0.85)	0.62 (0.55, 0.71)	<0.0001
Model 3 [f]	1.00	0.92 (0.82, 1.04)	0.85 (0.75, 0.97)	0.78 (0.68, 0.89)	0.65 (0.57, 0.74)	<0.0001
Model 4 [g]	1.00	0.97 (0.86, 1.09)	0.98 (0.86, 1.11)	0.93 (0.81, 1.06)	0.84 (0.73, 0.96)	0.02

[a] NAFLD, non-alcoholic fatty liver disease.

[b] Analysis by Cox proportional hazards model.

[c] Adjusted hazard ratios (95% confidence interval) (all such values).

[d] Crude

[e] Adjusted for age and waist circumference.

[f] Adjusted for age, waist circumference, smoking status, drinking status, metabolic syndrome, and family history of cardiovascular disease, hypertension, hyperlipidemia, and diabetes.

[g] Adjusted for age, body mass index, waist circumference, smoking status, drinking status, metabolic syndrome, and family history of cardiovascular disease, hypertension, hyperlipidemia, and diabetes.