Association of age at first birth and risk of non-alcoholic fatty liver disease in women: evidence from the NHANES

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Abstract

Background

Numerous studies have suggested that age at first birth (AFB) is inversely associated with metabolic diseases, but positively associated with liver cancer in women. Non-alcoholic fatty liver disease (NAFLD) is a canonical example of metabolic dysfunction and inflammation-based liver disease, while the association between AFB and risk of NAFLD remains unclear. We aimed to investigate the association between AFB and the odds of NAFLD in women.

Methods

Women older than 20 years at the time of the survey were analyzed using National Health and Nutrition Examination Survey (NHANES) data from 1999 to 2018 in the US. AFB was obtained with self-administered questionnaires. NAFLD was diagnosed as fatty liver index ≥ 60. Odds ratios (ORs) and 95% confidence intervals (CI) were estimated using logistic regression models.

Results

Of the 12,188 women included in this study, 5,670 (46.5%) had NAFLD. Compared to individuals with AFB of 30–32 years old (reference group), the fully adjusted ORs and 95% CI in women with AFB < 18 years, 18–20 years, 21–23 years, and 24–26 years were 1.59 (95% CI: 1.18, 2.13), 1.58 (95% CI: 1.20, 2.08), 1.38 (95% CI: 1.04, 1.83), and 1.33 (95% CI: 1.01–1.77), respectively. Yet there was no significant difference between AFB of 27–29 years, 33–35 years, or > 35 years compared with the reference group.

Conclusions

Women with younger AFB have higher odds of NAFLD in later life. Policymakers should consider focusing on those with earlier AFB for screening and prevention of NAFLD.

Background

Globally, the prevalence of non-alcoholic fatty liver disease (NAFLD) is reported to range from 25–45%. [1] The prevalence is increasing at an alarming pace as the rates of obesity continue to rise. NAFLD is a syndrome characterized by excessive triglyceride (TG) accumulation within hepatocytes due to a cause other than alcohol consumption, [2] and it has become the most common chronic liver disease. Furthermore, metabolic comorbidities are common in individuals with NAFLD and create a huge economic burden. The large number of patients with NAFLD has made screening a major challenge and, therefore, knowledge of risk factors for NAFLD would contribute to the identification of high-risk populations and benefit health policymaking.

Epidemiological evidence shows that NAFLD prevalence in women increases significantly after menopause. [3] Women's health and wellbeing are profoundly affected by estrogen levels, which can vary dramatically with age and decrease rapidly after menopause. [4] In addition to the putative protective effect of estrogen, other reproductive factors may also play a key role in the development of NAFLD.

Pregnancy is a fundamental factor affecting women's future health status. [5] During pregnancy, to support fetal development, the maternal body undergoes changes in hormones, immunity, and metabolism. [6] There are a number of studies showing conflicting results on the association between age at first birth (AFB) and women's health in later life. Some studies have suggested that women with an early AFB are at higher risk for later-life metabolic diseases and mortality, [7–11] while others found that an early AFB is associated with a decreased liver cancer risk. [12] NAFLD as a canonical example of metabolic dysfunction and inflammation-based liver disease is also an important risk factor for liver cancer. However, the association between AFB and the long-term consequences of NAFLD remains unclear. Thus, the present study aims to investigate the relationship between AFB and the risk of NAFLD using the National Health and Nutrition Examination Survey (NHANES) data from 1999 to 2018 in the US.

Methods

Study population

The NHANES is a complex, stratified, multistage, probability-cluster program designed to assess Americans' health and nutritional status. Females older than 20 years at the time of the survey from NHANES 1999–2018, a total of 10 cycles, were included in this analysis.

Of the 26,705 participants who attended the reproductive health interview, 14,171 were excluded due to: (1) missing information to define NAFLD (n = 3,106); (2) being pregnant or lactating at the time of the survey (n = 1,580); (3) self-reported previous malignancy (n = 2,146); (4) without live birth or

missing information of AFB (n = 7,339); (5) having elevated alcohol intake (> 14 drinks/week, n = 203); (6) positive hepatitis B surface antigen or hepatitis C RNA (n = 143). Finally, this analysis included 12,188 subjects (**Figure 1**).

The surveys were approved by the National Center for Health Statistics Ethics Review Board. All participants signed informed consent prior to their participation.

Definition of outcomes

The main outcome of the present study was NAFLD, which was defined as a fatty liver index (FLI) ≥ 60. We followed previous practice and constructed FLI using TG, body mass index (BMI), gamma-glutamyltransferase (GGT), and waist circumference (WC). [13] Population-based studies have verified the reliability of FLI ≥ 60 for predicting the presence of NAFLD, which shows high sensitivity and specificity. [14–16] Definitions of the secondary outcomes, i.e., metabolic-associated fatty liver disease (MAFLD), FLI (< 30, 30 to 59.9, or ≥ 60), NAFLD fibrosis score (NFS, < −1.455, −1.455 to 0.676, or > 0.676), and NAFLD-related comorbidities, are detailed in the supplementary file.

Reproductive factors

Reproductive factors were obtained from self-administered questionnaires. Participants recalled their AFB, age at menarche, and age at menopause at the time of the survey through the reproductive health questionnaires. Investigators also gathered their parity, personal medication (including birth control and hormone pills), and gynecologic surgical (e.g., oophorectomy or hysterectomy) history at the same time. Fertile lifespan was calculated by age at menopause minus age at menarche. Note that in this study, AFB refers to the first live birth; pregnancy loss (prior stillbirth, miscarriage, or ectopic pregnancy) and or stillbirth were not included.

Other covariates

Demographic information of each participant was collected with a questionnaire at the time of enrollment. Race was dichotomized as white or non-white, the latter including Mexican American, non-white Hispanic, Asian, and other races. Education level was categorized into less than 12th grade, high school or equivalent, and college graduate or above. Poverty–income ratio (PIR), a ratio of family income to the poverty threshold, reflects the annual family income level. Well-trained health technologists measured weight and height according to the anthropometry procedure manual. BMI was calculated as weight (kg) divided by height squared (m^2). Lifestyle factors including smoking status, alcohol intake, and leisure activity levels were assessed by separate questionnaires, respectively. In NHANES, diet was assessed using 24-hour dietary recalls, which collected information on everything the participants consumed in the preceding 24 hours. The healthy eating index (HEI) was calculated based on these data. One of our previous works described this assay in more detail, [17] with minor modifications.

Statistical analysis

Analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina), accounting for the Mobile Examination Center (MEC) exam sampling weights and the complex survey design of NHANES; *P* values of less than 0.05 were considered to be statistically significant. The missing variables were imputed as the most common value for categorical variables, and median imputation was used for missing continuous covariates. The preliminary analyses were descriptive statistics; continuous variables were shown as survey-weighted means with SE, whereas categorical variables were expressed as cases (n) and percentages (%).

For primary analyses, we performed multivariate logistic regression models to analyze the association between AFB and NAFLD. The lowest level of risk, i.e., AFB of 30–32 years, was used as the reference group. Odds ratio (OR) with 95% confidence interval (CI) was used to determine the degree of association. We did not adjust for any covariate in Model 0; and adjusted for age (years), race (Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black, other race), education level (less than 12th grade, high school or equivalent, college graduate or above), and family PIR in Model 1; Model 1 plus smoking status (never, ever, current), alcohol intake (drinks/week), leisure activity (MET-min/day), total energy intake (kcal/day), and HEI-2015 constituted Model 2; we additionally adjusted for parity (times), menopause status (yes/no), use of female hormones (never/ever), oral contraceptive use (never/ever), hysterectomy (yes/no), and both ovaries removed (yes/no) in Model 3, which was the fully adjusted model. Within the fully adjusted model, a restricted cubic spline in a random-effects dose–response model was used to illustrate the nonlinear association between AFB and NAFLD. The spline curve was drawn with Stata software version 15.1.

We further carried out stratified analysis according to age at the survey (< 45 or ≥ 45 years), menopause status (yes or no), and race (white or non-white) to explore potential sources of heterogeneity. Then six sets of sensitivity analyses were performed to test the robustness of the findings by excluding individuals who had undergone gynecologic surgery (had hysterectomy or ovaries removed), ever used female hormones, unnormal age at menarche (< 9 or > 18 years) or menopause (< 40 or > 55 years or premenopausal), or with parity more than 5, respectively.

Results

Of the 12,188 women included in this study, 5,670 (46.5%) had NAFLD. The baseline characteristics of the participants meeting inclusion criteria by categories of AFB are summarized in Table 1. Participants were grouped into AFB < 18 years, 18–20 years, 21–23 years, 24–26 years, 27–29 years, 30–32 years, 33–35 years, and > 35 years groups. With an increase of AFB, family PIR, HEI-2015 levels, and proportion with higher education

increased progressively. Women who gave birth first between 30 and 32 years of age had the lowest level of BMI, WC, ALT, AST, FLI, and NFS, and were less likely to be current smokers, postmenopausal, or to have ever used female hormones, and also the lowest proportion of having had hysterectomy and both ovaries removed; meanwhile, they had the highest leisure activity, age at menarche, age at menopause, and fertile lifespan. On the other hand, compared to non-NAFLD participants, individuals with NAFLD were older, with higher BMI, more parity, lower family PIR level, lower leisure activity level, lower dietary quality (HEI-2015), younger age at menarche, younger age at menopause, and younger AFB (**Supplemental Table 1**). Also, individuals with NAFLD were more likely to be non-white, have lower education levels, have postmenopausal status, and have had a hysterectomy and both ovaries removed.

Table 1
Basic characteristics of participants according to age at first birth.

		Age at first birth (years)								
	Total	< 18	18–20	21–23	24–26	27–29	30–32	33–35	> 35	*P*
Case/n	5670/12188	1047/1934	1869/3656	1320/2862	725/1731	406/1071	167/543	91/261	45/130	
Age (year)	51.71 ± 0.17	47.86 ± 0.39	51.77 ± 0.33	53.74 ± 0.34	52.47 ± 0.38	50.74 ± 0.44	50.66 ± 0.64	51.97 ± 0.96	52.33 ± 1.28	< 0.001
BMI (kg/m^2)	29.37 ± 0.10	30.86 ± 0.22	30.23 ± 0.17	29.41 ± 0.21	28.89 ± 0.22	27.95 ± 0.26	26.96 ± 0.38	27.98 ± 0.56	27.52 ± 0.70	< 0.001
Waist (cm)	97.13 ± 0.23	99.92 ± 0.51	99.24 ± 0.41	97.24 ± 0.43	96.10 ± 0.50	93.66 ± 0.60	92.01 ± 0.89	94.47 ± 1.28	93.06 ± 1.84	< 0.001
Family PIR	2.85 ± 0.03	1.99 ± 0.05	2.43 ± 0.04	2.90 ± 0.04	3.21 ± 0.05	3.48 ± 0.06	3.65 ± 0.07	3.74 ± 0.12	3.79 ± 0.13	< 0.001
Alcohol intake (drinks/week)	1.27 ± 0.04	1.03 ± 0.08	1.11 ± 0.06	1.10 ± 0.06	1.35 ± 0.09	1.72 ± 0.13	1.99 ± 0.21	1.92 ± 0.24	1.15 ± 0.28	< 0.001
Leisure activity (MET-min/day)	96.03 ± 2.59	75.81 ± 5.67	83.27 ± 4.16	91.20 ± 4.91	112.73 ± 6.77	111.17 ± 7.77	136.01 ± 8.72	119.39 ± 11.51	93.58 ± 15.28	< 0.001
HEI-2015	51.14 ± 0.23	47.63 ± 0.37	49.29 ± 0.30	51.09 ± 0.36	53.07 ± 0.46	53.13 ± 0.68	54.96 ± 0.70	56.48 ± 1.08	56.43 ± 1.77	< 0.001
Age at menarche	12.74 ± 0.02	12.30 ± 0.05	12.72 ± 0.04	12.82 ± 0.04	12.83 ± 0.05	12.89 ± 0.06	12.90 ± 0.10	12.82 ± 0.12	12.66 ± 0.29	< 0.001
Age at menopause	44.64 ± 0.18	41.51 ± 0.41	43.15 ± 0.29	44.84 ± 0.30	46.03 ± 0.35	47.34 ± 0.39	48.74 ± 0.51	48.19 ± 0.73	46.37 ± 0.77	< 0.001
Fertile lifespan [a]	31.87 ± 0.18	29.19 ± 0.42	30.38 ± 0.29	32.01 ± 0.30	33.16 ± 0.36	34.42 ± 0.37	35.70 ± 0.53	35.39 ± 0.76	33.71 ± 0.85	< 0.001
Parity	2.87 ± 0.02	3.55 ± 0.04	3.19 ± 0.03	2.86 ± 0.03	2.59 ± 0.03	2.40 ± 0.03	2.19 ± 0.04	2.01 ± 0.04	1.78 ± 0.11	< 0.001
ALT (U/L)	21.00 ± 0.14	21.22 ± 0.40	20.99 ± 0.27	20.94 ± 0.26	21.18 ± 0.31	20.80 ± 0.41	20.58 ± 0.76	20.74 ± 0.92	22.21 ± 1.74	0.76
AST (U/L)	22.86 ± 0.15	22.58 ± 0.30	22.91 ± 0.33	22.85 ± 0.21	22.98 ± 0.27	22.70 ± 0.35	22.42 ± 0.53	24.72 ± 2.28	22.92 ± 1.36	0.58
FLI	50.21 ± 0.49	56.29 ± 0.94	55.23 ± 0.77	50.45 ± 0.91	47.95 ± 1.11	42.73 ± 1.27	38.02 ± 1.86	43.07 ± 2.69	39.78 ± 3.86	< 0.001
NFS	-1.94 ± 0.02	-1.96 ± 0.04	-1.91 ± 0.04	-1.84 ± 0.04	-1.98 ± 0.04	-2.11 ± 0.05	-2.17 ± 0.07	-1.78 ± 0.11	-2.06 ± 0.12	0.012
≥College graduate (%)	5488 (54.1)	482 (28.5)	1217 (37.6)	1343 (54.6)	1019 (67.2)	751 (80.6)	399 (79.9)	188 (86.7)	89 (81.4)	< 0.001
Current smoker (%)	2062 (18.5)	522 (31.7)	779 (25.7)	406 (15.5)	179 (12.8)	103 (9.4)	42 (7.7)	19 (8.3)	12 (10.0)	< 0.001
Postmenopausal (%)	7561 (58.5)	1140 (54.8)	2358 (62.5)	1864 (63.1)	1090 (58.8)	607 (49.9)	284 (47.7)	140 (48.9)	78 (58.5)	< 0.001
Oral contraceptive (%)	8103 (73.9)	1295 (72.0)	2447 (72.4)	1858 (71.9)	1156 (75.2)	734 (79.2)	366 (78.6)	170 (76.7)	77 (75.0)	0.003
Use female hormones (%)	2862 (26.7)	363 (20.6)	907 (28.5)	731 (30.2)	446 (28.4)	234 (23.2)	104 (19.4)	51 (23.5)	26 (28.9)	< 0.001
Had a hysterectomy (%)	3159 (25.5)	544 (30.2)	1084 (30.4)	814 (28.4)	419 (23.4)	184 (16.8)	64 (9.8)	34 (11.9)	16 (18.0)	< 0.001

[a] Fertile lifespan = age at menopause – age at menarche;

Continuous variables were shown as survey weighted mean ± SE; Categorical variables expressed as No. (%);

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; FLI, fatty liver index; HEI, health eating index; MET, metabolic equivalent; NFS, NAFLD fibrosis score; Family PIR, ratio of family income to poverty.

		Age at first birth (years)								
Both ovaries removed	1498 (12.8)	240 (14.1)	502 (15.3)	401 (14.9)	204 (10.8)	95 (8.5)	30 (6.2)	18 (7.8)	8 (7.8)	< 0.001

[a] Fertile lifespan = age at menopause – age at menarche;

Continuous variables were shown as survey weighted mean ± SE; Categorical variables expressed as No. (%);

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; FLI, fatty liver index; HEI, health eating index; MET, metabolic equivalent; NFS, NAFLD fibrosis score; Family PIR, ratio of family income to poverty.

The survey-weighted percentages of NAFLD were 50.27%, 48.59%, 43.21%, 38.87%, 35.01%, 27.99%, 34.77%, and 28.11% for the eight groups, respectively (Table 2). Compared to participants with AFB between 30 and 32 years old, those with AFB ≤ 29 years showed higher ORs of NAFLD (from 1.39 to 2.60, $P < 0.05$). Further adjusting for confounding factors substantially reduced the identified associations in participants with AFB of 27–29 years. The association significance became weaker but persisted for the groups with AFB ≤ 26 years after adjustment of sociodemographic characteristics, lifestyle, and reproductive factors (Model 3); the fully adjusted ORs ranged from 1.33 to 1.59 with $P < 0.05$. However, there was no significant difference between AFB of 33 to 35 or > 35 years compared with the reference group. We examined the nonlinear association of AFB with NAFLD, and a U-shaped curve tendency was observed (Fig. 2).

Table 2
Survey weighted odds ratios (95% CI) for the association between age at first birth and the presence of NAFLD.

	Age at first birth (years)							
	< 18	18–20	21–23	24–26	27–29	30–32	33–35	> 35
Case/N	1047/1934	1869/3656	1320/2862	725/1731	406/1071	167/543	91/261	45/130
Percent (Mean ± SE)	50.27 ± 1.59	48.59 ± 1.13	43.21 ± 1.38	38.87 ± 1.62	35.01 ± 1.75	27.99 ± 2.61	34.77 ± 3.61	28.11 ± 6.29
Model 0	2.60 (1.95–3.46)	2.43 (1.87–3.16)	1.96 (1.48–2.59)	1.64 (1.24–2.16)	1.39 (1.04–1.85)	1.00 (Ref.)	1.37 (0.90–2.10)	1.01 (0.54–1.88)
Model 1	2.07 (1.55–2.75)	1.97 (1.51–2.57)	1.67 (1.26–2.21)	1.50 (1.13–1.98)	1.36 (1.02–1.81)	1.00 (Ref.)	1.38 (0.90–2.10)	1.00 (0.54–1.87)
Model 2	1.89 (1.42–2.52)	1.82 (1.39–2.39)	1.53 (1.16–2.02)	1.44 (1.10–1.88)	1.29 (0.97–1.73)	1.00 (Ref.)	1.38 (0.91–2.11)	0.95 (0.51–1.78)
Model 3	1.59 (1.18–2.13)	1.58 (1.20–2.08)	1.38 (1.04–1.83)	1.33 (1.01–1.77)	1.24 (0.93–1.67)	1.00 (Ref.)	1.38 (0.90–2.11)	0.92 (0.49–1.73)

Model 0, without adjustment;

Model 1, adjusted for age (years), race (Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black, other race), education level (less than 12th grade, high school or equivalent, college graduate or above), and family poverty income ratio;

Model 2, adjusted for model 1 + smoking status (never, ever, current), alcohol intake (drinks/week), leisure activity (MET-min/day), total energy intake (kcal/d), and HEI-2015;

Model 3, adjusted for model 2 + parity (times), menopause status (yes/no), use of female hormones (never/ever), oral contraceptive use (never/ever), hysterectomy (yes/no), and both ovaries removed (yes/no).

Despite no statistical subgroup interactions, results varied between prespecified subgroups of current age, menopause status, and race. A stronger association between AFB and NAFLD was observed in participants who were aged 45 years or older, postmenopausal, and white, than in those aged less than 45 years, premenopausal, and black, respectively (Table 3).

Table 3
Stratified analysis of the association between age at first birth and the presence of NAFLD.

	Case/N	Age at first birth (years)								*P*-interaction
		< 18	18–20	21–23	24–26	27–29	30–32	33–35	> 35	
Age at survey										0.90
< 45 years	2140/5250	1.50 (0.93–2.41)	1.29 (0.84–1.99)	1.28 (0.83–1.99)	0.99 (0.64–1.54)	1.18 (0.74–1.89)	1.00 (Ref.)	1.30 (0.64–2.67)	1.16 (0.45–2.97)	
≥ 45 years	3530/6938	1.83 (1.29–2.61)	1.99 (1.42–2.78)	1.59 (1.13–2.24)	1.57 (1.11–2.23)	1.30 (0.91–1.86)	1.00 (Ref.)	1.50 (0.91–2.48)	0.83 (0.38–1.83)	
Menopause status										0.87
No	1811/4626	1.75 (1.17–2.62)	1.53 (1.07–2.17)	1.43 (0.97–2.11)	1.13 (0.80–1.61)	1.39 (0.91–2.13)	1.00 (Ref.)	1.21 (0.60–2.41)	0.89 (0.41–1.93)	
Yes	3857/7558	1.67 (1.10–2.55)	1.81 (1.20–2.73)	1.48 (0.98–2.23)	1.55 (1.01–2.38)	1.14 (0.75–1.74)	1.00 (Ref.)	1.58 (0.89–2.80)	0.91 (0.37–2.24)	
Race*										0.65
White	2132/5013	1.69 (1.14–2.51)	1.86 (1.30–2.68)	1.61 (1.14–2.28)	1.60 (1.12–2.29)	1.45 (0.99–2.13)	1.00 (Ref.)	1.73 (1.05–2.84)	0.87 (0.41–1.87)	
Non-white	3538/7175	1.44 (1.02–2.05)	1.34 (0.94–1.92)	1.17 (0.82–1.66)	0.97 (0.68–1.40)	0.93 (0.62–1.38)	1.00 (Ref.)	0.84 (0.44–1.61)	1.36 (0.69–2.71)	
* White, non-Hispanic white; Non-white, including Mexican American, non-Hispanic black, and other race;										
Adjusted for model 3;										

We conducted six sets of sensitivity analyses and present the results in Table 4. The overall ORs were not significantly affected by the exclusion of people who had had a hysterectomy, both ovaries removed, ever used female hormones, age at menarche < 9 years or > 18 years, age at menopause < 40 years or > 55 years or premenopausal, or had given birth more than five times, indicating the robustness of the results in our research.

Table 4
Sensitivity analysis of the association between age at first birth and the presence of NAFLD.

Exclusion	Age at first birth (years)							
	< 18	18–20	21–23	24–26	27–29	30–32	33–35	> 35
Had a hysterectomy	1.80 (1.31–2.46)	1.64 (1.23–2.19)	1.38 (1.01–1.88)	1.26 (0.93–1.70)	1.24 (0.91–1.70)	1.00 (Ref.)	1.43 (0.88–2.31)	0.83 (0.41–1.65)
Both ovaries removed	1.65 (1.23–2.21)	1.65 (1.25–2.16)	1.37 (1.02–1.83)	1.28 (0.96–1.72)	1.25 (0.92–1.70)	1.00 (Ref.)	1.50 (0.95–2.36)	0.74 (0.37–1.47)
Ever use of female hormones	1.85 (1.33–2.57)	1.89 (1.39–2.58)	1.64 (1.20–2.26)	1.53 (1.12–2.08)	1.44 (1.04-2.00)	1.00 (Ref.)	1.75 (1.05–2.89)	0.90 (0.47–1.74)
Age at menarche < 9 or > 18 years	1.64 (1.22–2.19)	1.62 (1.23–2.14)	1.41 (1.07–1.87)	1.36 (1.03–1.79)	1.25 (0.93–1.68)	1.00 (Ref.)	1.42 (0.93–2.15)	0.92 (0.49–1.73)
Age at menopause < 40 or > 55 years or premenopausal	1.65 (1.23–2.21)	1.64 (1.25–2.17)	1.43 (1.08–1.89)	1.36 (1.03–1.80)	1.26 (0.94–1.69)	1.00 (Ref.)	1.41 (0.93–2.15)	0.92 (0.49–1.73)
Parity > 5	1.64 (1.22–2.21)	1.64 (1.24–2.17)	1.44 (1.09–1.91)	1.37 (1.03–1.82)	1.27 (0.95–1.71)	1.00 (Ref.)	1.41 (0.93–2.15)	0.93 (0.49–1.74)
Adjusted for model 3;								

In addition, FLI and NFS reflected the severity of liver injury. Similar to the primary analysis, the risk of elevated FLI and NFS was significantly higher for groups with younger AFBs (**Supplemental Table 2**). We also evaluated the association of AFB with MAFLD, a newly defined metabolic dysfunction-associated fatty liver disease, and the specific complications of NAFLD, including overweight, obesity, diabetes, hypertension, and dyslipidemia. Results were similar to those of the primary analysis network and details are provided in **Supplemental Tables 3 and 4**.

Discussion

In this large population-based study, we found that younger AFB (≤ 26 years) was associated with a higher risk of NAFLD in later life of women. An increasing trend of NAFLD risk was observed for higher AFB (> 32) compared with AFB of 30–32 years, but this did not reach statistical significance. Therefore, we can expect U-shaped associations between AFB and NAFLD, as shown by the spline.

Those who were white, postmenopausal, or with current age ≥ 45 years had a significantly stronger association between AFB and NAFLD than the other respective comparison groups. These results add to the accumulating evidence of age and menopause status differences in NAFLD. That is possibly due to the dramatic drop in estrogen levels with increasing age and menopause, and estrogen having the potential to inhibit the activation of hepatic stellate cells. [18,19]

The risk of NAFLD associated with AFB was higher in white women than in black, suggesting a modified effect of genetic background. In consist with the meta-analysis, notable racial disparities in NAFLD prevalence exist worldwide. Nonetheless, this finding should be interpreted with caution. Moreover, we also found similar results between AFB and NAFLD-related complications with the primary analyses, demonstrating the robustness of the synthetic strategy.

Numerous early studies have focused on AFB in women's health. Most shreds of evidence support that early AFB is related to an elevated risk of metabolic diseases but decreased risk of liver cancer in women. [7–12] Hepatitis is most closely related to both metabolic diseases and liver cancer. However, evidence of the relationship between AFB and hepatitis is scarce and inconsistent. Most relevant to this study is the one which suggested no significant association between AFB and hepatic steatosis among 331 women in Michigan, [20] but there was limited statistical power due to the small sample size. Besides that, there was another one conducted by Wang et al. [21] Regrettably, they compared the risk of NAFLD between women who had given birth and nulliparous women only, and did not illustrate the differences in NAFLD risk between the different AFB categories. NAFLD is not only the hepatic component of metabolic syndrome but also an emergent risk factor for liver cancer. Understanding the potential association between AFB and NAFLD is critical for the prevention and management of NAFLD, especially for older or postmenopausal women. [22]

The potential mechanisms are not fully understood, but several factors may account for these responses. First, the protective effect of estrogen against NAFLD has been reported by substantial studies. [23–25] Adolescent mothers have stronger metabolic plasticity of hormonal response to pregnancy; therefore, estrogen change trajectories may differ from those in women with older AFB, which may irreversibly influence estrogen levels in later life. Then, there are substantial and complex interactions between metabolism and reproduction. From an evolutionary standpoint, specific metabolic changes promote fetal growth and development at the expense of maternal benefits. [26] For example, pregnancy and childbirth are marked by increasing adipose tissue and lipolysis, insulin resistance, and inflammation, which may persist after giving birth, and can negatively affect subsequent NAFLD risks for the mother.

Apart from purely physiological reasons, the findings of the present study can be primarily interpreted on socioeconomic levels. As an illustration, women who were younger at the time of first birth were more likely to have lower educational attainment and lower family PIR, which were often accompanied by riskier health behaviors, including smoking, poor physical performance, and higher alcohol consumption. And those unhealthy lifestyles in turn lead to higher odds of NAFLD in later life. Second, those with younger AFB were also more likely to have had unintended pregnancies, which was associated with unhealthy behaviors or delays in getting health care during the pregnancy.

The prevalence of NAFLD is rapidly increasing paralleled by the rapid increment of obesity, diabetes, and other metabolic diseases. [27,28] With the increased prevalence, management practices are focused on screening and prevention. Therefore, the identification of individuals at high risk of developing NAFLD becomes particularly important. However, there is no satisfying screening strategy for targeting people at high risk of NAFLD. We found that women with AFB ≤ 26 years had higher odds of NAFLD, especially when they were older than 45 years or postmenopausal. These findings have important public health policy implications to prevent NAFLD development and reduce the disease burden. Furthermore, our results are ethnically diverse, which provides clues to suggest that different policies may be required for populations with different ethnic/racial backgrounds.

There are several strengths to this study. Firstly, this is one of the rare studies to examine the relationship between AFB and NAFLD. This finding was robust to different assessments of NAFLD risk factors and related comorbidities. Secondly, the present analysis was based on the NHANES database, a population-based design with a large sample size and an ethnically diverse and well-characterized study population, including detailed information on reproductive/hormone-related factors and other important covariates. The large sample size was powerful enough to support the stratified analysis of different ages, menopause status, and races.

However, one needs to be alert to some limitations when interpreting this study. A large number of self-reported data included in this study, such as reproductive health, physical activity, and history of liver disease, may contain sources of recall bias and reduced reliability of the results. Then, NAFLD

status was inferred based upon a previously validated noninvasive diagnostic index, but it is not a perfect proxy for NAFLD diagnosis based upon liver biopsy or other imaging examination methods. Data on lifestyle earlier in life, like BMI around pregnancy, alcohol drinking, and smoking status, which may affect the NAFLD risk later, were not available. Third, cause-and-effect relationships were not elucidated due to the cross-sectional design. Finally, because the data were from multiple cross-sectional studies, the design of the questionnaires was not uniform across the cycles; therefore, non-measurable bias would be included during the data merge. Thus, more work will be required to validate these findings.

Collectively, our findings support that earlier AFB relates to unfavorable outcome of NAFLD in later life of women. Policymakers should consider focusing on women with earlier AFB for screening and prevention of NAFLD.

Declarations

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Data availability

The continuous National Health and Nutrition Examination Survey (NHANES) dataset are publicly available at the National Center for Health Statistics of the Center for Disease Control and Prevention and the link to the database is https://www.cdc.gov/nchs/nhanes/index.htm.

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Huan-Huan Yang, Guo-Chong Chen and Zhihui Li. The first draft of the manuscript was written by Huan-Huan Yang and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

References

1. Younossi ZM, et al. Global epidemiology of nonalcoholic fatty liver disease-meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016;64:73–84. doi:10.1002/hep.28431.
2. Wong VW, et al. Asia-Pacific Working Party on Non-alcoholic Fatty Liver Disease guidelines 2017-part 1: definition, risk factors and assessment. J Gastroenterol Hepatol. 2018;33:70–85. doi:10.1111/jgh.13857.
3. Lonardo A, et al. Sex differences in nonalcoholic fatty liver disease: state of the art and identification of research gaps. Hepatology. 2019;70:1457–69. doi:10.1002/hep.30626.
4. Dietz BM, Hajirahimkhan A, Dunlap TL, Bolton JL. Botanicals and their bioactive phytochemicals for women's health. Pharmacol Rev. 2016;68:1026–73. doi:10.1124/pr.115.010843.
5. Cho GJ, et al. Adolescent pregnancy is associated with osteoporosis in postmenopausal women. Menopause. 2012;19:456–60. doi:10.1097/gme.0b013e3182337150.
6. Kumar P, Magon N. Hormones in pregnancy. Niger Med J. 2012;53:179–83. doi:10.4103/0300-1652.107549.
7. Patchen L, Leoutsakos JM, Astone NM. Early parturition: is young maternal age at first birth associated with obesity? J Pediatr Adolesc Gynecol. 2017;30:553–9. doi:10.1016/j.jpag.2016.12.001.
8. Sim JH, et al. Maternal age at first delivery is associated with the risk of metabolic syndrome in postmenopausal women: from 2008–2010 Korean National Health and Nutrition Examination Survey. PLoS ONE. 2015;10:e0127860. doi:10.1371/journal.pone.0127860.
9. Rosendaal NTA, Pirkle CM. Age at first birth and risk of later-life cardiovascular disease: a systematic review of the literature, its limitation, and recommendations for future research. BMC Public Health. 2017;17:627. doi:10.1186/s12889-017-4519-x.
10. Parikh NI, et al. Reproductive risk factors and coronary heart disease in the women's health initiative observational study. Circulation. 2016;133:2149–58. doi:10.1161/circulationaha.115.017854.
11. Merritt MA, et al. Reproductive factors and risk of mortality in the European Prospective Investigation into Cancer and Nutrition; a cohort study. BMC Med. 2015;13:252. doi:10.1186/s12916-015-0484-3.

12. Wu CH, Chan TF, Changchien CC, Yang CY. Parity, age at first birth, and risk of death from liver cancer: evidence from a cohort in Taiwan. J Gastroenterol Hepatol. 2011;26:334–9. doi:10.1111/j.1440-1746.2010.06365.x.
13. Bedogni G, et al. The Fatty Liver Index: a simple and accurate predictor of hepatic steatosis in the general population. BMC Gastroenterol. 2006;6:33. doi:10.1186/1471-230x-6-33.
14. Koehler EM, et al. External validation of the fatty liver index for identifying nonalcoholic fatty liver disease in a population-based study. Clin Gastroenterol Hepatol 213;11:1201–1204, doi:10.1016/j.cgh.2012.12.031.
15. Otgonsuren M, et al. Single non-invasive model to diagnose non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH). J Gastroenterol Hepatol. 2014;29:2006–13. doi:10.1111/jgh.12665.
16. Meffert PJ, et al. Development, external validation, and comparative assessment of a new diagnostic score for hepatic steatosis. Am J Gastroenterol. 2014;109:1404–14. doi:10.1038/ajg.2014.155.
17. Yang HH, et al. Serum iron and risk of nonalcoholic fatty liver disease and advanced hepatic fibrosis in US adults. Sci Rep. 2021;11:10387. doi:10.1038/s41598-021-89991-x.
18. Yasuda M, Shimizu I, Shiba M, Ito S. Suppressive effects of estradiol on dimethylnitrosamine-induced fibrosis of the liver in rats. Hepatology. 1999;29:719–27. doi:10.1002/hep.510290307.
19. Shimizu I, et al. Inhibitory effect of oestradiol on activation of rat hepatic stellate cells in vivo and in vitro. Gut. 1999;44:127–36. doi:10.1136/gut.44.1.127.
20. Kim C, et al. Reproductive history and chronic hepatic steatosis in the Michigan Study of Women's Health Across the Nation. J Womens Health (Larchmt). 2015;24:42–8. doi:10.1089/jwh.2014.4839.
21. Wang J, et al. Associations between reproductive and hormone-related factors and risk of nonalcoholic fatty liver disease in a multiethnic population. Clin Gastroenterol Hepatol. 2021;19(e1):1258–66. doi:10.1016/j.cgh.2020.08.012.
22. Yang JD, et al. Gender and menopause impact severity of fibrosis among patients with nonalcoholic steatohepatitis. Hepatology. 2014;59:1406–14. doi:10.1002/hep.26761.
23. Ballestri S, et al. NAFLD as a sexual dimorphic disease: role of gender and reproductive status in the development and progression of nonalcoholic fatty liver disease and inherent cardiovascular risk. Adv Ther. 2017;34:1291–326. doi:10.1007/s12325-017-0556-1.
24. Lonardo A, Carani C, Carulli N, Loria P. 'Endocrine NAFLD' a hormonocentric perspective of nonalcoholic fatty liver disease pathogenesis. J Hepatol. 2006;44:1196–207. doi:10.1016/j.jhep.2006.03.005.
25. Yang M, et al. Dysfunction of estrogen-related receptor alpha-dependent hepatic VLDL secretion contributes to sex disparity in NAFLD/NASH development. Theranostics. 2020;10:10874–91. doi:10.7150/thno.47037.
26. Sanghavi M, Rutherford JD. Cardiovascular physiology of pregnancy. Circulation. 2014;130:1003–8. doi:10.1161/circulationaha.114.009029.
27. Ward ZJ, et al. Projected U.S. state-level prevalence of adult obesity and severe obesity. N Engl J Med. 2019;381:2440–50. doi:10.1056/NEJMsa1909301.
28. Younossi ZM, et al. Changes in the prevalence of the most common causes of chronic liver diseases in the United States from 1988 to 2008. Clin Gastroenterol Hepatol. 2011;9:524–30. doi:10.1016/j.cgh.2011.03.020. :.e1; quiz e560.

Figures

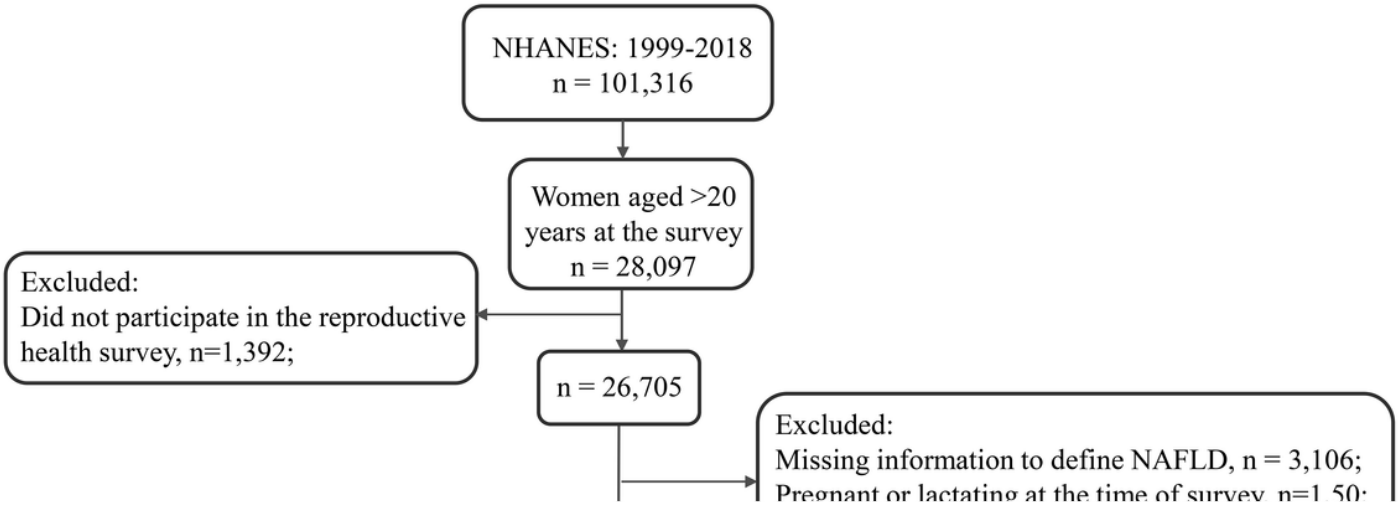

Figure 1

Flow chart of participants.

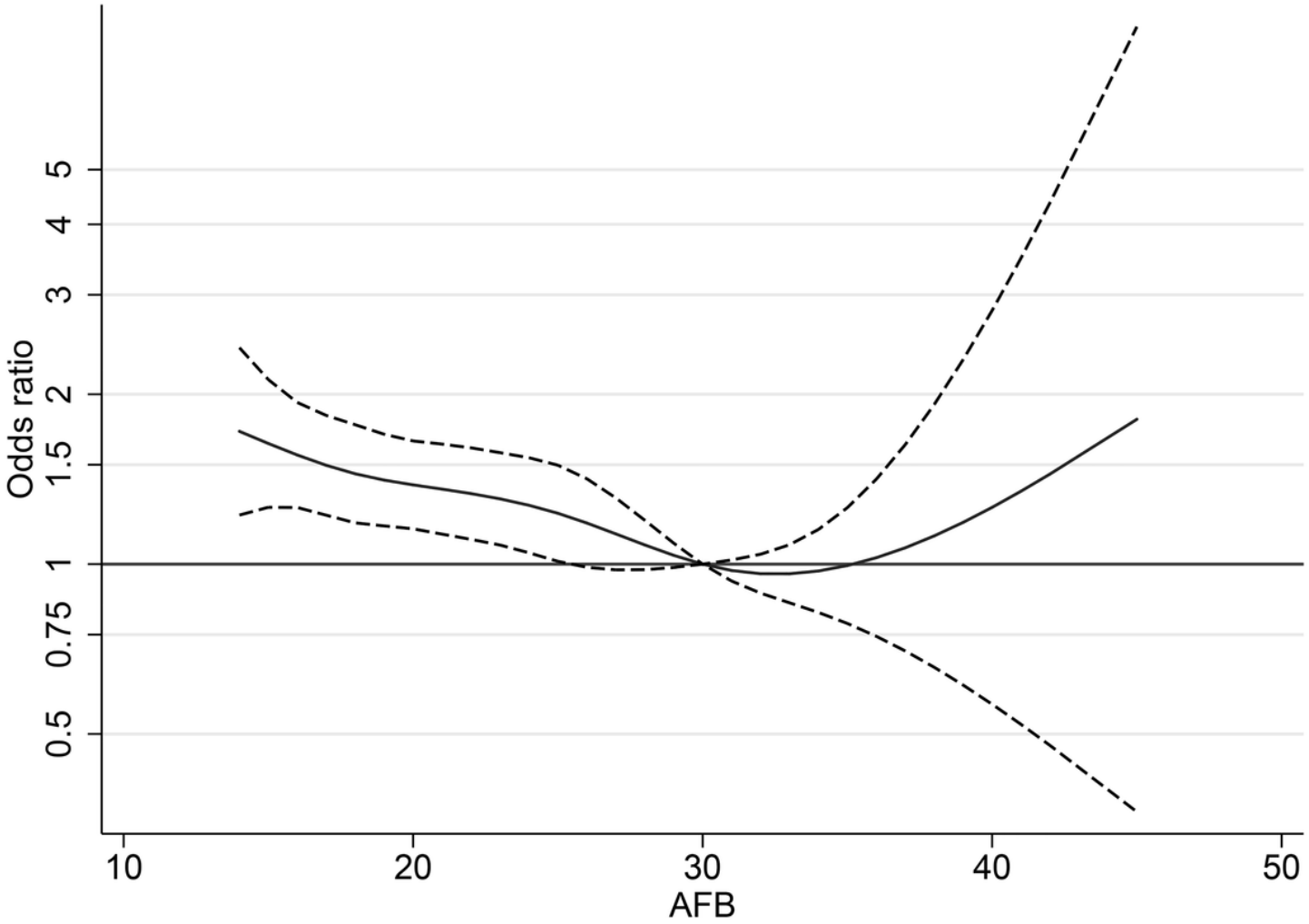

Figure 2

Nonlinear association between age at first birth and NAFLD.

Pooled dose-response association between age at first birth and odds of NAFLD. Age at first birth was modeled with restricted cubic splines in a random-effects dose-response model (grey line). Solid lines represent the odds ratio, dotted lines represent the 95% confidence interval for the spline model. The value of 30 years served as a reference, and model 3 was adjusted.

Supplementary Files

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