"Non-alcoholic fatty liver disease (NAFLD) association with cardiovascular disease: A cohort study"

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Introduction:

- NAFLD is a leading cause of **chronic liver disease** worldwide
- Defined as the **presence of hepatic steatosis** after excluding other causes of hepatic fat accumulation such as
  - Excessive alcohol consumption
  - Viruses
  - Drug-related hepatitis
- The global prevalence of NAFLD, **25.2%** in a meta-analysis of 86 studies by Younossi et al
- The increase in the prevalence of NAFLD has usually followed the **obesity** pandemic in children and adults globally although a considerable fraction of subjects are lean

Introduction:

- A number of hepatic complications from **simple steato-hepatitis to cirrhosis and hepatocellular carcinoma** can be attributed to NAFLD
- NAFLD is considered to be a hepatic manifestation of **metabolic syndrome**
- NAFLD may be associated with metabolic co-morbidities such as **diabetes mellitus (DM)** and **dyslipidemia**
- The non-liver related deaths remain far more common than liver-related deaths
- Our study Aim
  - To determine an independent association between NAFLD and CVD events

MATERIALS AND METHODS

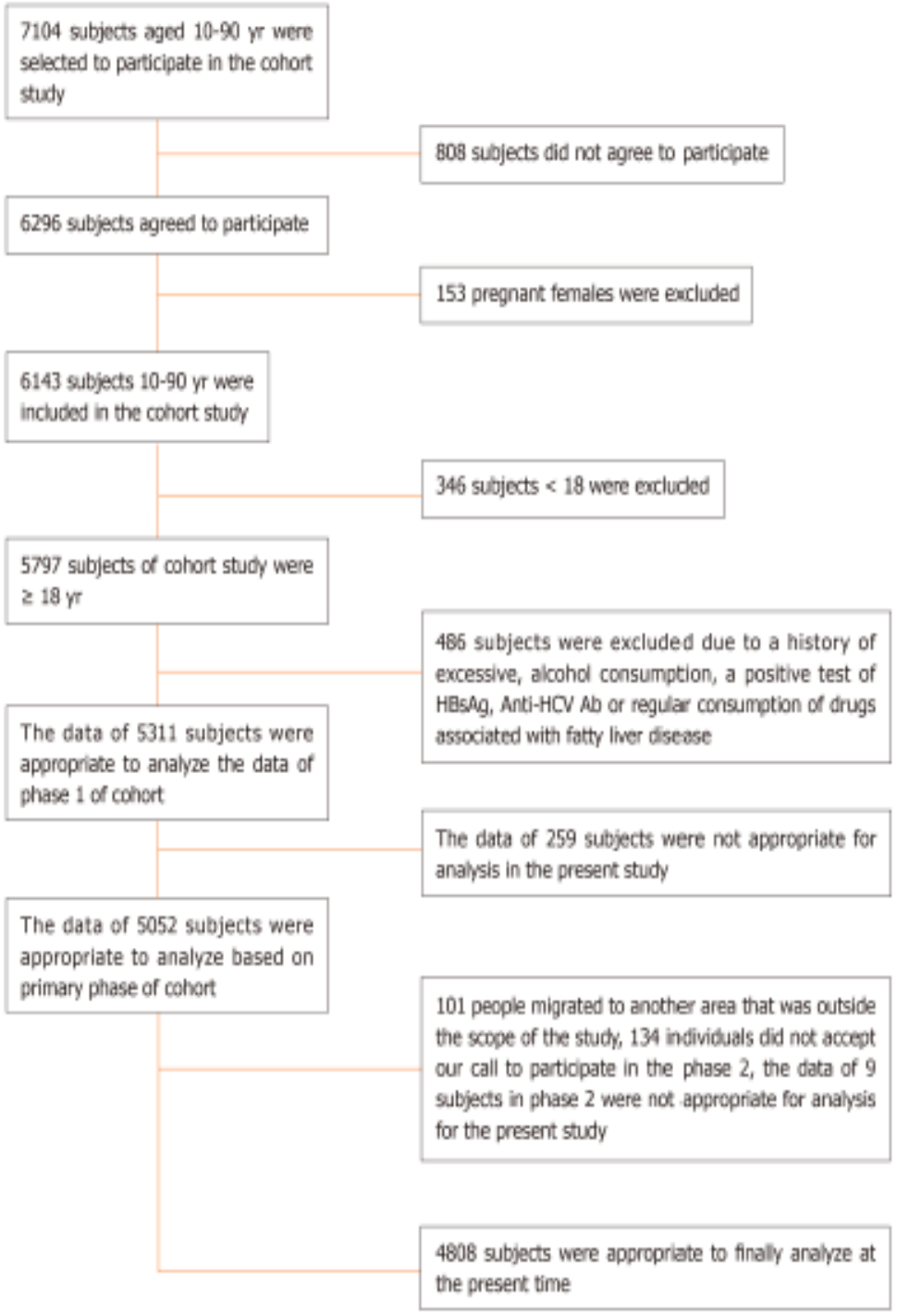
- **Study setting and sampling frame**
  - Phase 1 started in 2009-2010
  - Phase 2 started in 2016-2017

- Data obtained using primary health records in urban and rural areas

- 16 strata according gender and the following age group ranges within 10-90 years: 10-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79 and 80-89

- Members were contacted annually to provide the outcomes related to fatal and non-fatal CVD

Figure 1 Flow diagram of phase I and phase II included and excluded participants



MATERIALS AND METHODS

- Outcomes Evaluation
  - Atherosclerosis CVD (ASCVD) and the number of occurrences was considered as outcomes
  - Hospital discharge records and death certificates for fatal CVD events were recorded
  - Confirmation of associated outcomes was undertaken by an internist in the cohort study group

MATERIALS AND METHODS

- The diagnosis of NAFLD was by performed by sonography by one expert sonographer in phase 1 of the cohort in our research center
- NAFLD was defined as hepatic steatosis in participants with no history of excess consumption of alcohol, drug-related steatosis or viral or hereditary steatogenic hepatitis
- Anthropometric measures (height, weight) and blood pressure were measured by trained healthcare staff
- Whole blood samples (10 mL) were taken
  - Fasting blood sugar (FBS), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), triglycerides (TG)

RESULTS

- All cases were 4808:
  - 2667 were male and 2141 female
- NAFLD prevalence
  - 40.67% (95%CI: 38.89%-42.45%) for males and 43.58% (95%CI: 41.52%-45.65%) for females (P = 0.0359)
- The results indicate that all characteristics except HDL were significantly higher in participants with NAFLD than those without NAFLD
- DM prevalence
  - For males:
    - 14.79% (95%CI: 12.77%-16.81%) with NAFLD and 5.07% (95%CI: 4.04%-6.10%) without NAFLD (P < 0.001)
  - For females
    - 27.27% (95%CI: 24.47%-30.08%) with NAFLD and 8.06% (95%CI: 6.55%-9.57%) without NAFLD (P < 0.001)

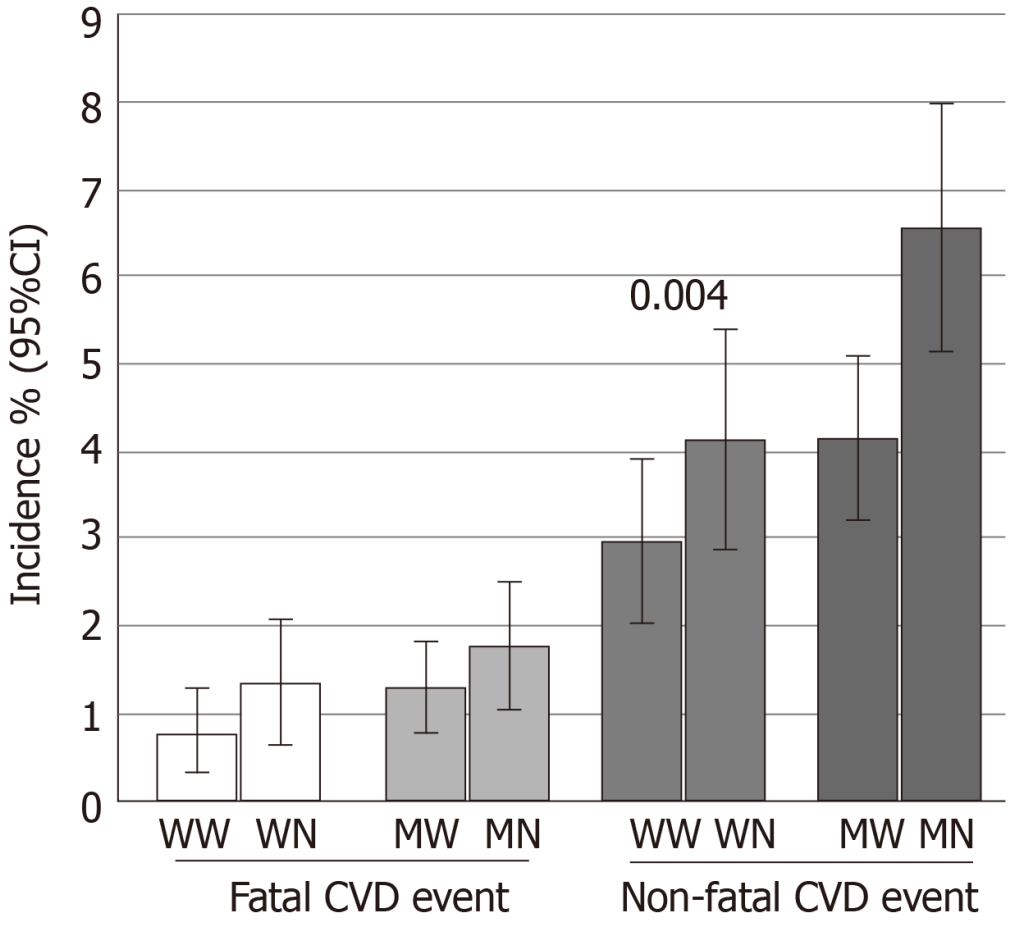
Table 1 Basic characteristics of population study in people without and with non-alcholic fatty liver disease

Characteristics	mean ± SD		*P* value
	Without NAFLD	With NAFLD	
Men (n = 2667)	n = 1149	n = 1518	
Age (yr)	42.02 ± 17.80	48.35 ± 14.24	< 0.001
BMI (kg/m^2)	24.35 ± 3.65	29.71 ± 3.96	< 0.001
WC (cm)	84.82 ± 10.39	99.57 ± 9.65	< 0.001
DBP (mmHg)	73.76 ± 12.18	80.72 ± 12.07	< 0.001
SBP (mmHg)	114.13 ± 14.65	121.81 ± 15.71	< 0.001
FBS (mg/dL)	94.48 ± 26.74	104.45 ± 33.03	< 0.001
HOMA-IR	1.75 ± 1.42	2.90 ± 2.33	< 0.001
TG (mg/dL)	123.35 ± 76.91	173.63 ± 101.92	< 0.001
HDL (mg/dL)	45.65 ± 11.51	40.31 ± 10.94	< 0.001
LDL (mg/dL)	99.99 ± 30.30	112.27 ± 30.42	< 0.001
Women (n = 2141)	n = 934	n = 1207	
Age (yr)	37.88 ± 15.09	50.20 ± 12.37	< 0.001
BMI (kg/m^2)	27.01 ± 4.83	33.11 ± 4.76	< 0.001
WC (cm)	84.72 ± 11.34	100.25 ± 10.48	< 0.001
DBP (mmHg)	72.32 ± 12.39	80.21 ± 12.88	< 0.001
SBP (mmHg)	110.34 ± 15.77	121.65 ± 18.03	< 0.001
FBS (mg/dL)	94.97 ± 30.36	115.22 ± 49.96	< 0.001
HOMA-IR	2.20 ± 1.62	3.43 ± 3.13	< 0.001
TG (mg/dL)	115.25 ± 67.10	173.92 ± 118.78	< 0.001
HDL (mg/dL)	48.92 ± 11.81	42.98 ± 11.68	< 0.001
LDL (mg/dL)	104.15 ± 30.62	116.51 ± 31.06	< 0.001

RESULTS

- In males, the incidence of non-fatal CVD events was significantly higher in individuals with NAFLD than those without NAFLD

- The incidence of fatal and non-fatal CVD events were higher in females with NAFLD than those without NAFLD; however, these differences were not statistically significant



W: Women
W: without NAFLD
M: Male
N: NAFLD case

RESULTS

- A positive simple association was detected between NAFLD and non-fatal CVD events in males (Hazard ratios = 1.606; 95%CI: 1.166-2.212; *P* = 0.004)
- No independent association was detected between them in the multiple Cox regression models
- No association between NAFLD and CVD events in females on the simple and multiple Cox proportional hazard models
- Age and diabetes mellitus have an association with fatal and non-fatal CVD events
- There were not any independent association between diabetes mellitus and fatal CVD events in women

Table 2 The results of Cox proportional hazard models on fatal and non- fatal cardiovascular events as outcome, and Non-alcholic fatty liver disease, diabetes mellitus and age as potential predictors

Sex	Outcomes	Simple Cox proportional model			Multiple Cox proportional model		
		Wald	HR (95% CI)	*P* value	Wald	HR (95% CI)	*P* value
NAFLD							
In men	Fatal CVD events	0.963	1.345 (0.744-2.430)	0.326	0.104	0.903 (0.486-1.677)	0.747
	Non-fatal CVD events	8.400	1.606 (1.166-2.212)	0.004	3.723	1.384 (0.995-1.925)	0.054
In women	Fatal CVD events	1.570	1.694 (0.743-3.863)	0.210	0.002	1.178 (0.491-2.829)	0.714
	Non-fatal CVD events	2.327	1.416 (0.906-2.214)	0.127	0.069	0.941 (0.584-1.516)	0.802
Diabetes mellitus							
In men	Fatal CVD events	37.13	6.692 (3.631-12.334)	< 0.001	8.398	2.688 (1.377-5.247)	0.004
	Non-fatal CVD events	30.98	2.999 (2.037-4.415)	< 0.001	8.789	1.885 (1.240-2.867)	< 0.001
In women	Fatal CVD events	10.99	4.034 (1.769-9.201)	< 0.001	2.165	1.867 (0.813-4.290)	0.141
	Non-fatal CVD events	40.71	4.358 (2.773-6.850)	< 0.001	14.35	2.507 (1.558-4.032)	< 0.001
Age							
In men	Fatal CVD events	75.35	1.122 (1.094-1.152)	< 0.001	62.82	1.114 (1.085-1.144)	< 0.001
	Non-fatal CVD events	69.12	1.043 (1.033-1.054)	< 0.001	56.86	1.041 (1.030-1.052)	< 0.001
In women	Fatal CVD events	47.49	1.134 (1.094-1.176)	< 0.001	44.91	1.133 (1.093-1.176)	< 0.001
	Non-fatal CVD events	63.59	1.068 (1.051-1.085)	< 0.001	48.60	1.062 (1.044-1.081)	< 0.001

CI: Confidence interval; CVD: Cardiovascular disease; HR: Hazard ratio; NAFLD: Non-alcholic fatty liver disease.

DISCUSSION

- Stepanova et al
  - An independent association between NAFLD and CVD events in the US population after a 14.3-year follow-up, although they found no association between CVD-related death and NAFLD
- Chan et al
  - No association between NAFLD and prevalent Ischaemic Heart Disease (IHD) events among patients with DM
- Hamaguchi et al
  - NAFLD as an independent predictor for CVD events
- Zeb et al
  - NAFLD can be considered a risk factor for non-fatal cardiac heart disease independent of traditional cardiovascular risk factors
- Kim et al
  - Found no association between CVD death and NAFLD

DISCUSSION

- Targher et al
  - Screening and surveillance strategies for cardiovascular diseases in patients with NAFLD, particularly those with steatosis
  - People with NAFLD will die of CVD before they die from an advanced liver disease
- Alexander et al
  - Meta-analysis of matched cohort study of 18 million European adults
  - Did not report any association between acute myocardial infarction or stroke and NAFLD, when the related analyses were adjusted based on the established cardiovascular risk factors
- Motamed et al
  - Found an association between NAFLD and 10-year CVD risk
- Han et al
  - A significant association between NAFLD and CVD risk

DISCUSSION

- There are common risk factors, such as
  - Obesity
  - Diabetes mellitus
  - Insulin resistance

- Our results emphasize that age and DM can be considered **major mediators** in the development of non-fatal CVD events in males with NAFLD
- A high prevalence of DM in individuals with NAFLD and a strong association between CVD and DM can increase the incidence of CVD events in patients with NAFLD
- The association between age with both NAFLD and CVD events are another cause of the increased incidence of CVD events in patients with NAFLD

DISCUSSION

- We evaluated the association between NAFLD and CVD events in a prospective study with a 7-year follow-up period
- Fatal CVD events
  - Increased slightly in individuals (males and females) with NAFLD compared to those without NAFLD, but this increase was not statistically significant
- Non-fatal CVD events
  - Males with NAFLD developed a significant slightly higher number of CVD events in the 7-year follow-up compared to males without NAFLD, this was not significant in females
- By considering DM and age as potential mediators between NAFLD and CVD events,
  - No independent relationship was detected between NAFLD at the beginning of the study and fatal and non-fatal CVD events in the 7-year follow-up in either males or females

DISCUSSION

- Our study showed that there is no independent association between NAFLD and CVD events
- The potential mediators of age and a history of DM were confounding variables for the association of NAFLD and the occurrence of new cases of CVD
- Our Study Limitations:
  - Duration of the follow-up: The 84-month follow-up for participants without a history of a CVD event may not be adequate to monitor and establish full associations of CVD events between individuals with and without NAFLD
  - NAFLD in this study was evaluated using sonography rather than liver biopsy, which is regarded as the 'golden standard'
  - Some patients with silent CVD events in data collection strategy would not have been included in the study

DISCUSSION

- In conclusion
  - Although we found a significant association between NAFLD and non-fatal CVD events in males, no independent association was detected between NAFLD and fatal and non-fatal CVD events in either males or females
  - Diabetes mellitus and age can be considered the principle mediators in CVD

Thank You For Your Kind Attention