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Review Article

The Prevalence of Non-Alcoholic Fatty Liver Disease in Iranian Children and Adult Population: A Systematic Review and Meta-Analysis

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Abstract

Background: Non-alcoholic fatty liver disease (NAFLD) is the world's most common etiology of chronic liver disease. In this systematic review and meta-analysis, we estimated the prevalence of NAFLD in the Iranian children and adult population.

Methods: A comprehensive search of five international databases, including PubMed, ISI/WOS, ProQuest, Scopus, and Google Scholar, was done from inception to Nov 2022. Studies on NAFLD patients and their risk factors were selected for meta-analysis. The quality of the included studies was assessed by The Joanna Briggs Institute (JBI) Critical Appraisal Checklist for cross-sectional, and cohort studies. The heterogeneity between studies was investigated using Cochran test and I^2 statistics. Random and fixed effect models were used for heterogenic and non-heterogenic studies, respectively. We used Comprehensive Meta-Analysis version 3 for conducting meta-analysis.

Results: Twenty studies were finally included. The total prevalence of NAFLD in children, boys, and girls was 6.7% (95% CI: 0.02-0.18), 12.5% (95% CI: 0.04-0.29) and, 10.1% (95% CI: 0.04-0.21), respectively. The total prevalence of NAFLD in obese children, obese boys, and obese girls was 42% (95% CI: 0.18-0.69), 44% (95% CI: 0.13-0.80), and 33 % (95% CI: 0.13-0.62), respectively. The total prevalence of NAFLD in adults was 36.9% (95% CI: 0.31-0.42). The prevalence of NAFLD in men and women was 33.8% (95% CI: 0.27-0.41) and 29.9% (95% CI: 0.21-0.40), respectively.

Conclusion: NAFLD prevalence in Iranian adults and obese children is considerable; however, data about the children population was insufficient.

Keywords: Epidemiology; Prevalence; Non-alcoholic fatty liver disease; Systematic review; Meta-analysis; Iran

Introduction

Non-alcoholic fatty liver disease (NAFLD) is considered the most common cause of chronic liver disease in the world (1, 2). It is estimated by 2030, NAFLD will become the major cause of liver transplantation (3).

NAFLD is defined as an accumulation of more than 5% fat deposition in liver parenchyma in the absence of other conditions like excess consumption of alcohol (>20 g/day in women, >30 g/day in men), viral and autoimmune hepatitis, use of hepatotoxic drugs and endocrine conditions (4-6). NAFLD is divided into three grades: mild (less than 33% fat accumulation), moderate (between 33% to 66% fat accumulation), and severe (more than 66% fat accumulation) (7).

The prevalence of NAFLD is estimated to be 25% in the world. East and South America are the highest regions, and Africa is the lowest regarding NAFLD prevalence (2). The prevalence of NAFLD in the United States has been steadily increasing over the past 20 years (8, 9). About 1 billion people worldwide and 80-100 million people in the United States are suffering from NAFLD (10, 11). Previous studies have shown not only adults but children and adolescents are also at risk of NAFLD. The prevalence of NAFLD in children is estimated between 5% and 10% (12). A recent meta-analysis study showed the prevalence of NAFLD is 26% in obese children (13). Although NAFLD is a common condition in children, most obese children don't have NAFLD (12).

Iran is a country with a high prevalence of metabolic conditions. The prevalence of diabetes, metabolic syndrome, and obesity is estimated at 21.1%, 14.1%, and 21.4%, respectively (14-16). A previous meta-analysis reported the prevalence of NAFLD in Iran at 33.9% in 2015 (17). Due to the significant increase of metabolic conditions in the Iranian population in recent years, in this systematic review and meta-analysis, we sought to estimate the epidemiology of NAFLD in the Iranian children and adult population.

Materials and Methods

The current study is a systematic review and meta-analysis of the prevalence of NAFLD in Iran. The Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guideline was admired for study protocol (18).

Inclusion and exclusion criteria

In this systematic review and meta-analysis, studies that met the following criteria were included: English written cross-sectional and cohort studies on children or adult populations with NAFLD. Those studies that their full-text was not available or were not in English were excluded. Also, systematic review, meta-analysis, narrative review, randomized clinical trial, case-control, editorial, commentary studies, and those who did not report the number of patients were excluded from the present study. In addition, studies assessed NAFLD in patients with a specific underlying disease like patients with diabetes mellitus (DM), polycystic ovary syndrome, lean adults, or immunocompromised patients got excluded.

Search strategy

The range of study cases was from the inception until Nov 2022. Two researchers examined five global databases, namely PubMed, ISI/WOS, ProQuest, Scopus, and Google Scholar, in November 2022. They conducted searches using various keywords such as "non-alcoholic fatty liver disease," "nonalcoholic fatty liver," "Nonalcoholic Steatohepatitis," "NAFLD," "epidemiology," "prevalence," "incidence," "risk factor," "Iranian population," and "Iran."

Quality assessment

The quality assessment of the included studies was conducted by two researchers, E.AS and S.H, independently. They utilized the Joanna Briggs Institute (JBI) Critical Appraisal Checklist specifically designed for cross-sectional and cohort studies. In cases where there were disagree-

ments, a third researcher, F.MG, was involved to reach a final resolution.

Data extraction

The eligible articles were surveyed and data extraction was performed by two independent researchers. The extraction process was conducted in accordance with the objectives of the current systematic review and meta-analysis. The following information was identified and recorded: the first author's name, year of publication, study location, study type (cross-sectional or cohort), prevalence of NAFLD, study population (adults, obese children, or children), and sample size.

Statistical analysis

The heterogeneity of the study was examined using Cochran's test (where the significance level was set at $P < 0.1$) and I^2 statistics (where the significance level was set at more than 50%). In cases where heterogeneity was detected, the random-effect model was employed, while the fixed-effect model was utilized for studies without heterogeneity. In addition, the random effect model was used for calculating the pooled prevalence when the number of available studies was less than 5. To assess each study's effect on pooled effect and heterogeneity, we performed sensitivity analysis. Subgroup analysis was conducted based on three groups of adults, obese children, and children, respectively. Adult people were defined as individuals older than 18 years. Comprehensive meta-analysis (CMA) statistical software version 3 was used for all the analyses of this systematic review and meta-analysis study.

Results

Study Selection

Upon searching all the international databases, a total of 139 articles were initially identified. After removing 24 duplicate articles, 115 unique studies remained. These studies were further screened based on their titles and abstracts, resulting in the exclusion of 61 studies. The remaining studies underwent a full-text review to assess their eligibility criteria, leading to the exclusion of an additional 34 articles. Eventually, 20 articles met the inclusion criteria and were selected for analysis (Fig.1).

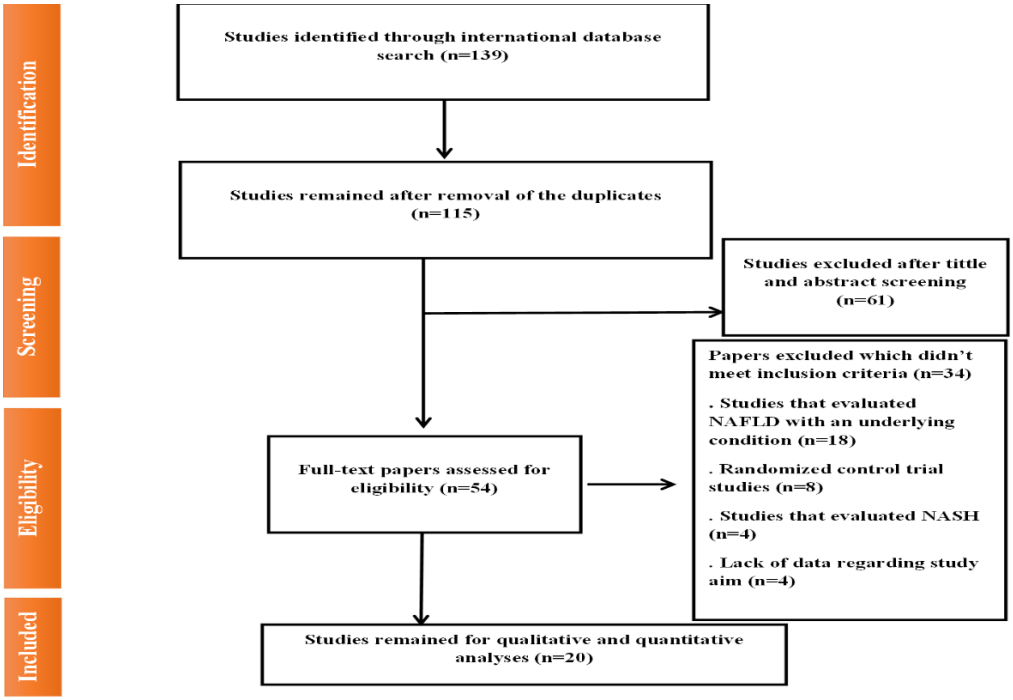

Fig. 1: Flowchart of the included eligible studies in a systematic review

Characteristics of included studies

Table 1 shows the feature of selected studies. Of 20 articles, 12 articles assessed NAFLD in adults (19-29), five studies in obese children (30-34), and three studies in children (35-37). One study was cohort (28), and the remaining were cross-sectional (19-27,29-37). Regarding the quality of included studies, nine studies were considered high (score more than 6 for cross-sectional and more than 9 for cohort studies) (20,24-26,29,31,33,34,36).

Table 1: Characteristics of included studies

Author, year (Ref)	*Region*	*Design of study*	*Prevalence of NAFLD%*	*Target population*	*Sample size*	*Total score*
Adibi ,2017 (19)	Isfahan	Cross-sectional	39.3	Adult	483	6/8
Adibi,2009 (35)	Isfahan	Cross-sectional	16.9	Children	952	6/8
Alavian, 2009 (36)	Tehran	Cross-sectional	7.1	Children	966	7/8
Amirkalali,2014 (20)	Amol	Cross-sectional	43.8	Adult	5023	8/8
Bagheri Lankarani,2013 (21)	Shiraz	Cross-sectional	21.5	Adult	819	6/8
Birjandi,2016 (22)	Kavar	Cross-sectional	22.4	Adult	1,600	6/8
Fattahi,2018 (23)	Sanandaj	Cross-sectional	35.4	Adult	410	6/8
Honarvar, 2019 (24)	Shiraz	Cross-sectional	19.8	Adult	478	8/8
MansourGhanaei, 2018 (25)	Soomehesara	Cross-sectional	43.5	Adult	960	8/8
Montazerifar,2014 (30)	Zahedan	Cross-sectional	44.1	Obese children	34	6/8
Motamed,2016 (26)	Amol	Cross-sectional	58.8	Adult	5,052	7/8
Motamed,2017 (27)	Amol	Cross-sectional	50.3	Adult	2804	6/8
Motamed,2020 (28)	Amol	Cohort	41.8	Adult	5797	9/11
Namakin,2018 (31)	Birjand	Cross-sectional	54	Obese children	200	8/8
Ostovaneh,2015(1) (29)	Amol	Cross-sectional	42.95	Adult	5645	8/8
Ostovaneh,2015(2) (29)	Zahedan	Cross-sectional	31.37	Adult	2078	5/8
Rafeey,2009 (37)	Tabriz	Cross-sectional	2.3	Children	1500	6/8
Saki,2014 (32)	Shiraz	Cross-sectional	54.9	Obese children	102	6/8
Taghavi ardakani,2017 (33)	Kashan	Cross-sectional	59	Obese children	200	8/8
Gheibi,2019 (34)	Urmia	Cross-sectional	11	Obese children	843	8/8

Results of heterogeneity

Table 2 demonstrates the heterogeneity of the included studies. Out of the 18 variables analyzed, four variables showed homogeneous results, namely the prevalence of NAFLD grade 2 in children, the prevalence of NAFLD grade 3 in children, the prevalence of NAFLD grade 3 in obese children, and the prevalence of NAFLD grade 3 in adults. However, significant heterogeneity was observed in the results of the remaining variables.

Table 2: The result of heterogeneity among included studies

Variables	*# of studies*	*Q value*	*I2 (%)*	*P-value*	*Selected model*
Prevalence of NAFLD in children	3	139.780	98.56	<0.001	Random
Prevalence of NAFLD in boys	2	24.150	95.85	<0.001	Random
Prevalence of NAFLD in girls	2	18.397	94.56	<0.001	Random
Prevalence of NAFLD grade 1 in children	2	35.986	97.22	<0.001	Random
Prevalence of NAFLD grade 2 in children	2	0.180	0.00	0.67	Random
Prevalence of NAFLD grade 3 in children	2	0.325	0.00	0.56	Random
Prevalence of NAFLD in obese children	5	272.765	98.53	<0.001	Random
Prevalence of NAFLD in obese boys	4	166.693	98.20	<0.001	Random
Prevalence of NAFLD in obese girls	4	87.920	96.58	<0.001	Random
Prevalence of NAFLD grade 1 in obese children	5	241.622	98.34	<0.001	Random
Prevalence of NAFLD grade 2 in obese children	5	17.658	77.34	<0.001	Random
Prevalence of NAFLD grade 3 in obese children	5	3.990	00.0	0.40	Fixed
Prevalence of NAFLD in adults	12	1177.730	99.06	<0.001	Random
Prevalence of NAFLD in men	7	115.533	94.80	<0.001	Random
Prevalence of NAFLD in women	7	285.677	97.89	<0.001	Random
Prevalence of NAFLD grade 1 in adults	3	5.766	65.31	0.05	Random
Prevalence of NAFLD grade 2 in adults	3	6.47	69.12	0.03	Random
Prevalence of NAFLD grade 3 in adults	3	2.80	28.72	0.24	Random

Results of meta-analysis

Prevalence of NAFLD in children

Among the studies we included, three studies surveyed the prevalence of NAFLD among children (35-37). The total prevalence of NAFLD among children was 6.7% (95% CI: 0.02-0.18) (Fig. 2A). Two studies also surveyed NAFLD prevalence in boys and girls (35,36). The total prevalence of NAFLD in boys and girls was 12.5% (95% CI: 0.04-0.29) and 10.1% (95% CI: 0.04-0.21), respectively (Fig.2B-C). Based on two studies, the prevalence of NAFLD grade 1, 2, and 3 in children was 2.7% (95% CI: 0.00-0.12), 0.9% (95% CI: 0.00-0.01), and 0.2% (95% CI: 0.001-0.005), respectively (Fig. 2D-F) (36,37). We conducted sensitivity analysis to assess the source of heterogeneity; however, no significant changes were observed after the removal of each study regarding heterogeneity.

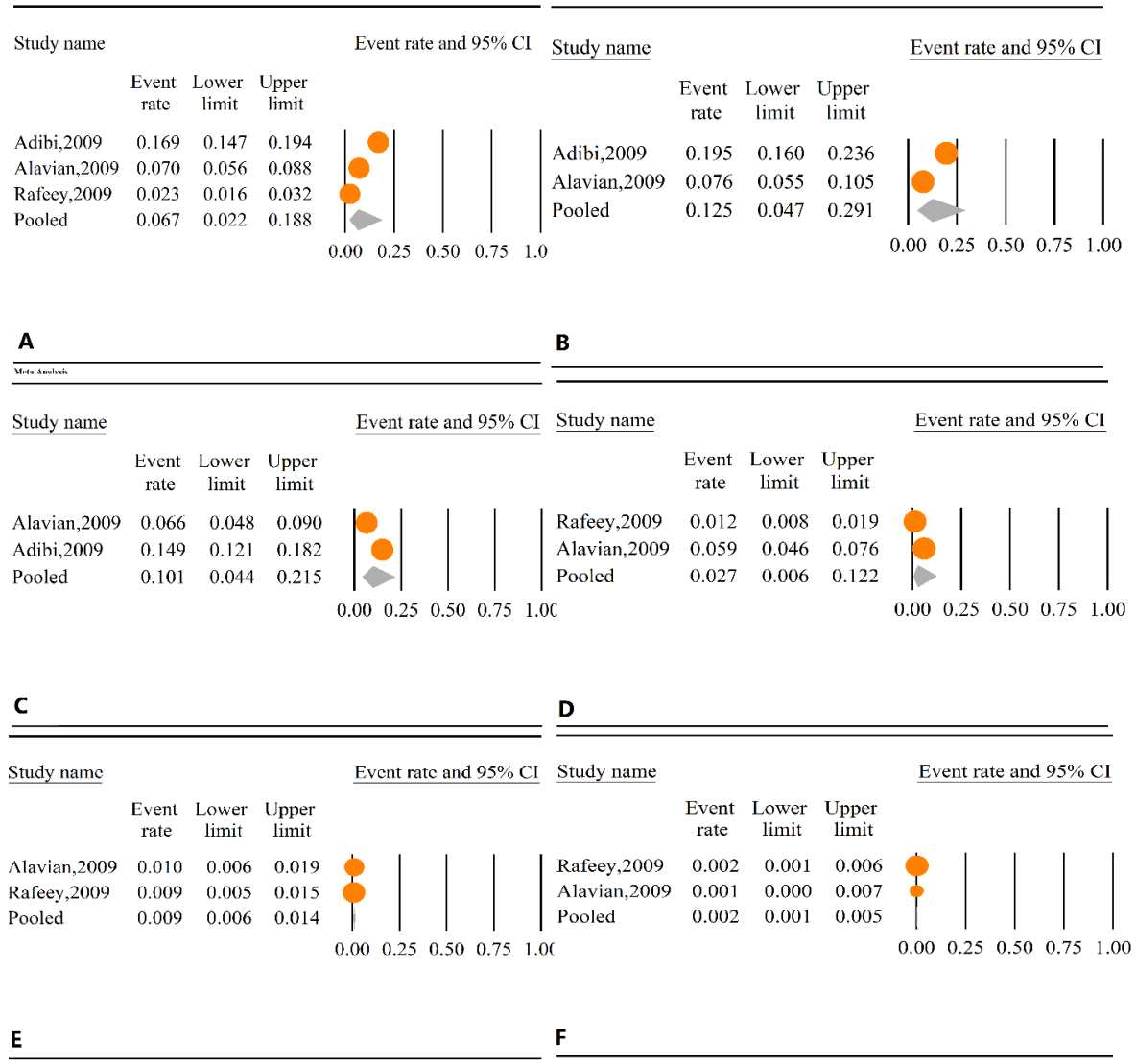

Fig. 2: A: Prevalence of NAFLD in children. **B:** Prevalence of NAFLD in boys **C:** Prevalence of NAFLD in girls **D:** Prevalence of children NAFLD grade 1 **E:** Prevalence of children NAFLD grade 2 **F:** Prevalence of children NAFLD grade 3

Prevalence of NAFLD in obese children

Five studies searched the prevalence of NAFLD and its grades in obese children (30-34). Four studies also surveyed the NAFLD prevalence in obese boys and girls (30,31,33,34). The total prevalence of NAFLD in obese children, obese boys, and obese girls was 42% (95% CI: 0.18-0.69), 44% (95% CI: 0.13-0.80) and 33 % (95% CI: 0.13-0.62), respectively (Fig.3A-C). The prevalence of NAFLD grade 1, 2, and 3 in obese children was 30% (95% CI: 0.27-0.33), 5.9% (95% CI: 0.03-0.10), and 0.6% (95% CI: 0.00-0.01) respectively (Fig.3D-F). The results of sensitivity analysis showed significant heterogeneity decrease by removal of Gheibi et al. (34) in the prevalence of NAFLD in obese children (I^2 =0.00%, P =0.40), obese boys (I^2 =0.45%, P=0.15), obese girls (I^2=0.00%, P=0.55), grade 1 (I^2=42%, P=0.16), and grade 2 (I^2=44%, P=0.14).

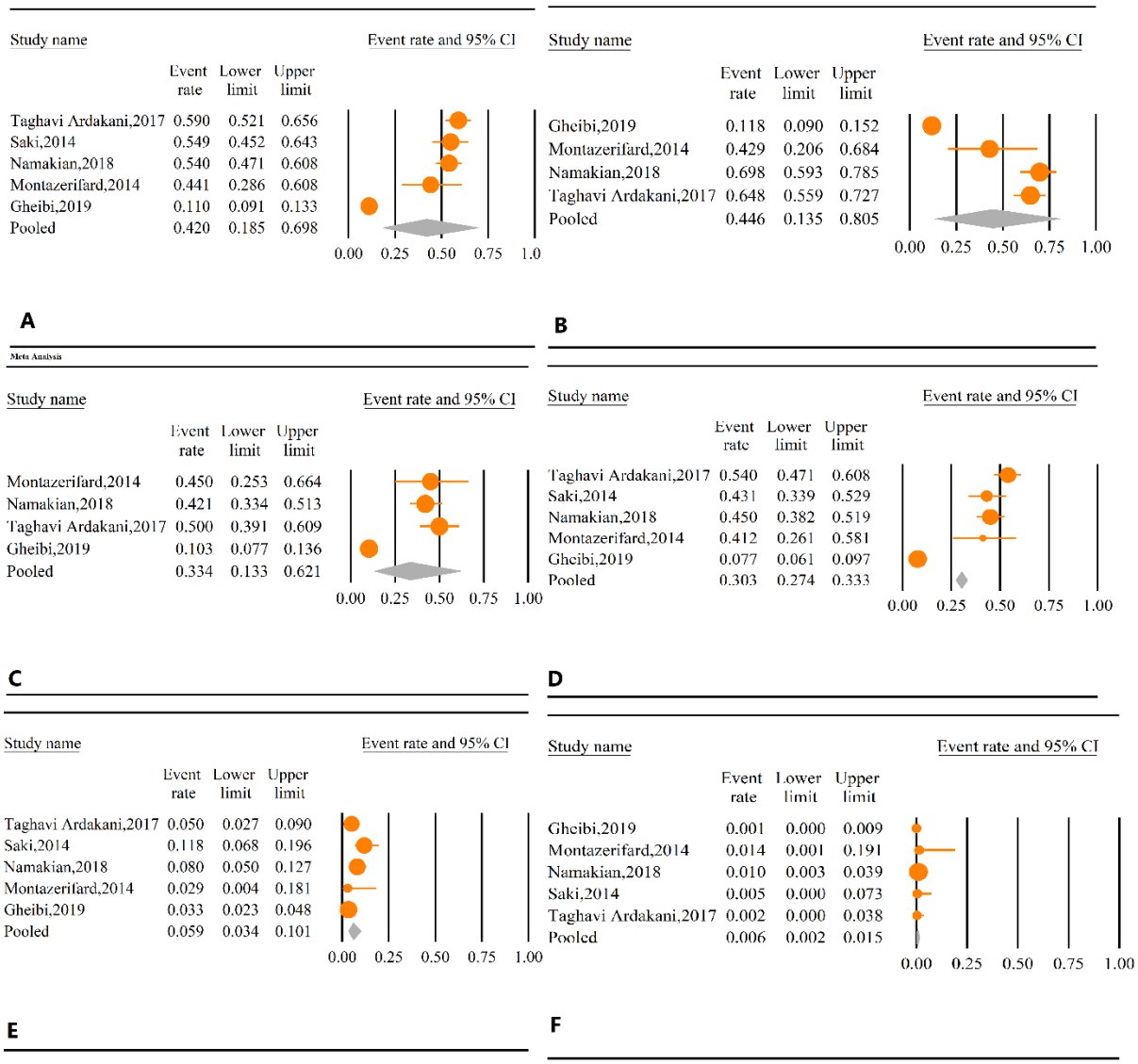

Fig. 3: A: Prevalence of NAFLD in obese children. **B:** Prevalence of NAFLD in obese boys **C:** Prevalence of NAFLD in obese girls **D:** Prevalence of obese NAFLD grade 1 **E:** Prevalence of obese NAFLD grade 2 **F:** Prevalence of obese NAFLD grade 3

Prevalence of NAFLD in adult

The total prevalence of NAFLD in adults was 36.9% (95% CI: 0.31-0.42). The prevalence of NAFLD in men and women was 33.8% (95% CI: 0.27-0.41) and 29.9% (95% CI: 0.21-0.40), respectively (Fig.4A-C). The prevalence of NAFLD grade 1, 2, and 3 in adults was 28.9% (95% CI: 0.25-0.32), 9.8% (95% CI: 0.07-0.12), and 1.1% (95% CI: 0.00-0.02), respectively (Fig.4D-F). The results of sensitivity analysis showed no significant difference in the total prevalence of NAFLD in adults and the prevalence of NAFLD in men and women; however, by omitting Fattahi et al. (23) and Adibi et al. (19) studies, significant decrease in grade 1 heterogeneity (I^2 =0%, *P*=0.94), and grade 2 heterogeneity (I^2 =0%, *P*=0.56) was observed.

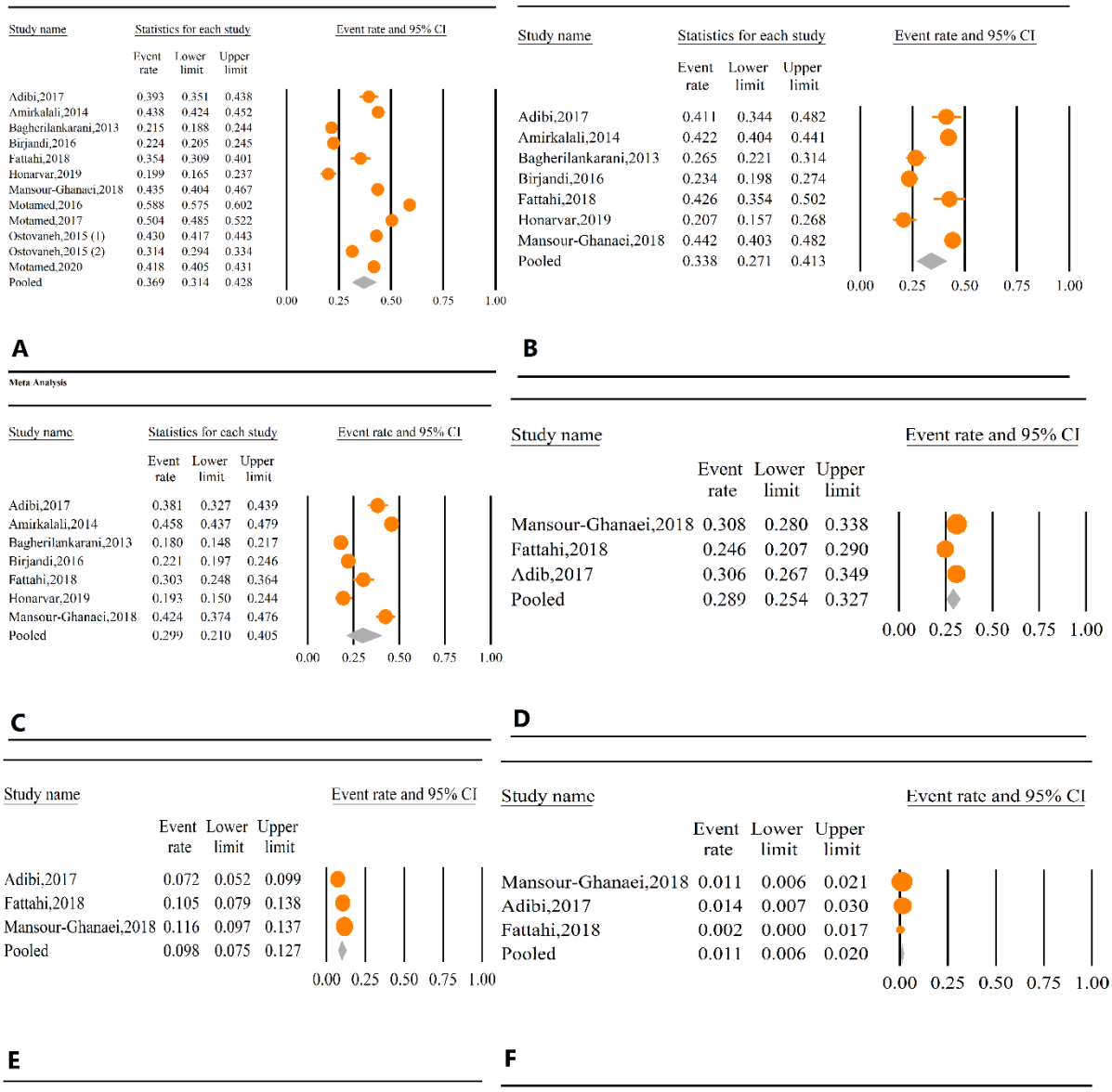

Fig. 4: **A:** Prevalence of NAFLD in adult. **B:** Prevalence of NAFLD in men **C:** Prevalence of NAFLD in women **D:** Prevalence of adult NAFLD grade 1 **E:** Prevalence of adult NAFLD grade 2 **F:** Prevalence of adult NAFLD grade 3

Discussion

The present study is a systematic review and meta-analysis estimating the prevalence of NAFLD in the Iranian population. In this study, we showed the distribution of NAFLD among children, obese children, and adults. We also showed the prevalence of three grades of this disease and its prevalence in both genders.

In our study, the total prevalence of NAFLD in children was 6.7% in the Iranian population. Other studies reported the prevalence of NAFLD in children between 5% and 10% (12). The Child and Adolescent Liver Epidemiology (SCALE) study reported the prevalence of NAFLD at 9.6% in children aged 2-19 (38). Pediatric NAFLD prevalence was reported at 4.5% in New York City (39). Although the previous stud-

ies diagnosed NAFLD by biopsy, all primary studies in our meta-analysis diagnosed NAFLD by ultrasound. A meta-analysis by Anderson et al. estimated the global prevalence of NAFLD in children at 7.6% in 2013, regardless of the method of diagnosis (40).

Based on the result of our study, the prevalence of NAFLD in obese children was 42%, which was almost six-fold higher than children's NAFLD prevalence. In another study, which surveyed NAFLD among obese children, the prevalence of simple steatosis and NASH were 54.9% and 10.5%, respectively (41). Jimenez-Rivera et al., reported the prevalence of NAFLD at 85% in 97 obese children (42).

The higher NAFLD prevalence in obese children compared to children from the general population was expected due to the close relation between NAFLD and obesity (43). The incidence of pediatric NAFLD has grown significantly from 36 per 100000 persons in 2009 to 58.2 per 100000 persons in 2018, along with the occurrence of the obesity epidemic phenomenon (44).

Previous studies surveyed the relationship between NAFLD and other metabolic conditions like insulin resistance, diabetes mellitus, metabolic syndrome, and dyslipidemia (45-49); however, NAFLD in pediatrics is usually asymptomatic, and unspecific symptoms like abdominal pain, fatigue, and concentration difficulties are sometimes present (50). Pediatric NAFLD diagnosis in the early stages of the disease is challenging as most patients are asymptomatic (51, 52). This issue causes the prevalence of NAFLD to be underestimated.

Based on the result of our study, the prevalence of grades 1, 2, and 3 in obese children was 34%, 5.9%, and 0.6%, respectively. These findings imply the progression of NAFLD in obese children. Current knowledge recommends that NAFLD can progress to NASH, described as necroinflammation of the liver (53). NASH can lead to cirrhosis and hepatocellular carcinoma (HCC) (54, 55). The pattern of NAFLD progression in childhood is not understood well. It is unexplored whether NAFLD follows an aggressive pattern, as many children with NAFLD will experience cirrhosis in early adulthood (56).

Based on the results of our study, the prevalence of NAFLD in adults, men, and women was 36.9%, 33.8%, and 29.9%, respectively. The prevalence of NAFLD in Asian countries is estimated at 29.6%, which has risen in recent years (57). In Europe, a recent meta-analysis study showed that the NAFLD prevalence is 26.9% (58). The increasing prevalence of NAFLD in Asian countries like Iran can result from industrialization, improvements in socioeconomic status, sedentary lifestyles, and high-caloric diets (59-62). The prevalence of NAFLD is reported to be higher in urban areas than in rural regions (63-67). The rise in the prevalence of the NAFLD population is accompanied by an increased prevalence of obesity in Asian countries (68, 69). In addition, Asian people are more amenable to obesity complications even with similar body mass index (BMI) as their Western equivalents (70).

Limitations

There were several limitations in our study. The number of studies surveyed NAFLD in children and obese children was low, and we recommend conducting more studies among these patients. In addition, data still need to be included for some provinces of Iran. High heterogeneity was observed among studies, and random-effect model was used for the analysis; hence the results should be interpreted cautiously.

Conclusion

We showed a high prevalence of NAFLD among the Iranian population. Our meta-analysis also showed a higher prevalence of NAFLD in adults compared to global prevalence. This is an alarm sign for us to consider this disease more serious than past. Governments should establish screening protocols in society to prevent the consequent complications and decrease the disease's

burden. People also should change their sedentary lifestyle and have aerobic exercises.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

The authors declare that they have no competing interest.

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