A systematic review on Factors Associated with Non-Alcoholic Fatty Liver Disease (NAFLD) among Adolescents

Vishnu Raj.S [1], Maslinor Ismail [1], Wah-Kheong Chan [2] and Hazreen Abdul Majid [1,3,4]

[1] Centre for Population Health, Department of Social and Preventive Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, 50603, Malaysia.

[2] Gastroenterology and Hepatology Unit, Department of Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, 50603, Malaysia.

[3] Department of Gizi, Faculty of Public Health, Universitas Airlangga, East Java, 60115, Indonesia.

[4] School of Health and Rehabilitation Sciences, AECC University College, Bournemouth, BH5 2 DF, United Kingdom.

*Corresponding author: Maslinor Ismail, Centre for Population Health, Department of Social and Preventive Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, 50603, Malaysia. The corresponding author will handle the correspondence at all refereeing, publication stages, and post-publication.

Abstract:

Background & Aims: Non-Alcoholic Fatty Liver Disease (NAFLD) is a global public health risk. The occurrence of adolescent NAFLD coincides with high rates of overweight and obesity, with an unhealthy lifestyle also playing a role. Data on prevalence and factors contributing to NAFLD among Asian adolescents is lacking as most studies focus on adults. This systematic review aims to determine the prevalence and factors contributing to NAFLD among adolescents.

Methods: A systematic search was conducted using five (5) databases: Cochrane, PubMed, Scopus, Science Direct, EBSCO and grey literature. Two reviewers independently screened studies using predefined inclusion and exclusion criteria and performed data extraction. Assessment of methodological quality was completed using the Newcastle-Ottawa checklist.

Results: The quality of most studies were of high quality, with the majority reporting no association between lifestyle factors and NAFLD. A total of 6 studies were included in this systematic review. The prevalence of NAFLD among adolescents varied between 8.0 % (Fraser et al., 2007) in a study on 5586 adolescents aged 12–19 and 16.0% (Chen et al.,2009) in another survey of 1,724 adolescents aged 12–13 years old. Snacking habits and lack of physical activity had potential associations with adolescent NAFLD. Current evidence shows that lifestyle factor (Western dietary pattern) is associated with a higher risk of developing NAFLD among adolescents.

Conclusions: Lifestyle factors, including snacking habits and lack of physical activity, were associated with a higher risk of developing NAFLD among adolescents from high-income countries. The difference in the prevalence of NAFLD between countries with different incomes requires further investigation.

Keywords: adolescents, NAFLD, prevalence, lifestyle factors, systematic review

1. Introduction

Non-Alcoholic Fatty Liver Disease (NAFLD) is a global public health risk. The prevalence of NAFLD among adolescents ranges from 24 % to 42 % in Western countries and from 5% to 40% in Asian countries. (Amarapurkar et al., 2007; Anderson et al., 2015; Chan & Wong, 2022; Goh, Ho, & Goh, 2013; Le et al., 2021; Zobair M Younossi et al., 2016) The occurrence of adolescent NAFLD coincides with high rates of obesity, with an unhealthy lifestyle also playing a role. (Chan & Wong, 2022)

NAFLD is a chronic liver disease associated with hepatic fat accumulation (steatosis) without excessive alcohol consumption. It can manifest with or without hepatic inflammation and fibrosis. (Temple, Cordero, Li, Nguyen, & Oben, 2016) Simple or bland hepatic steatosis is the abnormal fat accumulation in more than 5% of hepatocytes without hepatocellular damage or fibrosis. However, many patients with hepatic steatosis progress to a more severe form of Non-Alcoholic Steatohepatitis (NASH). In NASH, steatosis co-exists with hepatocellular injury and inflammation, resulting in hepatic necrosis, fibrosis, cirrhosis, and a significantly increased risk of hepatocellular carcinoma. (Le et al., 2021; Nobili et al., 2014; Temple et al., 2016; Z. M. Younossi et al., 2016; Younossi et al., 2021; Xin Zhang et al., 2021)

NAFLD among adolescents is understudied, underdiagnosed, and perhaps undermanaged. The overall approach to screening, diagnosis, management, and follow-up has significant gaps, particularly throughout adolescence to adulthood. This systematic review aims to determine the prevalence and lifestyle factors, namely dietary patterns and physical activity, contributing to NAFLD among adolescents.

2. Materials and Methods

This systematic review on the prevalence of NAFLD among adolescents followed the criteria of PRISMA 2020 guidelines (Preferred reporting items for systematic reviews and meta-analyses) and PICOS (Participant, Intervention, Comparison, Outcomes, and Study Design) criteria. (Table 1) The review protocol (PROSPERO Registration number. CRD42022348042) has been registered with the International Prospective Register of Systematic Reviews.

A series of steps have been taken to perform the systematic review, including determining the preliminary research questions, defining the inclusion and exclusion criteria of studies, performing a comprehensive literature search, setting screening methods, data extraction, data analysis and evaluation of study quality using the Newcastle Ottawa method. (Lo, Mertz, & Loeb, 2014)

2.1. Eligibility Criteria

Case reports, case series, dissertations, editorials, conference abstracts and non-peer-reviewed articles were excluded. All other eligible articles were included. This systematic review includes articles

reporting on adolescents between 10-19 years old. Any additional articles looking at the prevalence of NAFLD in children below ten and young adults above 19 years of age were excluded.

Table 1. The PICOS criteria used to construct the systematic review

Criteria	Description
Participants	Adolescents (10 to 19 years old)
Intervention/Exposure	Adolescent with NAFLD
Comparison	Adolescent without NAFLD
Outcomes	The prevalence of NAFLD, lifestyle factors and factors associated with NAFLD
Study Design	Randomised controlled trial (RCT), non-RCT, cohort, and cross-sectional studies

2.2.Information Sources

A comprehensive literature search has been conducted on five (5) databases: Cochrane, PubMed, Scopus, Science Direct and EBSCO. The database search was supplemented with grey literature, internet searches (e.g., Google Scholar), reference lists of studies included in the systematic review, and manual tracking. The last search was run on 1st October 2022.

2.3. Search strategy

The investigation covered all published studies between 1st January 2002 and 30th June 2022, and only articles written in English were included. The search strategies included a combination of keywords shown below:

((Adolescence) OR (Young Adult) OR (Adolescent) OR (Teenager) AND (NAFLD)) OR ((Fatty Liver Disease) OR (Non-Alcoholic Fatty Liver Disease)) OR (Non-alcoholic steatohepatitis))

All retrieved records were saved to the Endnote X9 database, and duplicate records were removed either using Endnote or manually.

2.4. Selection Process

Articles were chosen in three stages: selection based on titles, abstract consideration, and full-text assessment. Bibliographical data such as the authors' name, publication year, title, study design, country, inclusion and exclusion criteria, subject recruitment, age, gender, and the study's duration and

dates were recorded. The selection process was done by two reviewers independently.

2.5. Data Collection Process

The data were then exported to Endnote version 9, a reference manager software, and full texts in PDF format. Two reviewers independently performed the data extraction and analysis, cross-checked, and reviewed and resolved any discrepancies with a third reviewer.

2.6. Data Items

To meet the review's objective (e.g., understanding the factors associated with adolescents' NAFLD), tools utilised for diagnosing or determining NAFLD, blood biomarkers such as ALT and non-invasive scoring methods using a biomarker, and histopathology examination were included. Other variables such as sociodemographic characteristics, physical activity level, sleeping time and nutritional status were also extracted. The results of the measurements and the statistical methods used to assess their associations were then recorded along with the related conclusion and recommendations. All outcomes compatible with the outcome domain were sought in each study.

2.7. Study Quality Assessment

Study quality was rated by two reviewers using the Newcastle-Ottawa Scale, which is recommended for quality assessment of cohort and case-control studies and has a maximum score of nine. Studies scoring 7 to 9, 4 to 6, and 0 to 3 are considered high, moderate, and low, respectively. (Lo et al., 2014) (Table 2) Two different reviewers assessed each study independently, and the study quality rating was compared. Two independent reviewers were involved in the evaluation to avoid performance bias. Any disagreements were discussed with a third reviewer. The bias assessment was reported in this systematic review.

Table 2: Newcastle-Ottawa Scale assessment of pooled studies. (12)

Study	Selection			Comparability		Outcome			Total
	Representativeness of exposed cohort	**Selection of nonexposed cohort**	**Ascertainment of exposure**	**Outcome not present at the start of the study**	**Study controls for factors associated**	**Study controls for any extra factor**	**Assessment of outcome**	**Length of follow-up**	**Adequacy of follow-up**	*
Fraser et al., 2007(Fraser, Longnecker, & Lawlor, 2007)	*	*	*	*	*	-	*	*	*	8
Chen et al., 2009(Fu, Chen, Li, Liu, & Wang, 2009)	*	*	*	*	*	-	*	*	*	8
Wendy et al., 2013(Oddy et al., 2013)	*	*	*	*	*	*	*	*	*	9
Welsh et al., 2013(Welsh, Karpen, & Vos, 2013)	*	*	*	*	*	-	*	-	-	6
Schwimmer et al,	*	*	*	*	*	*	*	*	*	9

2014(Schwimmer et al., 2006)										
Liu et al., 2018(Liu, Peng, Chen, & Sun, 2018)	*	*	*	*	*	*	*	*	*	9

Articles were assessed for risk of bias using the Newcastle-Ottawa scale. (12) *: The study has met the criteria for a domain of the Newcastle-Ottawa Scale; -: The criteria not me

2.8. Outcome Measures

Binary and continuous outcomes were gathered, and practical measures such as mean, mean difference, and odds ratios of the outcomes were used to synthesise and present results. The review also included other calculations/statistics, such as quartiles.

2.9. Synthesis Methods

The results were presented in tabulation and visual display of methods. A narrative synthesis of findings detailing the prevalence and the factors contributing to NAFLD among adolescents was performed.

3. Results

3.1. Study Selection

Initial searches on the Cochrane, PubMed, Scopus, Science Direct, and EBSCO databases using the above search terms yielded 10 777 potentially relevant articles. After removing duplicates, the titles and abstracts of remaining records were screened using broad eligibility criteria, in which papers were excluded if they were irrelevant to the research topic. This process yielded 14 potentially eligible articles. Retained articles then underwent full-text screening using the Newcastle-Ottawa method. The articles that did not meet the inclusion criteria were excluded. When appropriate, authors were contacted to supply missing details of their publication. Throughout the screening and selection process, any discrepancies were resolved through discussion. The process is summarised in Figure 1 below.

3.2. Study Characteristics

A total of six (6) published studies with a total population of 19800 adolescents have been reviewed. The studies were conducted in four countries, as in Table 3. Five studies were conducted in HIC from the included research, and only one was shown in MIC. A total of two (33.2%) studies defined NAFLD among adolescents using a biomarker, the serum alanine aminotransferase (ALT) level, which is a biomarker commonly used in determining suspected NAFLD in extensive epidemiological studies. (13, 16) In one (16.6%) of the studies, NAFLD was confirmed histologically during an autopsy, while in three studies (49.8%), NAFLD was diagnosed based on sonographic evidence of a fatty liver.

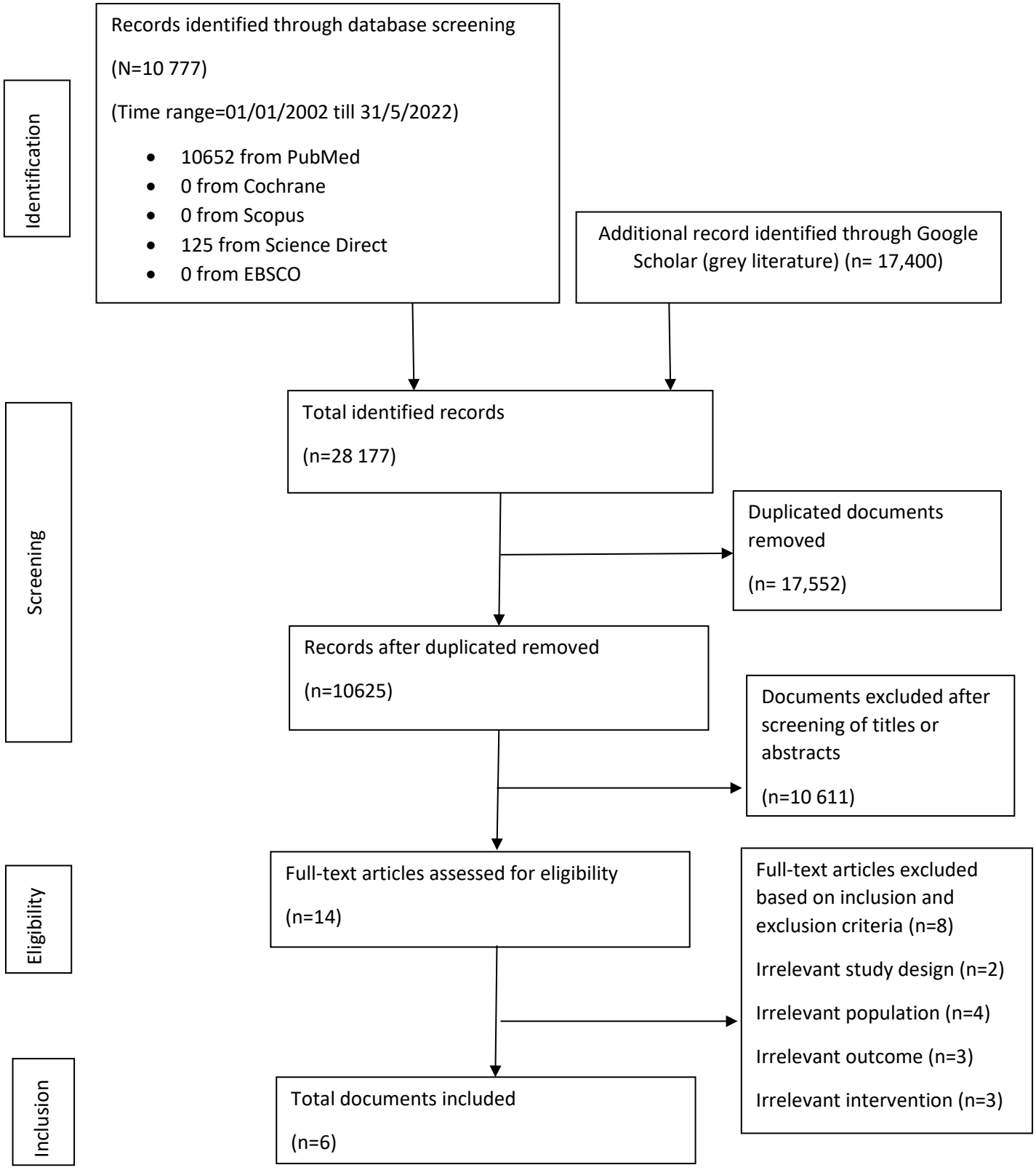

Figure 1: The Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) flow diagram for searching, screening and selection processes.

Table 3: Characteristics of the included studies

Author, Year (References)	Type of Study	Country (HIC, MIC, LIC)	Population	Sample	Quality Score (NOS)	Diet Measure	Diet Outcome	PA Measure	PA Outcome	Instruments/Tools used in determining NAFLD	Conclusion
Fraser et al., 2007(Fraser et al., 2007)	Cross section	USA (HIC)	12–19 years old	5586	High	NA	NA	NA	NA	Suspected NAFLD defined as elevated ALT (defined as ALT>30 U/L)	Prevalence of suspected NAFLD by elevated ALT was present in 8·0% of the study population.
Chen et al., 2009(Fu et al., 2009)	Cross section	Taiwan (HIC)	12 or 13 years old	1724	High	NA	NA	NA	NA	NAFLD was diagnosed based on sonographic evidence of a fatty liver and testing negative for serum HBsAg and anti-HCV antibody	The prevalence of NAFLD increased progressively from 16.0% in the standard group to 50.5% in the overweight group and 63.5% among the obese subjects. The ALT abnormality and elevated non-HDL cholesterol is all associated with adolescent NAFLD.
Wendy et al., 2013(Oddy et al., 2013)	Cohort Study	Australia (HIC)	14-17 years old	995	High	FFQ	Healthy and Western dietary pattern score	OQ	PA	NAFLD was diagnosed based on sonographic evidence of a fatty liver.	The prevalence of NAFLD is 15.2 %. A higher Western dietary pattern score is associated with a greater risk of NAFLD (odds ratio (OR) 1.59; 95 % confidence interval (CI) 1.17 – 2.14; P < 0.005)
Welsh et al., 2013(Welsh et al., 2013)	Cross section	USA (HIC)	12–19 years old	12,714	Moderate	NA	NA	NA	NA	Suspected NAFLD defined as elevated ALT in overweight or obese children (body mass index [BMI] for age and sex (BMI >85th percentile).	Prevalence of suspected NAFLD is 11% of adolescents and one-half of obese males (NAFLD prevalence rate of 3.9% in 1998-1994 and 10.7% in 2007-2008)
Schwimmer et al, 2014(Schwimmer et al., 2006)	Cross section	USA (HIC)	2-19 years old	742	High	NR	NR	NR	NR	NAFLD was confirmed histologically (autopsy)	The prevalence of NAFLD is 9.6%.
Liu et al., 2018(Liu et al., 2018)	Cross section	China (MIC)	16-23 years old	1875	High	FFQ	Traditional Chinese, Western and High-energy dietary pattern score	OQ	PA	NAFLD diagnosis was defined as individuals whose ultrasound examination disclosed hepatic steatosis at any stage in the absence of excess intake of alcoholic beverages.	The prevalence of NAFLD is 13.5%. After adjustment for several potential confounders, participants in the highest quartile of the traditional Chinese pattern scores had lower OR for NAFLD (OR=0.726; 95% CI: 0.383–0.960, P<0.05) than did those in the lowest quartile, whereas those in the highest Western pattern score had greater OR for NAFLD (OR=1.197; 95% CI: 1.013– 1.736, P<0.01) than those in the lowest quartile. The Western pattern score was associated with a higher risk of NAFLD (OR=1.197; 95% CI: 1.013-1.736, P<0.01). No statistically significant link was found between the high-energy pattern and the risk of NAFLD. The traditional Chinese dietary pattern was associated with a lower risk, whereas the Western dietary pattern was associated with a higher risk of NAFLD.

Note: USA, United States of America; NOS, Newcastle-Ottawa Scale; NR, Not Reported; NA, Not Available; MVPA, Moderate to Vigorous Physical Activity; BMI, Body Mass Index; FFQ, Food Frequency Questionnaire; PA, Physical Activity; OQ, Other Questionnaire; HIC, High Income Country; MIC, Middle Income Country

3.3.Quality of included studies

The quality rating of the six (6) included studies varied according to the relevant Newcastle Ottawa Study Quality Assessment Tools assessment results. A total of 5 (83.4%) studies were graded as high quality, and one (16.6%) was graded as moderate quality. (12)

3.4. The Prevalence of NAFLD

The prevalence of NAFLD among adolescents varied between 8.0 % (Fraser et al., 2007) in a study on 5586 adolescents aged 12–19 years old and 16.0% (Chen et al.,2009) in a study on 1,724 adolescents aged 12–13 years old (Table 3). Only two studies reported the association between lifestyle factors (dietary intake and physical activity) and NAFLD.

3.5. Association between Various Lifestyle Factors with NAFLD

3.5.1. Association between Physical Activity and NAFLD

Two studies by Wendy et al. and Liu et al. (Table 4) reported the association between physical activity and NAFLD. The two studies used the International Physical Activity Questionnaire (IPAQ) or the Physical Activity Questionnaire for Children (PAC-C) to measure physical activity. The physical activity level was categorised into low (less than one time per week), moderate (1-3 times a week) and high (more than four times a week). Both studies reported that physical activity was inversely associated with NAFLD suggesting that physical activity could decrease the risk of developing NAFLD. (Liu et al., 2018; Oddy et al., 2013)

Table 4: Summary of association between physical activity and NAFLD

Author, year	Association	p-value
Wendy et al., 2013	**Physical Activity Level** - Low (Yes NAFLD, n: 13(9.0%)) vs (No NAFLD, n:79(9.7%)) - Moderate (Yes NAFLD, n: 97(66.9%)) vs (No NAFLD, n:447 (54.9%)) - High (Yes NAFLD, n: 35 (24.1%)) vs (No NAFLD, n:288 (35.4%))	0.020
Liu et al., 2018	**Physical Activity Level** - Low (Yes NAFLD, n: 168 (76.0%)) vs (No NAFLD, n: 478 (33.7%)) - Moderate (Yes NAFLD, n: 42 (19.0%)) vs (No NAFLD, n: 761 (53.7%)) - High (Yes NAFLD, n: 11 (5.0%)) vs (No NAFLD, n:179(12.6%))	<0.001

Abbreviations: Categorical variables are presented as sum and percentages, and continuous variables are presented as mean ± SD, NAFLD=non-alcoholic fatty liver disease, $p < 0.05$.

3.5.2. Association between dietary intake and NAFLD

Two studies by Wendy et al. and Liu et al. (Table 5) reported the association between dietary intake and NAFLD. In the studies considered in this review, nutritional patterns were grouped into three categories: healthy, Western and local (Chinese) dietary pattern scores. In both studies, the healthy and Chinese dietary habits did not correlate with the odds of NAFLD. However, a higher score for the Western dietary pattern was positively associated with the odds of NAFLD in both studies. (Liu et al., 2018; Oddy et al., 2013)

The study by Wendy et al. reported that a Western dietary pattern score at 14 years was associated with a higher risk of NAFLD at 17 years. However, after adjusting for body mass index at 14 years, these associations were no longer significant. A healthy dietary pattern at 14 years appeared protective against NAFLD at 17 years in centrally obese adolescents, while a Western dietary pattern was associated with an increased risk of NAFLD. (Oddy et al., 2013)

Table 5 below shows the summary of association between dietary intake and NAFLD. The odds ratio (OR) and 95% confidence interval (CI) were estimated for the dietary pattern adherence scores using logistic regression analysis in both studies. The study by Liu et al. reported significant differences in whole grain, tuber, and vegetable intake between the traditional Chinese and Western patterns (p-value =0.5). Furthermore, when compared to adolescents in the lowest quartile, those in the highest quartile for whole grains intake had a lower OR for NAFLD (OR=0.72; 95% CI: 0.61-0.98; P.05), whereas those in the higher quartile for red meat and soft drink consumption had a higher OR for NAFLD (OR=1.34; 95% CI: 1.06-1.72; OR=1.69; 95% CI: 1.34-2.56).

Table 5: Summary of association between dietary intake and NAFLD

Author, year	Association	p-value
Wendy et al., 2013	- Western dietary pattern score (OR: 1.59; 95 % CI: 1.17 – 2.14)	< 0.005
	- Healthy dietary pattern score (OR 0.63; 95 %CI 0.41 – 0.96)	0.033
Liu et al., 2018	- Western dietary pattern score OR=1.197; 95% CI: 1.013–	<0.01
	- 1.736,)	
	- Chinese dietary pattern score (OR=0.726; 95% CI: 0.383–0.960)	<0.05

Abbreviations: OR =odds ratio, CI =confidence interval, NAFLD=non-alcoholic fatty liver disease, p< 0.05.

3.5.3. Association between smoking habit and NAFLD.

The studies by Liu et al. observed the association between smoking habits and NAFLD. The study by Liu et al. grouped smoking status by smoker and non-smoker. A total of 7% of this study's participants are smokers. Of the 7% of participants that smoked, only 4.5% had NAFLD, and from the 93% of participants that do not smoke, only 13.2% had NAFLD (P=0.082). Hence, no statistically significant association was found between smoking habits and the risk of NAFLD. (Liu et al., 2018)

4. Discussion

To our knowledge, based on the search, data on prevalence and factors contributing to NAFLD among adolescents is lacking as most studies have focused mainly on adults. It has been presumed that the prevalence of NAFLD is low among adolescence. The prevalence of NAFLD among adolescents has been reported to be between 8.0% and 16.0 %. (13, 14) Based on this systematic review, the prevalence of NAFLD among adolescents with adiposity (overweight and obesity) is higher than the standard group. (15, 16)

The results of the reviewed studies indicate that a higher physical activity level seems to be an essential factor that can have beneficial effects for preventing long-term gain in weight, with adiposity being a significant risk factor for NAFLD. Both studies by Wendy et al. and Liu et al. reported that physical activity could decrease the risk of developing NAFLD. (Liu et al., 2018; Oddy et al., 2013)

The healthy Chinese food pattern was mainly characterised by a high intake of whole grains, tubers, vegetables, fresh fruits, salted/ preserved eggs, soybean and its products, bean, fruit or vegetable juice, and tea. (Abdullah, Teo, & Foo, 2016; Liu et al., 2018) The Western dietary pattern was characterised by high red meat, processed and preserved meat, fish and shrimp, seafood, dairy products, western fat food, snack food, carbonated beverages, alcoholic beverages, and coffee. (Abdullah et al., 2016; Liu et al., 2018) The present study found a positive association between adolescents' Western dietary patterns and NAFLD. (Liu et al., 2018) In the study by Liu et al., another pattern was named as high-energy nutritional pattern, which is characterised to have a high consumption of mushrooms, poultry and organs, freshwater fish and shrimp, eggs, fat/oils, nuts, snacks, chocolates, and carbonated beverages. Sugar-sweetened beverages (SSB), carbonated soft drinks, or sodas containing a high amount of added sugar is associated with a higher risk of obesity, insulin resistance and inflammation. Furthermore, the metabolism of SSB is not controlled by insulin. The intake of SSB also increases hepatic gluconeogenesis and de novo lipogenesis (DNL). (Xinrong Zhang et al., 2020) The SSB intake also inhibits fatty acid catabolism by lowering liver beta-oxidation activity. In SSB, 50% of the sucrose molecule is made up of glucose, and the fructose content of high-fructose corn syrup is nearly identical. Recent research suggests that glucose may promote fatty liver accumulation by being converted to fructose in the liver via the Embden-Meyerhof pathway. (24) No statistically significant association was found between the high-energy pattern and the risk of NAFLD. A Western diet increases the risk of NAFLD. In contrast, a healthy dietary pattern (a diet with high dietary fibre, antioxidant and phytonutrient-rich vegetables and fruits) reduces the risk of NAFLD (acts as a protective agent against NAFLD) among adolescents. In these two studies, adolescents at risk of NAFLD may be advised to change dietary habits during the entrance examination, such as limiting the intake of high-energy foods. (Liu et al., 2018; Oddy et al., 2013)

The other lifestyle factors, such as sleeping time and smoking habits, were investigated by one study with non-statistically significant results. On the other hand, the included studies did not evaluate sleeping time. (Liu et al., 2018)

A total of two different classification systems (ALT biomarker and liver autopsy for histological assessment) were used to diagnose NAFLD, with somewhat different cut-offs across the systems. Future reviews should consider subgroup analysis or meta-analysis. Since the associations observed

between lifestyle factors and NAFLD development may result from shared genetic and environmental factors, the Mendelian randomisation meta-analysis approach may be employed to establish a more robust causal inference.

The usual phenomenon of unequal distributions of research effort in health (a higher number of published research on diseases more prevalent in rich countries than poorer countries) is not observed in the current study. Population difference exists in the form of NAFLD prevalence in the study by Wendy et al., which is more common, severe, and of earlier onset in Caucasians than Asians. Thus, one would expect that more research studies originate from countries with higher GDPs. In short, we postulate that it could manifest the trade-off between quantity and quality for a well-developed country like the USA. Nevertheless, this hypothesis has to be supported by a more detailed ecological study capturing all the publications related to adolescent NAFLD from countries such as the USA or other countries in the future.

Strengths

It is hoped that the findings of this study review will also provide insight into the development of clinical practice guidelines that will aid in improving adolescent health, increase awareness and understanding of NAFLD, and assist stakeholders in the decision-making process by providing evidence-based data.

Based on the systematic search, no cross-sectional study has been conducted to observe the relationship between lifestyle factors and NAFLD among adolescents in LIC. In addition, only one study has examined adolescents' longitudinal relationship between lifestyle factors and NAFLD. Conducting a longitudinal study looking into the factors associated with NAFLD among adolescents will give public health value to the importance of physical activity and a balanced diet in the prevention of NAFLD among adolescents.

Limitations

This present systematic review has limitations that must be discussed when interpreting the results. The studied country is limited to only HIC as fewer studies focused on NAFLD among adolescents in MIC and LIC. This systematic review predominantly includes studies in HICs such as the USA, Australia and Taiwan and only one MIC, China. This is possible because these countries have a more significant number of health and research professionals, with affiliated professional associations having research funding and clinical interest in adolescent NAFLD. The USA is recognised as the country that publishes the most clinical papers. The most commonly detected problem was using hospital or clinical facility patients as controls in a few studies. Hospital controls may have a higher prevalence of NAFLD than the actual case source population. Recruitment of NAFLD patients from the hospital will also be a limitation because NAFLD patients referred to and seen in the hospital may have a more severe form of liver disease than the general population.

All the included studies differ considerably in terms of the sampled population, with a few randomly recruiting from the general population and others conveniently recruiting by clinical population. Sample size also varied substantially between studies, ranging from 742 to 12,714, highlighting that possible low statistical power may occur in studies of typical sample size, leading to a false positive result.

From the six included studies, the USA was the leading contributor (50.0% of the studies with a total of 19042 participants(n)), followed by Australia (16.6%, n:995), China (16.6%, n:1875), and Taiwan (16.6%, n:1724). Few other external factors are causing less research on adolescent NAFLD in MIC and LIC. The external factors include the country's gross domestic product (GDP), the number of healthcare professionals, population size, and publications in public health nutrition, gastroenterology and hepatology.

5. Conclusions

This systematic review summarises the factors associated with non-alcoholic fatty liver disease (NAFLD) among adolescents. A healthier lifestyle (dietary pattern and physical activity) was associated with minimising the risk of developing NAFLD among adolescents. The difference in the prevalence of NAFLD among adolescents can be influenced by income level. The increasing prevalence of NAFLD foreshadows the future burden of NAFLD among adolescence and has a substantial socioeconomic impact globally. As a result, proactive interventional measures to reduce obesity and presumably increase physical activity should be implemented.

Funding: This work received no grant from any funding agencies in public, commercial, or not-for-profit sectors.

Declaration of Interests: The authors declare that they have no competing interests.

Authors' Contribution: V.R.S. and H.A.M. conceptualised and designed the protocol and search terms. M.I. and V.R.S. conducted screening and data extraction. V.R.S. wrote the paper. All four authors critically reviewed the manuscript draft and approved the final version.

Acknowledgements: Prof. Dr Hazreen Bin Abdul Majid, Prof. Dr Chan Wah Kheong, Dr Maslinor Binti Ismail, Dr Munazieraa Binti Ab Aziz and Dr Ng Ah Kah are gratefully acknowledged for their guidance and support throughout this work.

6. References

Abdullah, N.-F., Teo, P. S., & Foo, L. H. J. N. (2016). Ethnic differences in the food intake patterns and its associated factors of adolescents in Kelantan, Malaysia. *8*(9), 551.

Amarapurkar, D. N., Hashimoto, E., Lesmana, L. A., Sollano, J. D., Chen, P. J., Goh, K. L., . . . hepatology. (2007). How common is non-alcoholic fatty liver disease in the Asia–Pacific region and are there local differences? *, 22*(6), 788-793.

Anderson, E. L., Howe, L. D., Jones, H. E., Higgins, J. P., Lawlor, D. A., & Fraser, A. J. P. o. (2015). The prevalence of non-alcoholic fatty liver disease in children and adolescents: a systematic review and meta-analysis. *10*(10), e0140908.

Chan, W. K., & Wong, V. W. S. J. L. I. (2022). Meaning of non-overlapping patients between the MAFLD and NAFLD definitions. In (Vol. 42, pp. 271-273): Wiley Online Library.

Fraser, A., Longnecker, M. P., & Lawlor, D. A. J. G. (2007). Prevalence of elevated alanine aminotransferase among US adolescents and associated factors: NHANES 1999–2004. *133*(6), 1814-1820.

Fu, C.-C., Chen, M.-C., Li, Y.-M., Liu, T.-T., & Wang, L.-Y. J. A. A. o. M. S. (2009). The risk factors for ultrasound-diagnosed non-alcoholic fatty liver disease among adolescents. *38*(1), 15.

Goh, S. C., Ho, E. L., & Goh, K. L. (2013). Prevalence and risk factors of non-alcoholic fatty liver disease in a multiracial suburban Asian population in Malaysia. *Hepatol Int, 7*(2), 548-554. doi:10.1007/s12072-012-9359-2

Le, M. H., Yeo, Y. H., Li, X., Li, J., Zou, B., Wu, Y., . . . Nguyen, M. H. (2021). 2019 Global NAFLD Prevalence: A Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol*. doi:10.1016/j.cgh.2021.12.002

Liu, X., Peng, Y., Chen, S., & Sun, Q. J. M. (2018). An observational study on the association between major dietary patterns and non-alcoholic fatty liver disease in Chinese adolescents. *97*(17).

Lo, C. K.-L., Mertz, D., & Loeb, M. J. B. m. r. m. (2014). Newcastle-Ottawa Scale: comparing reviewers' to authors' assessments. *14*, 1-5.

Nobili, V., Liccardo, D., Bedogni, G., Salvatori, G., Gnani, D., Bersani, I., . . . Raponi, M. (2014). Influence of dietary pattern, physical activity, and I148M PNPLA3 on steatosis severity in at-risk adolescents. *Genes & Nutrition, 9*(3), 392. doi:10.1007/s12263-014-0392-8

Oddy, W. H., Herbison, C. E., Jacoby, P., Ambrosini, G. L., O'sullivan, T. A., Ayonrinde, O. T., . . . ACG. (2013). The Western dietary pattern is prospectively associated with nonalcoholic fatty liver disease in adolescence. *108*(5), 778-785.

Schwimmer, J. B., Deutsch, R., Kahen, T., Lavine, J. E., Stanley, C., & Behling, C. J. P. (2006). Prevalence of fatty liver in children and adolescents. *118*(4), 1388-1393.

Temple, J. L., Cordero, P., Li, J., Nguyen, V., & Oben, J. A. J. I. j. o. m. s. (2016). A guide to non-alcoholic fatty liver disease in childhood and adolescence. *17*(6), 947.

Welsh, J. A., Karpen, S., & Vos, M. B. J. T. J. o. p. (2013). Increasing prevalence of nonalcoholic fatty liver disease among United States adolescents, 1988-1994 to 2007-2010. *162*(3), 496-500. e491.

Younossi, Z. M., Koenig, A. B., Abdelatif, D., Fazel, Y., Henry, L., & Wymer, M. (2016). Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology, 64*(1), 73-84. doi:10.1002/hep.28431

Younossi, Z. M., Koenig, A. B., Abdelatif, D., Fazel, Y., Henry, L., & Wymer, M. J. H. (2016). Global epidemiology of nonalcoholic fatty liver disease—meta-analytic assessment of prevalence, incidence, and outcomes. *64*(1), 73-84.

Younossi, Z. M., Rinella, M. E., Sanyal, A. J., Harrison, S. A., Brunt, E. M., Goodman, Z., . . . Loomba, R. J. H. (2021). From NAFLD to MAFLD: implications of a premature change in terminology. *73*(3), 1194-1198.

Zhang, X., Goh, G. B. B., Chan, W. K., Wong, G. L. H., Fan, J. G., Seto, W. K., . . . Lee, H. W. J. L. I. (2020). Unhealthy lifestyle habits and physical inactivity among Asian patients with non-alcoholic fatty liver disease. *40*(11), 2719-2731.

Zhang, X., Wu, M., Liu, Z., Yuan, H., Wu, X., Shi, T., . . . Zhang, T. J. B. o. (2021). Increasing prevalence of NAFLD/NASH among children, adolescents and young adults from 1990 to 2017: a population-based observational study. *11*(5), e042843.