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Global and national prevalence of nonalcoholic fatty liver disease in adolescents: An analysis of the global burden of disease study 2019

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Abstract

Background and Aims: NAFLD in adolescents is an increasing health crisis worldwide, but its exact global, continental, and national prevalence, its relationship with other metabolic conditions, and the human development index (HDI) globally are not known.

Approach and Results: We analyzed data from the Global Burden of Disease Study 2019 to compare global, continental, and national prevalence rates of adolescent NAFLD and associations with other metabolic conditions and HDI. The global NAFLD prevalence in adolescents increased from 3.73% in 1990 to 4.71% in 2019 (a relative increase of 26.27%). The prevalence for the male and female populations was 5.84% and 3.52% in 2019, respectively. The Oceanian and North American continents had the highest adolescent NAFLD prevalence (median: 6.54% and 5.64%, respectively), whereas Europe had the lowest prevalence (median: 3.98%). South America and North America had the highest relative increase in adolescent NAFLD prevalence from 1990 to 2019 (median: 39.25% and 36.87%, respectively). High body mass index and type 2 diabetes mellitus increased significantly in adolescents worldwide. However, only high body mass index and not type 2 diabetes mellitus correlated with NAFLD

Abbreviations: BMI, body mass index; HDI, human development index; IQR, interquartile range; prev, prevalence; rel, relative; SEV, summary exposure value; T2DM, type 2 diabetes mellitus.

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prevalence in adolescents globally. Countries with a higher HDI had larger increases in adolescent NAFLD prevalence from 1990 to 2019 although countries with the highest HDI (HDI: > 0.9) had the lowest NAFLD prevalence in 2019.

Conclusions: NAFLD in adolescents is an increasing health problem on all continents. Improving environmental factors, including lifestyle but also healthcare policies, can help to prevent NAFLD from developing in children and adolescents and help to improve outcomes in children and adolescents with NAFLD.

INTRODUCTION

Pediatric NAFLD encompasses NAFL, its more severe form NASH, and liver fibrosis up to cirrhosis.[1–3] It is an increasing global health problem, which has far-reaching implications for the affected subjects for their childhood and adolescence but also their adulthood.[1,4] Children and adolescents with NAFLD are more likely to have cardiovascular risk factors and metabolic syndrome than controls.[5] Children, adolescents, and young adults with biopsy-confirmed NAFLD also have significantly higher rates of overall cancer, liver, and cardiometabolic-specific mortalities.[6] In adults, NAFLD is now the second most common indication for liver transplantation in some parts of the world, including the US.[7,8]

Although an increasing global prevalence rate of pediatric NAFLD has been documented,[9] an updated global comparison of NAFLD prevalence rates in adolescents between countries and particularly continents—including male and female populations—is lacking. Similarly, a relationship between NAFLD with obesity and type 2 diabetes mellitus (T2DM) has been described in adolescents in some areas,[10] but a global assessment by countries and continents is missing. Although adult studies indicate a higher prevalence of metabolic conditions with higher human development index (HDI),[11,12] a possible relationship with the HDI has not been investigated yet for NAFLD in adolescents on a global level.

In this study, we aimed to analyze data from the Global Burden of Disease Study 2019 to compare global, continental, and national prevalence rates of NAFLD in adolescents to correlate NAFLD prevalence with other metabolic conditions, that is, high body mass index (BMI) and T2DM prevalence in adolescents on a global level and to assess for possible associations of NAFLD prevalence with HDI values. We hypothesized that Asian and North American countries had the highest adolescent NAFLD prevalence and African countries the lowest. Furthermore, we expected significant correlations of NAFLD with obesity and T2DM in adolescents, as all conditions are related to metabolic dysfunction.[2,13] Finally, we hypothesized that higher HDIs were significantly correlated with higher NAFLD prevalence rates in adolescents, as adult studies have shown increasing rates of overweight and obesity to correlate with increasing HDIs.[11,12]

METHODS

Data sources

This study is based on data obtained from the Global Burden of Disease Study 2019 (https://vizhub.healthdata.org/gbd-results/), which was overseen by the Institute for Health Metrics and Evaluation.[14–16] The Global Burden of Disease Study 2019 estimates disease parameters for 369 diseases and injuries across various age groups for male and female populations in 204 countries and territories. The prevalence rates were based on a systematic review of published studies, searches of government and international organization websites, published reports, primary data sources, such as the Demographic and Health Surveys, and contributions of data sets by the Global Burden of Disease collaborators. A total of 86,249 sources were used for the Global Burden of Disease Study 2019, including 19,773 reporting prevalence.[15] As first introduced by the Global Burden of Diseases, Injuries, and Risk Factors Study 2015, summary exposure values (SEVs) quantify the risk exposure to certain risk factors, which allows comparisons over time and across places.[17] The SEV is the relative risk-weighted prevalence of exposure[17] and is effectively excess risk-weighted prevalence for a specific risk factor, such as high BMI.[18] It is, hence, an indirect measure of overweight and obesity. It ranges from 0% (no excess risk for a population) to 100% (highest risk level).[17] The World Health Organization defines the pediatric age range from birth to 19 years of age, with adolescence being the phase of life between childhood and adulthood, from ages 10 to 19.[19] Of the pediatric age ranges, the NAFLD prevalence was

available in the Global Burden of Disease Study 2019 for the adolescent age range of 15–19 years only,[14] and we, therefore, used these data for our analysis. Given the global nature of the study, the methodologies varied between different countries on how the NAFLD prevalence was determined, for example, liver enzyme elevation, imaging studies, and/or liver biopsy. To overcome the intrinsic variability due to the different approaches and possible data scarcity in certain geographical areas, the Global Burden of Disease Study 2019 used an integrative metaregression modeling tool, DisMod-MR 2.1.[15] This tool comprehensively incorporates all dimensions of health data, accounts for temporal and spatial differences and differences in data sources and biases, corrects for inconsistencies, and analyzes disease parameters, including prevalence and SEVs within the same computational framework, which facilitates comparison across geographies, over time, and across disease categories.[15,20] For the disease prevalence comparisons per HDI, we assigned each country their respective 2019 HDI value and HDI group, which we obtained from the "United Nations Development Program"[21] (Supplemental Table S1, http://links.lww.com/HEP/F686). The HDI is composed of scores of the 3 basic dimensions of human development per the United Nations Development Program, that is, a long and healthy life, knowledge, and a decent standard of living.[21] The HDI can be between 0 and 1, with 1 being consistent with the highest level of human development. Countries are generally grouped into low (HDI: < 0.55), medium (HDI: $0.55 - < 0.70$), high (HDI: $0.70 - < 0.80$), and very high human development (HDI: ≥ 0.80) per their HDI.[21]

Statistical analyses

Results are expressed as the median and interquartile range (IQR) unless stated otherwise. Two groups were compared using the Wilcoxon-Whitney-Mann rank-sum test. Three or more groups were compared using the Kruskal-Wallis test; if the Kruskal-Wallis test was statistically significant, a pairwise Wilcoxon-Whitney-Mann rank-sum test was performed with Bonferroni correction, and significant adjusted p values were shown as indicated in the figures. All statistical tests were 2-sided. To correlate various variables, Pearson correlations were conducted, and p values were adjusted with the Bonferroni correction for multiplicity as indicated. For all analyses, p values below 0.05 were considered statistically significant. Statistical analyses were performed using R statistical software, version 2022.07.1 for Mac 2020, the R Foundation for Statistical Computing.

RESULTS

Countries on the Arabian Peninsula and African and Asian countries bordering the Mediterranean Sea have the highest prevalence of NAFLD in adolescents worldwide

In 2019, the countries with the highest prevalence of NAFLD in adolescents were countries in Northern Africa and Western Asia surrounding the Mediterranean Sea and countries on the Arabian Peninsula (Figure 1A, Supplemental Table S1, http://links.lww.com/HEP/F686). In particular, Egypt (18.44% NAFLD prevalence in adolescents), Qatar (17.04%), Kuwait (15.67%), United Arab Emirates (14.97%), and Saudi Arabia (14.39%) had the highest prevalence rates worldwide. Similarly, countries with the highest prevalence of NAFLD in adolescent males were Egypt (22.82%), Qatar (19.00%), Kuwait (17.91%), United Arab Emirates (17.19%), and Saudi Arabia (16.30%) (Supplemental Figure S1A, http://links.lww.com/HEP/F685). The same 5 countries had also the highest prevalence in adolescent females, despite having overall lower prevalence rates compared with adolescent males: Qatar (14.08% NAFLD prevalence in adolescent females), Egypt (13.68%), Kuwait (13.28%), United Arab Emirates (12.57%), and Saudi Arabia (11.99%) (Supplemental Figure S1B, http://links.lww.com/HEP/F685). Furthermore, countries with the highest relative differences in NAFLD prevalence between adolescent males and females comprised South Africa (adolescent females with a 68.13% lower relative NAFLD prevalence than adolescent males), next Japan (62.78%), Ukraine (57.70%), Indonesia (56.22%), Argentina (55.51%), China (53.70), the Russian Federation (53.42%), and Australia (50.85%), among others (Figure 1B). In contrast, countries with the highest absolute differences in NAFLD prevalence between adolescent males and females included Egypt (9.14% higher prevalence in males), followed by South Africa (6.41%), American Samoa (5.38%), Cook Islands 5.11%, Guam (5.05%), and Qatar (4.92%) (Supplemental Figure S1C, http://links.lww.com/HEP/F685).

The global prevalence of NAFLD in adolescents increased steadily between 1990 and 2019

The NAFLD prevalence in adolescents on a global level increased consistently from 3.73% in 1990 to 4.71% in 2019 (Pearson correlation coefficient $R = 1.00$ and $p < 0.001$), which corresponds to a relative increase of 26.27% (Figure 2A). This also holds true for adolescent males (4.68% prevalence in 1990 and 5.84% in 2019; R

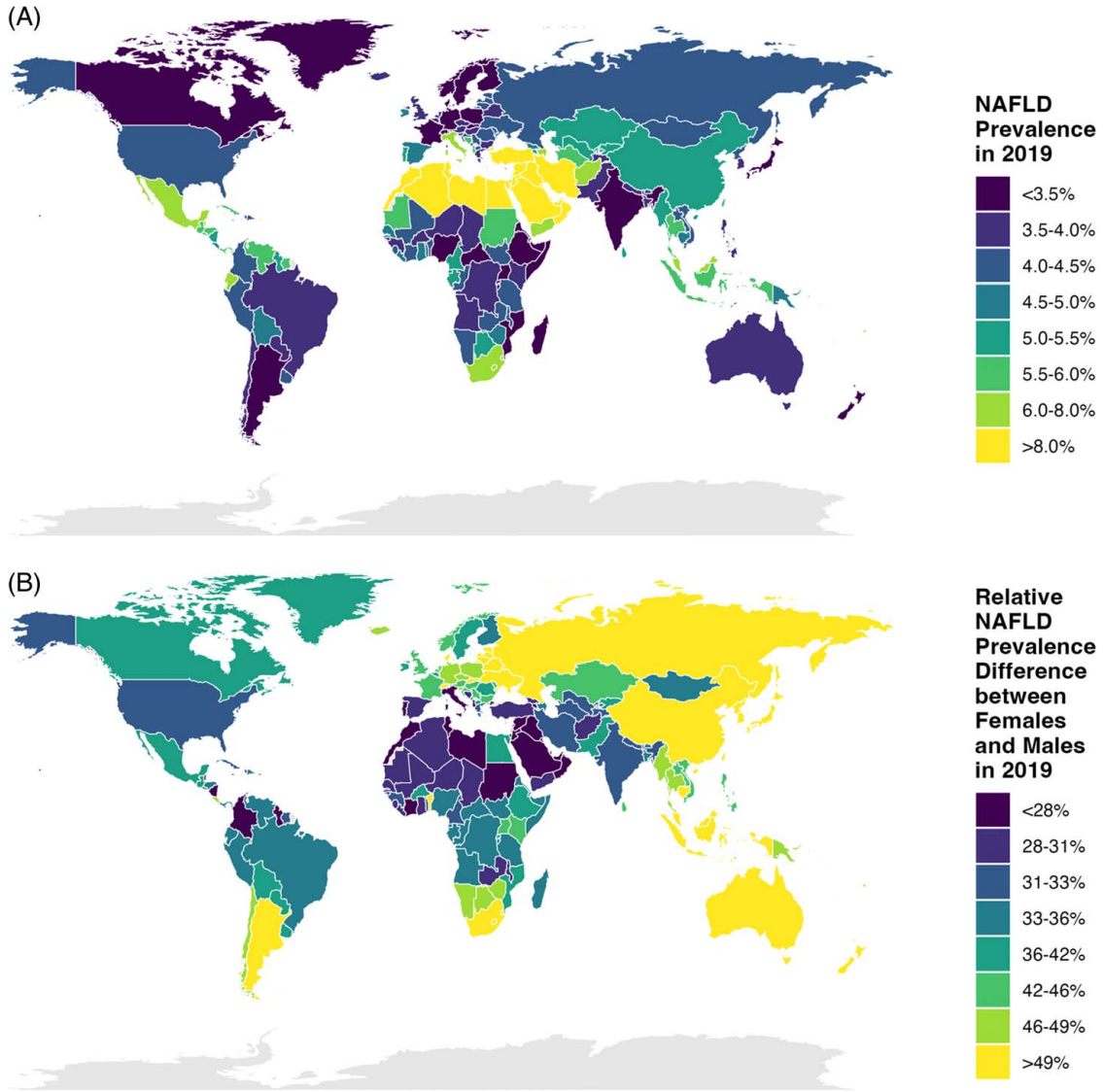

FIGURE 1 Countries on the Arabian Peninsula and African and Asian countries bordering the Mediterranean Sea have the highest global prevalence of NAFLD in adolescents. Countries and territories, n = 202. (A) Prevalence of adolescent NAFLD per country and territory in 2019. (B) Relative prevalence difference of adolescent NAFLD between female population and male population per country and territory in 2019.

= 0.99 and $p < 0.001$; and relative increase of 24.65%) and adolescent females equally (2.74% prevalence in 1990 and 3.52% in 2019; $R = 0.99$, $p < 0.001$, and a relative increase of 28.33%) (Figure 2A). The relative annual change in global NAFLD prevalence was positive in the entire adolescent population (averaged 0.81%) and for adolescent males (averaged 0.76%) and females (averaged 0.86%) separately in each year between 1990 and 2019 (Figure 2B). Despite fluctuations, there was a significant downward trend of the relative annual increase in NAFLD for the total and female adolescent populations between 1990 and 2019 (0.69% relative annual increase for 1990–1991 and 0.57% for 2018–2019, $R = -0.52$, and $p = 0.012$ for total population; 1.05% relative annual increase for 1990–1991, 0.56% for 2018–2019, $R = -0.48$, and $p = 0.023$ for adolescent females), but the trend was not significant for adolescent males (0.79% relative annual increase for 1990–1991, 0.58% for 2018–2019, $R = -0.15$, and $p = 1.00$ for adolescent males) (Figure 2B).

Similar to 2019, the countries with the highest prevalence of NAFLD in adolescents in 1990, 2000, and 2010 were the Arabian Peninsula, and African and Asian countries bordering the Mediterranean Sea (Supplemental Figure S2A–C, http://links.lww.com/HEP/F685). Egypt (15.54%, 17.53%), Qatar (13.90%, 14.42%), Kuwait (12.45%, 13.10%), United Arab Emirates (11.14%, 11.52%), and Bahrain (11.13%, 11.53%) were the countries with the highest prevalence rates globally in 1990 (Supplemental Figure S2A, http://links.lww.com/HEP/F685) and 2000 (Supplemental Figure

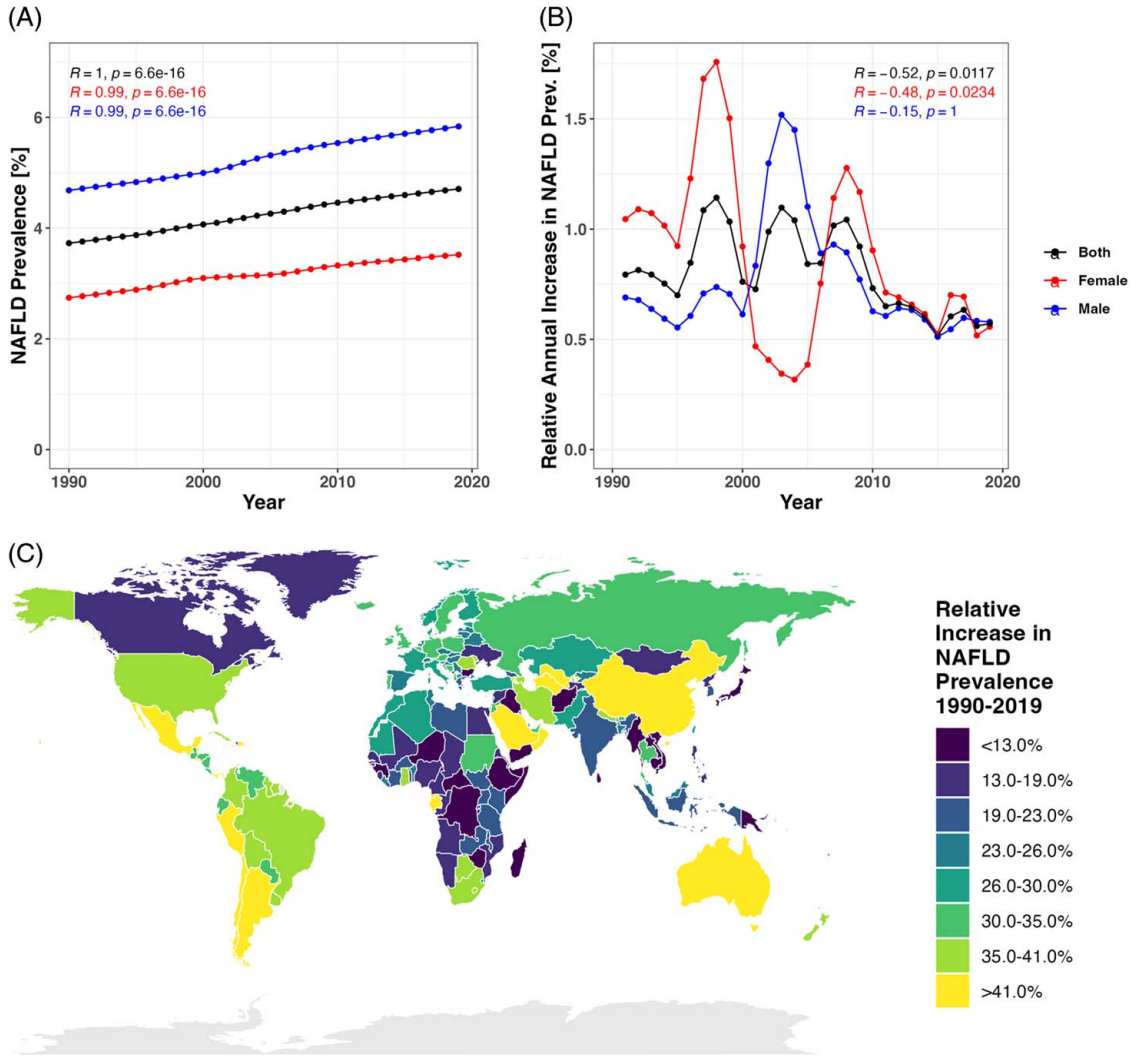

FIGURE 2 The NAFLD prevalence in adolescents increased consistently on a global level from 1990 to 2019. (A) Global NAFLD prevalence in adolescents from 1990 to 2019. (B) Global relative annual increase in NAFLD prevalence in adolescents between 1990 and 2019. (C) Relative increase in adolescent NAFLD prevalence per country and territory between 1990 and 2019 (n = 202). Total adolescent population is in the black, male population is in the blue, and female population is in the red. For A and B, the Pearson correlation coefficient *R* indicates the strength of correlation and adjusted *p* values after the Bonferroni correction is shown. Statistical significance is indicated by $p < 0.05$. Abbreviation: NAFLD, nonalcoholic fatty liver disease; prev, prevalence.

S2B, http://links.lww.com/HEP/F685), whereas, in 2010, the highest NAFLD prevalence rates in adolescents were recorded for Egypt (19.22%), Qatar (15.87%), Kuwait (14.50%), United Arab Emirates (13.76%), and Saudi Arabia (12.76%) (Supplemental Figure S2C, http://links.lww.com/HEP/F685). The highest increase in adolescent NAFLD prevalence between 1990 and 2019 was in Peru (64.24% in total relative prevalence increase for 1990–2019 or 1.73% average annual relative prevalence increase for 1990–2019), Equatorial Guinea (62.53%, 1.69%), Oman (50.86%, 1.43%), Turkmenistan (48.68%, 1.38%), and Saudi Arabia (48.60%, 1.38%) (Figure 2C, Supplemental Figure S3, http://links.lww.com/HEP/F685). Other countries with high increases during that time period include Chile (45.01%, 1.29%), China (44.36%, 1.27%), Australia (43.21%, 1.25%), Argentina (41.51%, 1.20%), and Mexico (41.07%, 1.19%) (Figure 2C, Supplemental Figure S3, http://links.lww.com/HEP/F685).

The prevalence of NAFLD in adolescents is increasing on all continents and is the highest in Oceania, North America, and Asia

Next, we compared the prevalence of adolescent NAFLD in all continents (except Antarctica). The continents with the highest, second highest, and third highest NAFLD prevalences in adolescents in 2019 were Oceania (median: 6.54% and IQR: 1.76%), North America (median: 5.64% and IQR: 0.91%), and Asia (median: 5.44% and IQR: 6.31%),

respectively, and their prevalences were all significantly higher than those of the 2 continents with the lowest prevalences (Europe with median: 3.98% and IQR: 0.85%; Africa with median: 4.20% and IQR: 1.43%) (Figure 3A). The prevalence of South America (median: 4.32% and IQR: 1.50%) was not significantly different from any other prevalence after the Bonferroni correction (Figure 3A). The relative annual change in adolescent NAFLD prevalence medians was always positive for each continent between 1990 and 2019 (except for Oceania between 2006 and 2010) with a significant downward trend for each continent during that time period except for Africa (no significant trend) and Asia (significant upward trend) (Figure 3B). South America and North America had the highest relative increase in NAFLD prevalence in adolescents from 1990 to 2019 (median: 39.25% and IQR: 6.02%; median: 36.87% and IQR: 10.77%), which were significantly higher than all other four continents: Europe (median: 27.37% and IQR: 6.14%), Asia (median: 25.22% and IQR: 19.07%), Africa (median: 19.37% and IQR: 11.26%), and Oceania (median: 17.99% and IQR: 16.61%), respectively (Figure 3C). Similarly, North America and South America had the highest absolute increase in NAFLD prevalence in adolescents from 1990 to 2019 (median: 1.47% and IQR: 0.35%; median 1.27% and IQR: 0.41%), which were each significantly higher than the continents with the lowest absolute increase in prevalence, Europe (median: 0.81% and IQR: 0.24%) and Africa (median: 0.70% and IQR: 0.72%) (Figure 3D). The absolute increase in adolescent NAFLD prevalence of Asia (median: 1.11% and IQR: 1.11%) and Oceania (median: 0.85% and IQR: 0.62%) was not significantly different from that of any other continent after adjustment with the Bonferroni correction (Figure 3D). As already stated (Figure 3B–D), all continents had a higher NAFLD prevalence in adolescents in 2019 than they did in 1990. However, North America, Europe, and Africa were the only continents, for which the prevalences in 2010 and/or 2019 significantly increased after adjustment with the Bonferroni correction compared with the years 1990 and/or 2000 (Figure 3E).

High body mass index and type 2 diabetes mellitus are increasing in adolescents globally

NAFLD is characterized by metabolic dysfunction and is related to overweight and obesity, as well as T2DM.[2,13] The Global Burden of Diseases, Injuries, and Risk Factors Study 2015 quantified risk exposure by computing a SEV.[17] The SEV is the relative risk-weighted prevalence of exposure [17] and is effectively excess risk-weighted prevalence for a specific risk factor, such as high BMI.[18] The SEV-high BMI is, hence, an indirect measure of overweight and obesity. It ranges from 0% (no excess risk for a population) to 100% (highest risk level).[17] The global SEV-high BMI in adolescents increased consistently from 7.58% in 1990 to 15.83% in 2019, which corresponds to a relative increase of 108.68% (Figure 4A). The upward trend was highly significant for the total adolescent population but also for adolescent males and females separately ($R = 1.00$ and $p < 0.001$, for each total, males, and females) (Figure 4A). The countries and territories with the highest SEV-high BMI globally in 2019 were Guam (51.84%), the Cook Islands (49.20%), the Northern Marian Islands (47.02%), Qatar (45.98%), and Kuwait (45.15%) (Figure 4B, Supplemental Table S2, http://links.lww.com/HEP/F686). Other countries with very high SEV-high BMI were Saudi Arabia (42.76%), the USA (38.14%), New Zealand (37.91%), Mexico (37.32%), and Egypt (35.79%) (Figure 4B, Supplemental Table S2, http://links.lww.com/HEP/F686). Largely the same countries, including Saudi Arabia, the USA, New Zealand, Mexico, and Egypt, had markedly elevated SEV-high BMI in male and female adolescents (Supplemental Figure S4A, B, http://links.lww.com/HEP/F685). The SEV-high BMI increased in all countries worldwide from 1990 to 2019, with the highest averaged relative annual increase during that time period in Equatorial Guinea (8.44%), Myanmar (5.69%), and Bhutan (5.57%) but also in Angola (5.00%), China (4.81%), Ghana (4.80%), Indonesia (4.19%), and India (3.57%) (Supplemental Figure S5A–D, http://links.lww.com/HEP/F685).

Similarly, the prevalence of T2DM in adolescents increased consistently from 182.04 per 100,000 adolescents in 1990 to 303.53 per 100,000 in 2019, which corresponds to a relative increase of 66.74% (Figure 4C). It increased by 73.83% for male adolescents from 162.03 to 281.66 per 100,000 and by 61.09% for female adolescents from 202.71 to 326.55 per 100,000 adolescents during that time period (Figure 4C). Likewise, the upward trend was highly significant for the total, male, and female adolescent populations ($R = 0.98$ and $p < 0.001$ for each) (Figure 4C). The highest adolescent T2DM prevalence in 2019 globally was recorded in Oceanian, North American, and South American countries and territories, including the Marshall Islands (1177.85 per 100,000), American Samoa (1137.06 per 100,000), Suriname (893.24 per 100,000), Haiti (789.33 per 100,000), Papua New Guinea (761.43 per 100,000), Honduras (752.65 per 100,000), and Mexico (719.91 per 100,000) (Figure 4D, Supplemental Table S3, http://links.lww.com/HEP/F686). The overall lower T2DM prevalence in adolescent males compared with females becomes evident compared with the color-coded world maps in (Supplemental Figure S4C, D http://links.lww.com/HEP/F685), although both sexes had the same countries and territories with the highest T2DM prevalence, as detailed earlier. The global T2DM prevalence in adolescents increased between 1990 and 2019, as described above (Figure 4C); the largest increases in that time period were noted in Japan, Greenland,

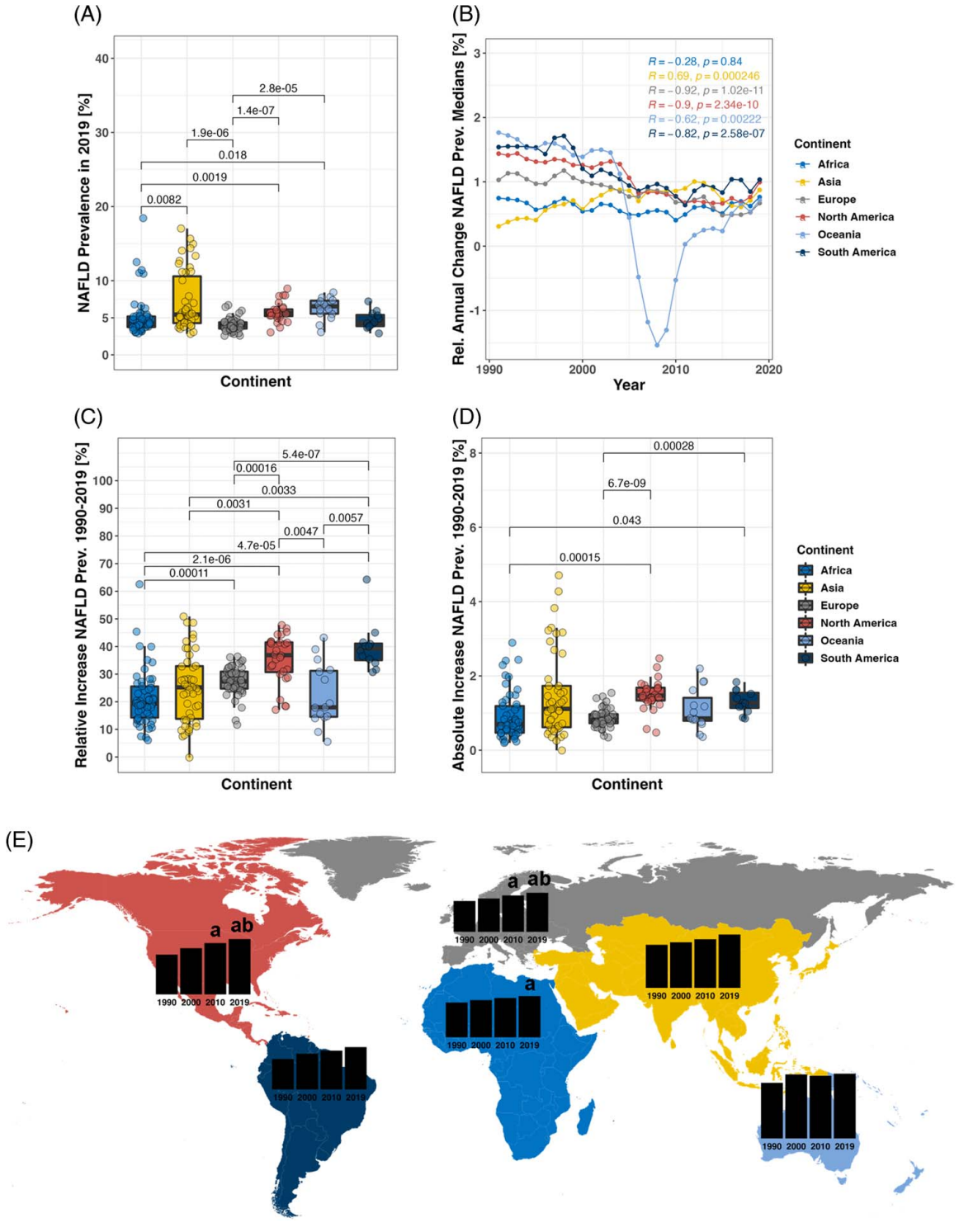
(A)
NAFLD Prevalence in 2019 [%]
Continent
2.8e-05
1.4e-07
1.9e-06
0.018
0.0019
0.0082
(B)
Rel. Annual Change NAFLD Prev. Medians [%]
Year
R = −0.28, p = 0.84
R = 0.69, p = 0.000246
R = −0.92, p = 1.02e-11
R = −0.9, p = 2.34e-10
R = −0.62, p = 0.00222
R = −0.82, p = 2.58e-07
Continent
Africa
Asia
Europe
North America
Oceania
South America
(C)
Relative Increase NAFLD Prev. 1990-2019 [%]
Continent
5.4e-07
0.00016
0.0033
0.0031
0.0057
0.0047
4.7e-05
2.1e-06
0.00011
(D)
Absolute Increase NAFLD Prev. 1990-2019 [%]
Continent
0.00028
6.7e-09
0.043
0.00015
Continent
Africa
Asia
Europe
North America
Oceania
South America
(E)
a
ab
1990 2000 2010 2019

FIGURE 3 Oceania and North America have the highest NAFLD prevalence in adolescents. Countries and territories overall, n = 202. Africa (n = 54), Asia (n = 47), Europe (n = 46), North America (n = 28), Oceania (n = 15), and South America (n = 12). (A) Prevalence of adolescent NAFLD per continent in 2019. (B) Relative annual change in adolescent NAFLD prevalence medians per continent between 1990 and 2019. (C) Relative increase in NAFLD prevalence in adolescents per continent from 1990 to 2019. (D) Absolute increase in adolescent NAFLD prevalence per continent from 1990 to 2019. (E) Longitudinal comparison of medians in 1990, 2000, 2010, and 2019 separately by continent. North America [$median_{2019}$ 5.64% (IQR: 0.91%) vs $median_{1990}$ 4.06% (IQR: 0.83%), $p < 0.001$; $median_{2019}$ vs $median_{2000}$ 4.71% (IQR: 0.95%), $p = 0.036$; and $median_{2010}$ 5.24% (IQR: 0.82%) vs $median_{1990}$, $p = 0.002$], Europe [$median_{2019}$ 3.98% (IQR: 0.85%) vs $median_{1990}$ 3.14% (IQR: 0.71%), $p < 0.001$; $median_{2019}$ vs $median_{2000}$ 3.40% (IQR: 0.59%), $p = 0.029$; and $median_{2010}$ 3.71% (IQR: 0.63%) vs $median_{1990}$, $p = 0.002$], and Africa [$median_{2019}$ 4.20% (IQR: 1.43%) vs $median_{1990}$ 3.55% (IQR: 0.83%), $p = 0.031$] were the only continents, for which the prevalences in 2010 and/or 2019 were significantly increased compared with the years 1990 and/or 2000. For the box and whisker plots (A, C, and D), the box extends from the 25th to 75th percentiles, with the center line indicating the median; the bottom whiskers indicate the minimum values, and the top whiskers indicate the 75th percentile plus 1.5-fold the interquartile distance (the distance between the 25th and 75th percentiles). For A, C, D, and E, the Kruskal-Wallis test was statistically significant, and significantly adjusted *p* values per pairwise (A, C, and D) unpaired or (E) paired Wilcoxon-Whitney-Mann rank-sum test with the Bonferroni correction are shown as indicated. For B, the Pearson correlation coefficient *R* indicates the strength of correlation and adjusted *p* values after the Bonferroni correction is shown. (A–D) Statistical significance is present if $p < 0.05$ and is indicated for E by "a" = significant difference between the respective column and 1990, and "b" = significant difference between the respective column and 2000. Abbreviations: NAFLD, nonalcoholic fatty liver disease; prev, prevalence; rel, relative.

Singapore, the USA, Finland, New Zealand, Niger, and Egypt, among others (Supplemental Figure S6A–D, http://links.lww.com/HEP/F685).

High body mass index but not type 2 diabetes mellitus correlates with NAFLD prevalence in adolescents when countries and territories are compared on a global level

When over 200 countries and territories are compared, the measure for overweight and obesity, SEV-high BMI, correlated with NAFLD in the general adolescent population in 2019 ($R = 0.50$ and $p < 0.001$) (Figure 5A) and also in the male and female adolescent populations equally ($R = 0.47$ and $p < 0.001$; $R = 0.49$ and $p < 0.001$, respectively) (Supplemental Figure S7A, B, http://links.lww.com/HEP/F685). On a continental level, Asia, Africa, and North America all displayed a significant correlation between SEV-high BMI and NAFLD ($R = 0.83$ and $p < 0.001$; $R = 0.70$ and $p < 0.001$; and $R = 0.61$ and $p = 0.003$, respectively), whereas Europe, Oceania, or South America do not show significant correlations (Figure 5B).

There was no significant correlation between T2DM and NAFLD prevalences in the total, male, and female populations on a global level (Figure 5C, Supplemental Figure S7C, D, http://links.lww.com/HEP/F685). However, when continents are compared, a significant positive correlation between T2DM and NAFLD prevalences existed in North American countries ($R = 0.60$ and $p = 0.004$), and a nonsignificant trend was noted in Oceanian countries ($R = 0.65$ and $p = 0.053$) (Figure 5D). Interestingly, a negative correlation between T2DM and NAFLD prevalences was present in African countries ($R = -0.45$ and $p = 0.004$) (Figure 5D).

Countries with high human development index have larger increases in NAFLD prevalence in adolescents, although countries with the highest human development index have the lowest NAFLD prevalence

Adult studies have demonstrated that higher rates of obesity correlate with higher HDI values.[11,12] We, therefore, investigated the relationship of another metabolic condition, NAFLD, in adolescents with the HDI for each country globally. The overall trend between 2019 NAFLD prevalence and HDI value for each country was not significant ($R = 0.08$ and $p = 0.28$) (Figure 6A), but the relative and absolute increase in the NAFLD prevalence from 1990 to 2019 correlated significantly with the HDI values ($R = 0.44$ and $p < 0.001$; $R = 0.28$ and $p < 0.001$, respectively) (Figure 6B, C). Of note, when the correlations between those NAFLD prevalence measures and HDI values were analyzed per HDI group, the very high HDI group demonstrated trends opposing the overall correlations: it showed a significant negative correlation between NAFLD prevalence and HDI value, no significant correlation between the relative increase in NAFLD prevalence and HDI value, but again a significant negative correlation between the absolute increase in NAFLD prevalence and HDI value (Supplemental Figure S8A–C, http://links.lww.com/HEP/F685). When medians of the respective NAFLD measures were compared among the HDI groups, the low HDI group had a lower NAFLD prevalence and a lower relative and absolute NAFLD prevalence increase than the medium HDI group, which had lower medians than the high HDI group; however, the very high HDI group had significantly lower medians for NAFLD prevalence and absolute increase in NAFLD prevalence compared with the high HDI group (Figure 6D–F). The findings became even more evident when countries with the highest HDI values (HDI > 0.9) were compared with countries with HDI ≤ 0.9. The adolescent NAFLD prevalence was significantly lower in the highest HDI group than in the countries with HDI ≤ 0.9

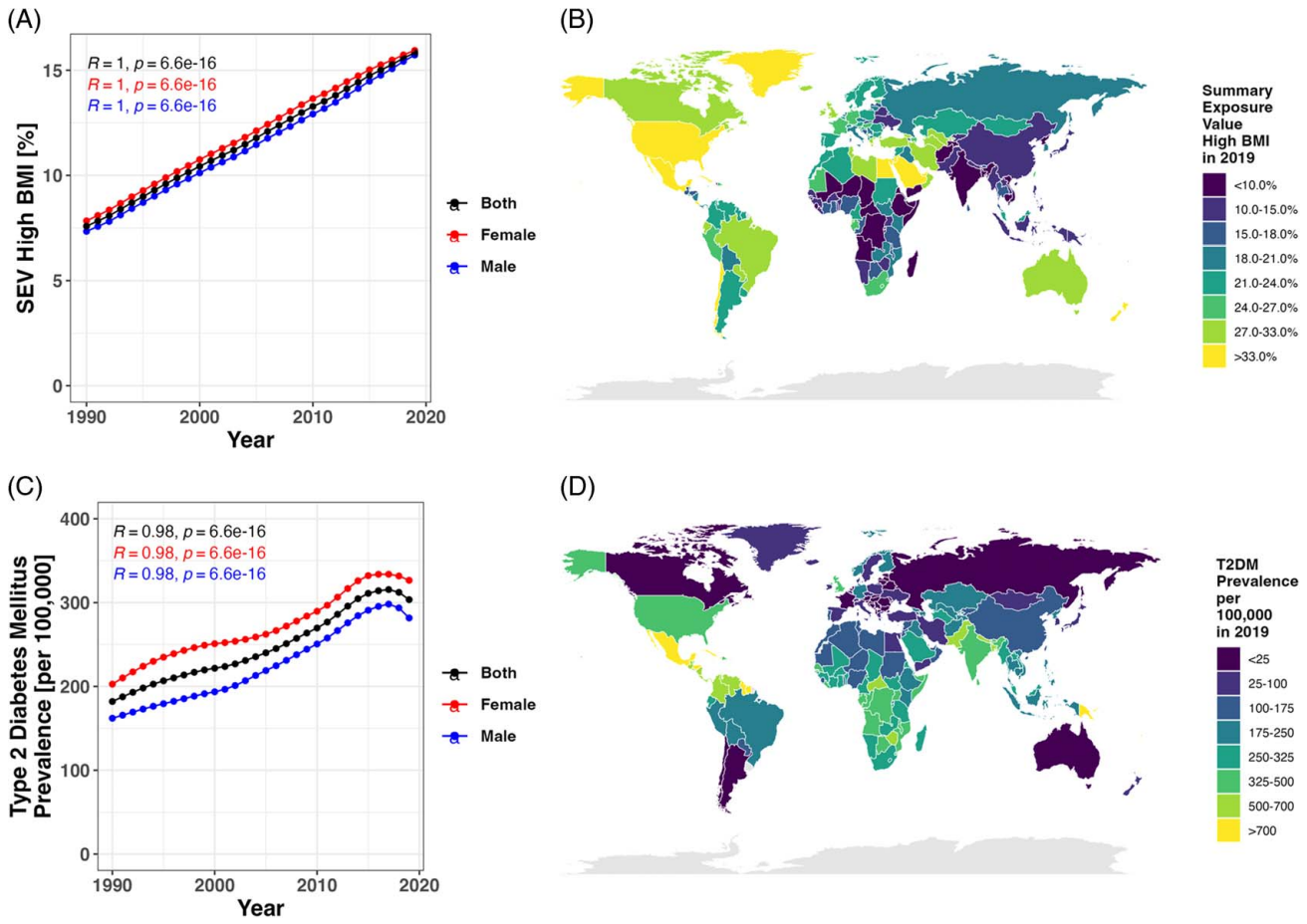

FIGURE 4 High BMI and T2DM prevalence increased significantly globally in adolescents from 1990 to 2019. (A) Global rate of overweight/obesity marker SEV-high BMI from 1990 to 2019. (B) Rate of SEV-high BMI per country and territory in 2019 (n = 202). (C) Global T2DM prevalence in adolescents from 1990 to 2019. (D) T2DM prevalence in adolescents per country and territory in 2019 (n = 201). Total adolescent population is in the black, male population is in the blue, and female population is in the red. For A and C, the Pearson correlation coefficient *R* indicates the strength of correlation and adjusted *p* values after the Bonferroni correction is shown. Statistical significance is indicated by $p < 0.05$. Abbreviation: BMI, body-mass index; NAFLD, nonalcoholic fatty liver disease; SEV, summary exposure value; T2DM, type 2 diabetes mellitus.

[$\text{median}_{\text{HDI}>0.9}$ 3.58% (IQR 1.03%) vs $\text{median}_{\text{HDI}\leq 0.9}$ 4.89% (IQR 1.87%), $p < 0.001$] (Figure 6G). The relative NAFLD prevalence increase was similar between the groups [$\text{median}_{\text{HDI}>0.9}$ 29.07% (IQR: 7.83%) versus $\text{median}_{\text{HDI}\leq 0.9}$ 25.40% (IQR: 15.98%), $p = 0.17$], but the absolute NAFLD prevalence increase was significantly lower in the HDI > 0.9 group compared with the HDI ≤ 0.9 group [$\text{median}_{\text{HDI}>0.9}$ 0.80% (IQR: 0.31%) vs $\text{median}_{\text{HDI}\leq 0.9}$ 1.02% (IQR: 0.80%), $p = 0.038$] (Figure 6H, I).

Similar to the relative and absolute NAFLD prevalence increases, there was a significant positive correlation between SEV-high BMI and HDI values ($R = 0.57$ and $p < 0.001$), which was not as clear when compared by HDI groups separately (Supplemental Figure S8D, E, http://links.lww.com/HEP/F685). In contrast, the T2DM prevalence correlates negatively with HDI values, with the lowest values in the very high HDI group (Supplemental Figure S8F, G, http://links.lww.com/HEP/F685).

DISCUSSION

To the best of our knowledge, this is the first time that the prevalence rate of adolescent NAFLD in countries was compared globally between different continents, as was their relationship with other metabolic conditions, including overweight/obesity and T2DM in adolescents, as well as their relationship with the HDI value of each country. Here, we show that the globally highest adolescent NAFLD prevalence rates are in countries on the Arabian Peninsula (eg, Qatar and Kuwait) and African and Asian countries bordering the Mediterranean Sea, such as Egypt. The global prevalence rate of NAFLD in adolescents increased markedly between 1990 and 2019, during which time the prevalence in adolescent males stayed ~2% higher than that in adolescent females. Similarly, the prevalence of NAFLD in adolescents increased on all continents between 1990 and 2019 and was highest in Oceania, North America, and Asia in 2019. The related metabolic conditions of overweight and

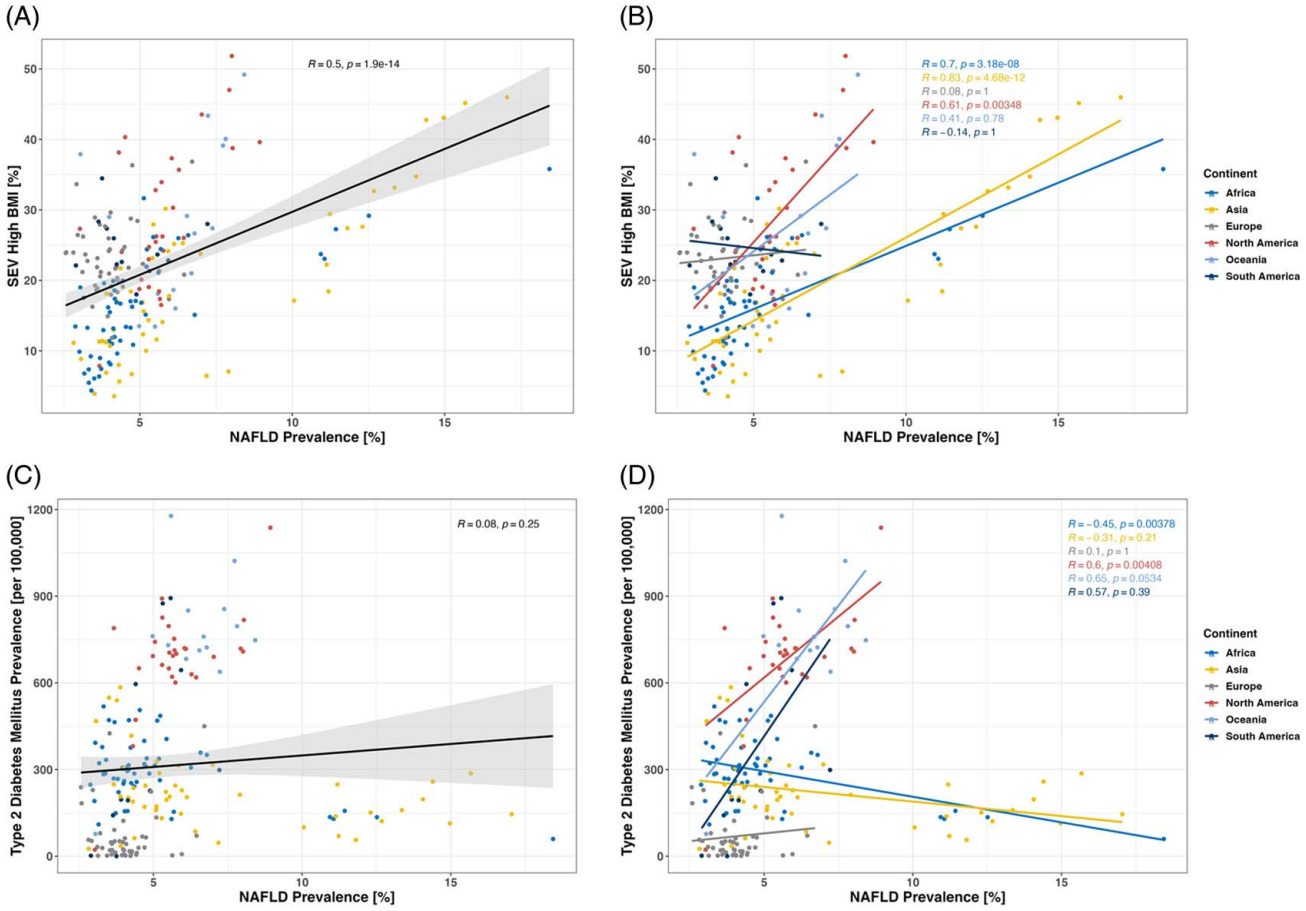

FIGURE 5 High BMI but not T2DM correlates with NAFLD prevalence in adolescents overall, but T2DM correlates with NAFLD on certain continents. Countries and territories overall, n = 202 [except (C and D) n = 201]. Africa (n = 54), Asia (n = 47), Europe (n = 46), North America (n = 28), Oceania (n = 15), and South America [n = 12, except (C and D) n = 11]. (A and B) Relationship between rate of overweight/obesity marker SEV-high BMI and NAFLD prevalence in adolescents in 2019 (A) with overall correlation and (B) correlation per continent. (C and D) Relationship between prevalence of T2DM and NAFLD in adolescents in 2019 (C) with overall correlation and (D) correlation per continent. The Pearson correlation coefficient *R* indicates the strength of correlation (overall in black, other colors per continent), and (B and D) adjusted *p* values after the Bonferroni correction are shown. Statistical significance is indicated by $p < 0.05$. Abbreviation: BMI, body-mass index; NAFLD, non-alcoholic fatty liver disease; SEV, summary exposure value; T2DM, type 2 diabetes mellitus.

obesity (represented as SEV-high BMI) and T2DM increased consistently as well from 1990 to 2019. The overweight and obesity marker SEV-high BMI correlated significantly with adolescent NAFLD, whereas there was no clear correlation between T2DM and NAFLD in adolescents on a global level. Finally, we show that countries with higher HDIs had larger relative and absolute increases in adolescent NAFLD prevalence but also that countries with the highest HDIs (> 0.9) had the lowest NAFLD prevalence.

A prior pediatric NAFLD study based on the Global Burden of Disease Study 2017 compared 195 countries and territories, showed an increasing global prevalence of pediatric NAFLD over recent decades similar to our study and demonstrated that the highest prevalence of pediatric NAFLD worldwide was in American Samoa and Saudi Arabia.[9] The biggest differences to our study are that the Global Burden of Disease Study 2019 database was updated to include more countries and territories (n = 202) and was based on more data sources (Global Burden of Disease Study 2019 with over 86,000 vs Global Burden of Disease Study 2017 with 69,000 data sources), which resulted in a change of the countries with the highest prevalence, now being Egypt, Qatar, and Kuwait. Furthermore, the current study also investigated the differences in NAFLD prevalence among different continents, correlated the NAFLD prevalence with overweight/obesity and T2DM in adolescents, and comprehensively analyzed its relationship with the HDI of each country and territory. Another study in adolescents and young adults based on the Global Burden of Disease Study 2019 found that the proportion of NAFLD among chronic liver diseases has been increasing in all age ranges, including 15–19-year-olds, in recent decades.[22] Of note, this study also demonstrated that the death rate due to NAFLD increased in adolescents and young adults between 2015 and 2019 (an annual increase of 0.05%–0.59%).[22]

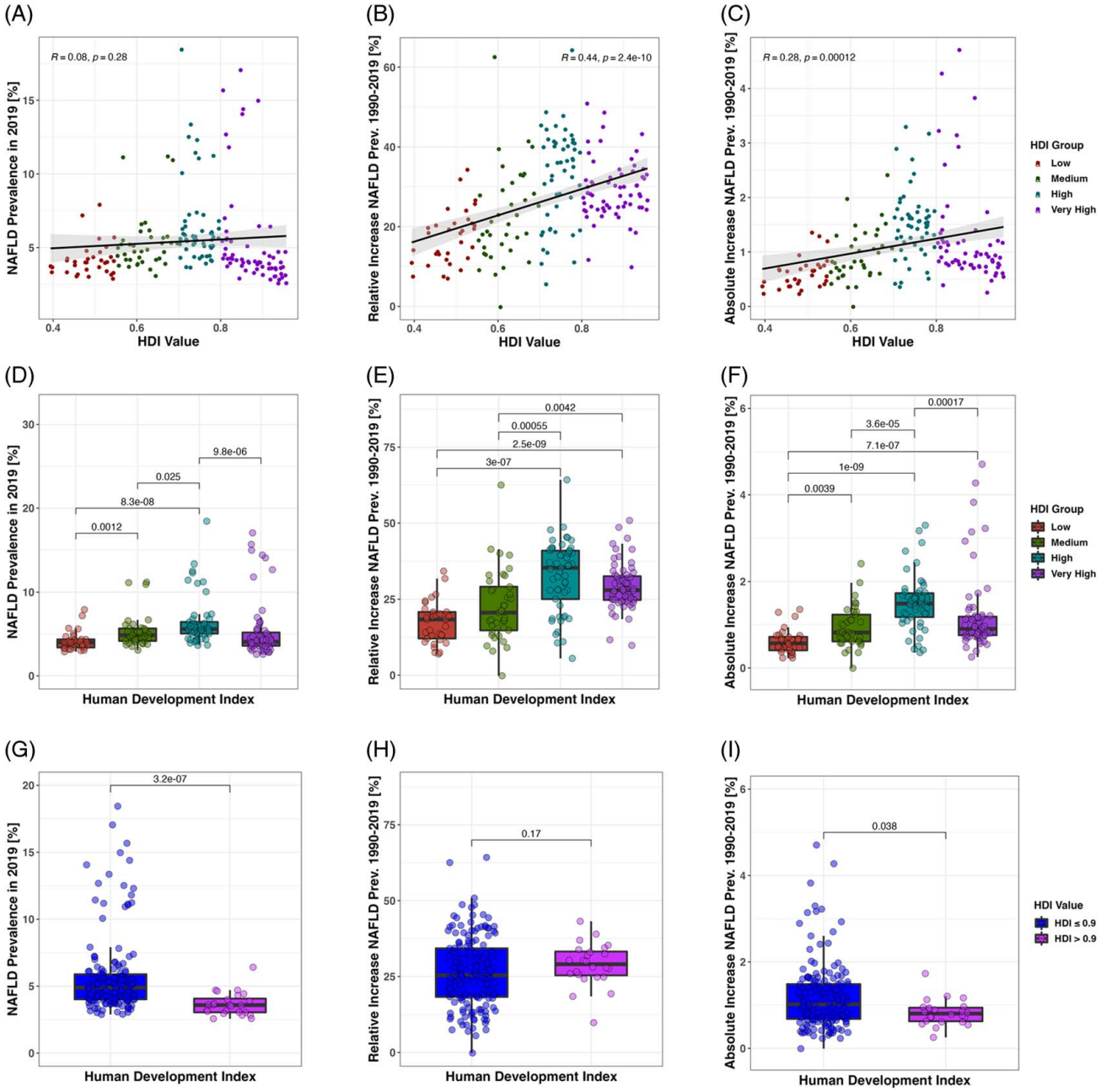

FIGURE 6 Countries with higher HDIs have greater increases in NAFLD prevalence, although countries with the highest HDIs (HDI > 0.9) have the lowest NAFLD prevalence in adolescents. Countries and territories overall, n = 187. "Low HDI", HDI < 0.55 (n = 33); "medium HDI", HDI 0.55- < 0.70 (n = 37); "high HDI", HDI 0.70- < 0.80 (n = 53); and "very high HDI", HDI ≥ 0.80 (n = 64). (A–C) Relationship between (A) HDI and prevalence of NAFLD in adolescents in 2019, (B) HDI and relative increase in NAFLD prevalence in adolescents from 1990 to 2019, and (C) HDI and absolute increase in NAFLD prevalence in adolescents from 1990 to 2019. (D) Prevalence of adolescent NAFLD per HDI group in 2019. (E) Relative increase in NAFLD prevalence in adolescents per HDI group from 1990 to 2019. (F) Absolute increase in adolescent NAFLD prevalence per HDI group from 1990 to 2019. (G) Prevalence of NAFLD in adolescents between HDI > 0.9 and HDI ≤ 0.9 groups in 2019. (H) Relative increase in adolescent NAFLD prevalence between HDI > 0.9 and HDI ≤ 0.9 groups from 1990 to 2019. (I) Absolute increase in adolescent NAFLD prevalence between HDI > 0.9 and HDI ≤ 0.9 groups from 1990 to 2019. For the box and whisker plots (D–I), the box extends from the 25th to 75th percentiles, with the center line indicating the median; the bottom whiskers indicate the minimum values, and the top whiskers indicate the 75th percentile plus 1.5-fold the interquartile distance (the distance between the 25th and 75th percentiles). For D–F, the Kruskal-Wallis test was statistically significant, and significantly adjusted *p* values per the pairwise Wilcoxon-Whitney-Mann rank-sum test with the Bonferroni correction are shown as indicated. For G–I, *p* values per the Wilcoxon-Whitney-Mann rank-sum test are shown. The Pearson correlation coefficient *R* indicates the strength of correlation. Statistical significance is indicated by $p < 0.05$. Abbreviation: HDI, human development index; NAFLD, nonalcoholic fatty liver disease; prev, prevalence.

Our NAFLD prevalence findings in adolescents (Figure 1A, Supplemental Table S1, http://links.lww.com/HEP/F686) are in line with adult data, where the highest NAFLD prevalence rates on a global level were found in the Middle East and Egypt with prevalence rates in excess of 30%.[23,24] Genetic factors could be considered for this concentration in these regions, such as the pathogenic variants of the well-known *PNPLA3* and *TM6SF2* genes, which promote the development and progression of NAFLD.[24] However, their pathogenic allele frequency does not seem to be significantly higher in those populations.[24,25] Nevertheless, other not yet identified gene variants or epigenetic factors could play a role therein. Certainly, environmental factors, including dietary habits and physical activity, likely contribute, as an unhealthy lifestyle is associated with metabolic dysfunction, such as NAFLD.[3] A recent study compared global dietary quality across 185 countries and found that the Middle East and Northern Africa were among the two regions worldwide with the lowest diet quality (the other region being Latin America/Caribbean), and children and adolescents had an even lower diet quality than adults,[26] which likely contributes to the elevated NAFLD prevalence in adolescents in these regions. Our demonstrated increasing prevalence rates of adolescent NAFLD over the last decades (Figure 2, Supplemental Figure S2 and S3, http://links.lww.com/HEP/F685) are also consistent with adult data, where prevalence rates of metabolic conditions, including NAFLD, have been increasing over multiple decades.[27] Adult NAFLD studies also show markedly higher prevalence rates for male adolescents than female adolescents,[27] similar to our findings (Figures. 1B and 2A, and Supplemental Figure S1, http://links.lww.com/HEP/F685).

On a continental level, Oceania, North America, and Asia had the highest adolescent NAFLD prevalence in 2019, and Europe had the lowest (Figure 3A). Of note, Mexico and other Latin American countries have a particularly high pathogenic *PNPLA3* allele frequency[24,25] and, as mentioned, a lower dietary quality compared with other global regions,[26] both of which likely contribute to the high NAFLD prevalence in adolescents on the North American continent. South America and North America had the highest increase in NAFLD prevalence in adolescents between 1990 and 2019, and Oceania had the lowest (Figure 3C), which shows that Oceania had the highest NAFLD prevalence during the entire time period. These higher prevalence rates in Oceania are also consistent with adult data.[28]

The global prevalence of other metabolic conditions, that is overweight/obesity and T2DM, increased as well in adolescents between 1990 and 2019 (Figure 4). Of note, female adolescents had a higher T2DM prevalence than male adolescents (Figure 4C-D), which is a common finding in the pediatric population, and the sex prevalence proportions reverse later in life.[29] The higher T2DM in the female adolescent population is likely due to puberty-related hormonal changes.[30,31] However, only the overweight/obesity marker SEV-high BMI correlated significantly with NAFLD prevalence, in particular, in Asian, North American, and African countries (Figure 5A, B). T2DM prevalence in adolescents did not correlate with NAFLD prevalence overall; however, there was a positive relationship between the two conditions in North America and Oceania (Figure 5C, D). Conversely, African countries showed a significant negative correlation between the two measures (Figure 5D). It is unclear what causes this difference as NAFLD and T2DM are usually associated metabolic conditions.[2,32] It could be argued that a difference in subcutaneous and visceral fat distribution could help explain this observation.[33] A large study in the US combined the "Mediators of Atherosclerosis of South Asians Living in America (MASALA)" and "Multiethnic Study of Atherosclerosis (MESA)" studies and provided some evidence that there might be divergent propensities toward T2DM and NAFLD per ethnic group.[34] In this study, Chinese Americans and African Americans had significantly less visceral fat and lower T2DM prevalence rates than South Asians living in the US, but they had significantly more liver fat.[34] This difference among ethnic groups might help to partially explain the observed opposing correlations on different continents between NAFLD and T2DM prevalences in our study. Furthermore, multiple regression analysis for the amount of visceral fat in another study identified a significant interaction between age and race when Asian American and European American women were compared.[35] Extrapolated to the pediatric population, it could mean that different ethnicities might have a different onset when they produce significant amounts of visceral fat, which could translate into varying risks toward NAFLD and T2DM across pediatric ethnicities. Finally, NAFLD usually presents slightly earlier on average than T2DM in the pediatric population (10–13 vs ~13–14 y of age).[36,37] It is possible that the age of onset of the 2 conditions could vary markedly across the various ethnicities, which could explain the opposing relationships between adolescent NAFLD and T2DM observed on the different continents in our study. However, more targeted, prospective investigations have to be conducted to explore this apparent divergent relationship between different continents more closely.

Finally, we demonstrate that countries with higher HDIs had greater relative and absolute increases in adolescent NAFLD prevalence globally and interestingly also that countries with the highest HDIs (>0.9) had a significantly lower NAFLD prevalence than countries with HDI $\leq$ 0.9 (Figure 6, Supplemental Figure S8, http://links.lww.com/HEP/F685). Adult studies have shown that increasing rates of overweight and obesity correlate with increasing HDI values,[11,12] similar to our findings (Supplemental Figure S8D, E,

http://links.lww.com/HEP/F685). Obesity is a major risk factor for NAFLD. Higher HDI, hence, confers a higher risk of NAFLD. However, a higher HDI also includes higher scores for the 3 basic dimensions of human development per the United Nations Development Program: a long and healthy life, knowledge, and a decent standard of living.[21] Possibly, healthier lifestyles and better healthcare with more preventative policy measures could contribute to the lower adolescent NAFLD prevalence in the highest HDIs of >0.9 compared with all other rated countries and territories (Figure 6G).

Strengths of this study include that all prevalence data were obtained from one unified data set, which also represents the most recent global NAFLD prevalence estimates in adolescents. Furthermore, this study provides a comprehensive comparison of NAFLD prevalence in adolescents by continent. It also comprehensively compares NAFLD prevalence with overweight/obesity and T2DM prevalence in adolescents on a global level. Another surprising finding is that, despite increasing rates of adolescent NAFLD prevalence with higher HDI, countries with the highest HDIs actually have a significantly lower NAFLD prevalence in adolescents than all others combined.

Limitations of this study are mainly related to the restrictions of the data set. The inclusion of other risk factors for NAFLD or other metabolic disorders, such as dyslipidemia or abdominal circumference, would have been advantageous. However, these data were not available in the data set for the adolescent population but will hopefully be included in future iterations of the Global Disease Burden Study. The current study focused on the age group of 15–19 years. Although pediatric NAFLD is much more prevalent in adolescence,[38] it would provide more insights if future data sets included the NAFLD prevalence in younger age groups as well. Finally, due to the global nature of the study, the methodologies varied between different countries on how the NAFLD prevalence was determined (including liver enzyme elevation versus imaging studies vs the gold standard liver biopsy, or a combination thereof). A more unified approach in all countries would possibly provide even more exact estimates in the future.

NAFLD in adolescents is an increasing health problem on all continents. It is related to a genetic predisposition but also, importantly, to an unhealthy lifestyle with a poor diet and insufficient physical activity. Improvement of environmental factors, including lifestyle but also healthcare policies on the macroscopic level, can help to prevent NAFLD from developing in children and adolescents and help to improve health outcomes in children and adolescents with NAFLD.

AUTHOR CONTRIBUTIONS

Phillipp Hartmann designed the study, developed the method, directly accessed and verified the underlying data reported in the manuscript, analyzed, and interpreted the data, and wrote the manuscript. Xinlian Zhang directly accessed and verified the underlying data reported in the manuscript, provided statistical assistance, and edited the manuscript. Rohit Loomba edited the manuscript. Bernd Schnabl supervised the work and edited the manuscript.

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CONFLICTS OF INTEREST

Bernd Schnabl consults for Ambys Medicines, Ferring Research Institute, Gelesis, HOST Therabiomics, Intercept Pharmaceuticals, Mabwell Therapeutics, Patara Pharmaceuticals and Takeda. Bernd Schnabl's institution UC San Diego has received grant support from Artizan Biosciences, Axial Biotherapeutics, BiomX, CymaBay Therapeutics, NGM Biopharmaceuticals, Prodigy Biotech and Synlogic Operating Company. The remaining authors have no conflicts to report.

DATA AVAILABILITY

The raw data is available (https://vizhub.healthdata.org/gbd-results/).

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