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Diversity and inclusion in chronic hepatitis B randomised controlled trials: A systematic meta-epidemiological review

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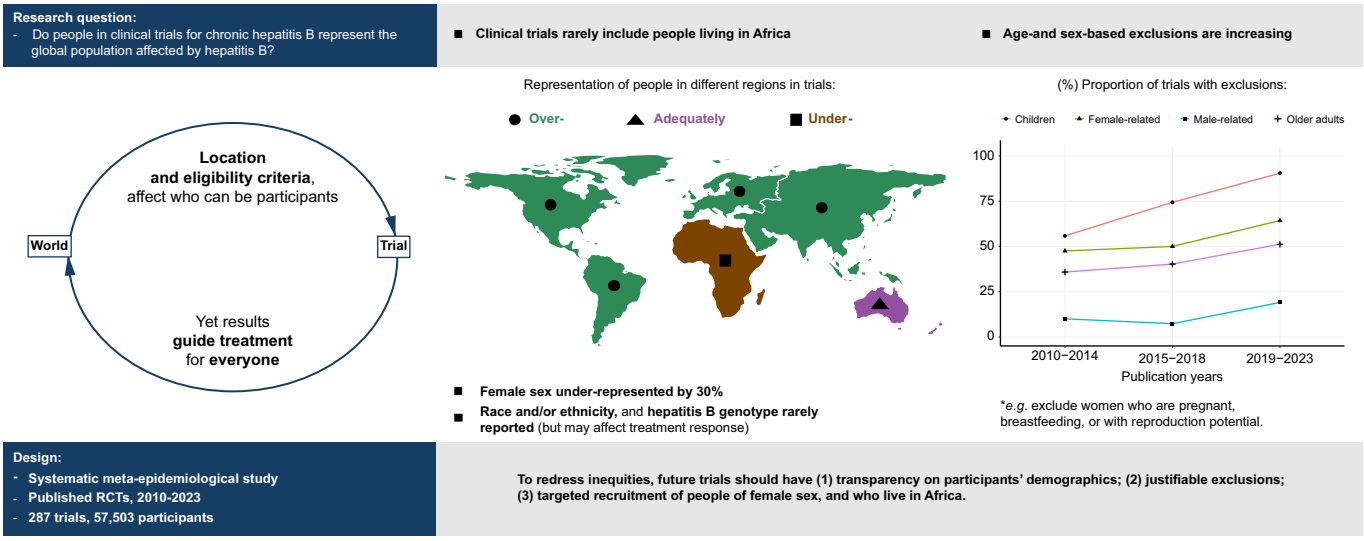
Graphical abstract



Highlights:

- Chronic hepatitis B clinical trials under-represent women and people living in Africa.
- Participants' race and ethnicity, and HBV genotype, are rarely reported.
- Age- and sex-based trial exclusions increased over time.

Impact and implications:

Clinical trials must balance the need to recruit homogenous participants to efficiently measure an intervention's effectiveness, with the need to produce evidence that can be applied to the whole population affected by a disease. We found chronic hepatitis B (CHB) clinical trials often failed to report basic demographic characteristics of participants, and had under-representation of women and people living in Africa. Given varied disease pathophysiology and treatment needs among different groups, this suggest a mismatch of evidence generation compared with the populations needing treatment, whereby the benefits and harms of different interventions across populations are not being adequately studied. We suggest relevant stakeholders, including researchers, funders, and publishers of CHB clinical trials, should actively recruit under-represented populations, target interventions to those most at need, and either consider demographic factors in results reporting and analysis, or make data easily available for interrogation.

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Diversity and inclusion in chronic hepatitis B randomised controlled trials: A systematic meta-epidemiological review

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Background & Aims: Chronic hepatitis B (CHB) affects global populations unequally, with variable prevalence and pathophysiology. Clinical trials must balance efficiency with adequate representation of the populations most likely to benefit from the interventions they test. We aimed to investigate diversity and inclusion in CHB trials.

Methods: We performed a meta-epidemiological study of randomised controlled trials recruiting people with CHB published in MEDLINE and Embase, January 2010 to July 2023. We extracted participant age, sex, country of recruitment, race and ethnicity, and hepatitis B genotype. We calculated proportions of trials reporting participant demographics and results by demographics (transparency). We compared participants proportionately to global populations affected by CHB of different demographics (representation), and examined demographic-based trial exclusion criteria.

Results: Among 287 trials (81.9% single-country, 18.1% multinational) with 57,503 participants (median size: 102, IQR: 60–185), 97.9% tested drug interventions. Most trials reported participants' age distribution (285, 99.3%) and sex (278, 96.9%). However, only 37.3% (107) trials reported race and ethnicity, 84 (29.3%) reported genotype, and, among multinational trials, only 19 (36.5%) reported recruitment numbers by country. Less than 3% trials reported demography-stratified results. Female sex was under-represented (42.0% people with CHB, 28.7% trial participants). Geographic disparities between those affected by CHB and trial participation were marked for Africa (31.0% *vs.* 0.01%; under-representation), and Americas or Europe (5.7% *vs.* 14.0%; over-representation). Many trials had exclusion criteria based on age (71.4% children, 41.5% older adults) or sex-related (157, 54.7%), mostly excluding women who were pregnant, breastfeeding, or of reproduction potential.

Conclusions: Clinical trials for CHB are not inclusive of women and people in Africa. Researchers, funders, and publishers should actively consider diversity and inclusion of trials.

Introduction

Chronic hepatitis B (CHB), which affected 4.1% of the global population in 2019, is an important global cause of morbidity and mortality, and often needs life-long treatment.[1] While both the World Health Organization (WHO) and the United Nations (UN) Sustainable Development Goals (SDG) aim to eliminate hepatitis B virus (HBV) infection as a public threat by 2030, this currently appears unachievable.[1,2] Intervention improvements targeted to those most at need are hence required, and there are multiple ongoing randomised controlled trials (RCTs) aiming to improve CHB outcomes.

Clinical trials must balance regulation, cost and time pressures (which can push triallists to use smaller and homogenous groups of participants for high internal validity) with the need for ensuring diversity of included participants (for external validity, whereby the evidence generated can be applied to the whole population in need).[3] Triallists may select a limited scope of recruiting sites and/or participant eligibility either with a view to efficiency (*e.g.* expenses in setting up trial sites, or translating documents), or perceived risks, regarding trial success (*i.e.* needing larger numbers of participants for a positive result to overcome heterogeneity of effects in varied participants) or safety (*e.g.* testing new drugs in children).[4] This can lead to exclusion of key populations that often have unmet needs (*e.g.* people in low- and middle-income countries) or a different balance of risk/benefit from interventions (*e.g.* children and older adults), and a failure to generate high-quality evidence that can be applied to groups most at need.[4,5] In an effort to improve diversity and inclusion in clinical trials, international bodies recommend trials report both participants' demographics and demographic-stratified results, and recruit participants representative of the population to whom an intervention will be applied,[6,7] but adoption of these recommendations can be lacking. Other strategies for applying evidence from RCT more broadly include evidence synthesis using reported demographics from trial results, or re-analysis of shared data applied to subgroups.

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Age,[1,8,9] sex,[8,10,11] and HBV genotype,[12] which clusters geographically, are known to affect CHB pathophysiology and treatment responses. Treatment advancement is arguably most critical for those in low- and low-middle-income countries, facing the highest prevalence of CHB,[8,13] yet where current models of care are often inaccessible.[1] If the landscape of clinical trials in CHB fails to consider the whole population affected, this can exacerbate inequities in disease outcomes, whereby new models of care in different settings (*e.g.* Africa) are not adequately studied, or the treatment risks and benefits in subgroups such as the young or older people remain poorly understood.

A recent comprehensive analysis of the entire historical landscape of HBV clinical trials by Delphin and colleagues[14] revealed under-representation in the number of trials conducted in Africa compared to the high prevalence of CHB in the region. Although their work highlighted this geographical inequity in trial numbers, other aspects of diversity and inclusion in global CHB trials have not been studied, such as considerations of participant sex and age, which require more detailed analysis of participant characteristics, exclusions, and result reporting. In this study, we aimed to describe the transparency in reporting of participants' demographics in contemporary CHB clinical trials, and the representation of the global population affected by CHB. We also aimed to examine factors relating to diversity and inclusion of participants in trial design. By focusing on contemporary trials, we provide insights into the current trial landscape and identify opportunities for addressing structural inequalities and health inequities.

Participants and methods

We conducted a systematic review and meta-epidemiological analysis of published RCT recruiting participants with CHB, examining transparency and representation of participant characteristics. We registered this study on International Prospective Register of Systematic Reviews (PROSPERO), CRD42023457318, and reported according to Standards of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Statement,[15] and meta-epidemiological reporting guidelines defined by Murad and Wang.[16]

Inclusion and exclusion criteria

Trial inclusion criteria required all of: (1) study population: people with CHB and not primarily co-infected with other hepatitis viruses or HIV; (2) study design: interventional RCT; and (3) publication time frame: January 1, 2010, and July 31, 2023 (to focus on contemporary trials). No language restrictions were applied, to maximise the coverage of clinical trials. Reports were excluded where they were only available in abstract forms, or as interim analyses where participant recruitment was not completed, owing to incomplete information availability. Where a trial was reported more than once, we grouped reports by trial and included the trial cohort only once in results.

Search strategy

We searched MEDLINE and Embase via OVID using terms "((“Hepatitis B, Chronic/” OR “chronic hepatitis B”) AND (“randomi?ed controlled trial” OR “RCT”).mp.)” on August 27, 2023 (full search strategies: Table S1). Reference lists of retrieved publications were inspected for additional or primary clinical trials. Grey literature searching for conference abstracts in conference programs was not performed as the reporting of demographics in this format is often lacking because of space constraints. However, where records were excluded because of incomplete results or abstract format, additional searches were performed to identify any full reports of such excluded studies.

Study selection

Titles and abstracts were screened by a single researcher (XH) using Covidence,[17] with 20% records randomly selected for double screening by a second author (KW). Full-text screening was conducted by one author (XH). For records published in languages other than English, manuscripts were reviewed and extracted by a native speaker, where available (XH, Chinese language), or online tools were used to translate into English language.

Data collection and categorisation

We collected information from manuscripts and supplementary material, supplemented with clinical trial registry data if a clinical trial ID was provided. For each included study, data were extracted into a standardised spreadsheet by a single author (XH), with double extraction by a second author (KW) of a random 20% sample to check quality. Extracted data included: (1) article information, including title, author, journal of publication, and publication year; (2) study design, including recruitment location(s) (by country), funding sources, clinical trial phase of drug intervention, intervention details, inclusion and exclusion criteria related to age, sex, race and ethnicity, and trial registration details; and (3) study results, including total number of participants, number of participants categorised by age, sex, country of recruitment, race or ethnicity, HBV genotype, including missing information; and whether demographic-stratified results were reported.

Children were defined as people aged under 18 years of age, and older adults were defined as people aged over 65 years, per international standards.[18] Although we acknowledge that gender and biological sex are distinct and both may affect disease pathophysiology and treatment responses, this study focused only on biological sex, owing to available baseline data. We grouped countries of recruitment according to United Nations geographic regions: Africa, Asia, Americas, Europe, and Oceania,[19] and by income status per World Bank classification.[13] The conceptualisation and reporting of race and ethnicity varied between trials, with differences by study country and no clear international standard.[20] We used the United States National Institutes of Health guidelines for homogenising reporting of race and ethnicity[21] (Table S2). Intervention types were categorised into drug (including nucleos[t]ide analogues, interferons, and other drugs), complementary and alternative medicines and extracts, and non-drug interventions.

We did not contact authors to request missing data, because only transparent information can serve as best available evidence to improve health outcomes, aligning with the WHO's 2015 statement and the Declaration of Helsinki on public disclosure of clinical trial results.[6,7] However, data in supplementary material and trial registration records were used to minimise missing data. We did not collect any subjective data.

Outcomes and analysis

The three outcomes were: (a) transparency in reporting participants' demographics in recruitment and results, including country of recruitment, age, sex, race and ethnicity, and HBV genotype; (b) the representation of participants, by age, sex, geographic regions of recruitment, and HBV genotype, and (c) inclusion and exclusion criteria related to age, sex, or race and ethnicity. We defined the representation ratio of a population as the ratio between the proportion of participants in CHB clinical trials and the proportion of people affected by CHB globally, as extracted from the 2021 Global Burden of Disease (GBD) Collaborative Network[8] (Supplementary Methods). A representation ratio >1 reflects over-representation, and <1 means under-representation of the population. The weighted average age of all participants was calculated according to the trial size and central tendencies of age (mean or median), and compared with the average age of those affected by CHB, calculated from the GBD (Supplementary Methods). Because of a lack of global prevalence reference data, we compared representation of HBV genotypes to the burden reported in literature.[12] We did not compare proportions of participants in CHB clinical trials by race and ethnicity to the global population living with CHB, given there is neither comparable baseline global prevalence data nor a consensus definition of race and ethnicity. We visualised trial representation geographically at a country-level (Supplementary Methods). Outcomes were reported as frequency and proportion of included trials where appropriate. All analysis and figures were generated using the *rworldmap* and *ggplot2* package in R statistical software version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria).[22–24]

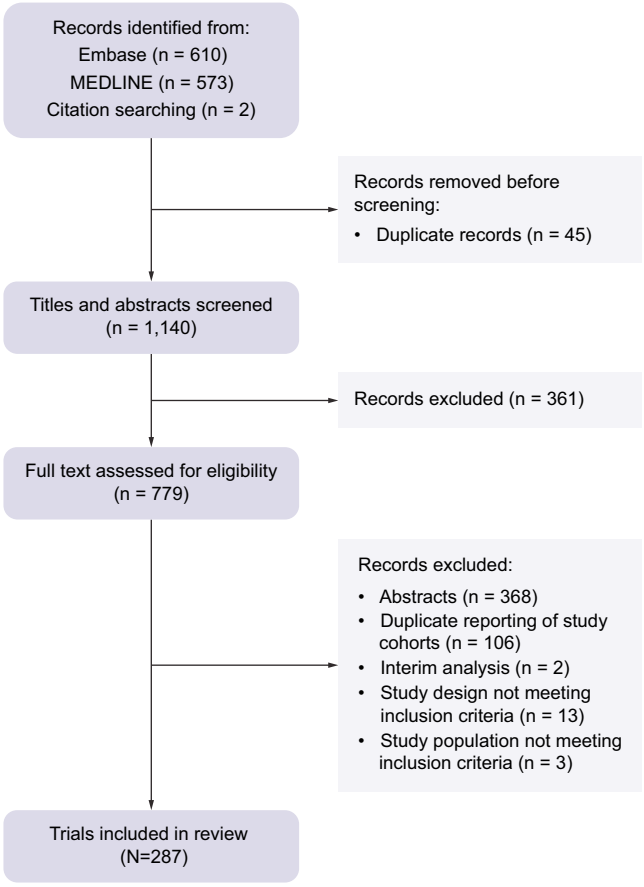

Fig. 1. PRISMA flowchart of search and record inclusion.

Results

Overview of included trials

We included 287 trials, with a total of 57,503 participants (Fig. 1). Of these, 156 trials (54.4%) reported a clinical trial ID. The median trial size was 102 participants (IQR: 60.0–185.0). Many trials (114, 39.7%) received funding from industry, and government (104, 36.2%), whereas fewer (<10%) received funding from universities, hospitals, or charity. Funding was not reported for 74 (25.8%) trials. Most trials (220, 76.7%) tested drug interventions, 61 (21.3%) tested complementary and alternative medicines and extracts, and six (2.1%) investigated non-drug interventions (Table 1). Drug interventions were mostly nucleos(t)ide analogues (120, 54.5%) and interferons (59, 26.8%). Interventions involving 'other drugs' (41, 18.6%) comprised novel agents for CHB clearance (32 trials, *e.g.* an antisense oligonucleotide 'bepirovirsen') or the repurposing of existing drugs (nine trials, *e.g.* metformin, steroids).

Most trials were conducted in a single country (235, 81.9%), comprising 34,623 (60.2%) participants. Most single-country trials were in Asia (213, 90.6%), and none were in Africa. Among 52 (18.1%) multinational trials, comprising 22,880 (39.8%) participants, 45 trials listed a total of 359 entries in recruiting countries, and the remaining seven trials were reported only as 'global studies'. Many of the countries multinational trials recruited from were in Europe (141, 39.3%) and Asia (121, 33.7%), whereas almost none were in Africa (2, 0.6%) (Table S3).

Transparency of cohort recruitment and results reporting

Trials with reported registration ID were significantly more likely to report participants' race and ethnicity, region of recruitment, and HBV genotypes (p <0.001, Table S4). All (156, 100%) registered trials reported cohort recruitment regions. Of the 52 multinational trials, only 19 (36.5%) reported the number of participants recruited from each country, but these accounted for most of the participants within multinational trials (17,218, 75.3%). Including single-country trials, recruiting countries were known for 51,841 (90.2%) participants. Most participants were recruited in Asia (44,782, 86.4%), and in upper-middle-income countries (37,089, 71.5%). No participants were recruited from low-income countries.

Most trials reported cohort age distribution (285, 99.3%) and sex (278, 96.9%) (Table 2). Only 37.3% (107) of trials reported race and ethnicity, including 78/156 (50.0%) trials with registration ID. The weighted average age of 56,172 participants among the 279 trials which reported age by central tendencies was 38.8 years (Table S5). The sex of 56,111 (97.6%) participants, and the race and ethnicity of 32,943 (57.3%) participants was reported. Most participants were male (39,584, 68.8%) and Asian (27,497, 83.5%) (Table S6). Few participants were White (4,796, 14.6%), or of Black race or African ethnicity (486, 1.5%).

Only 29.3% (84) trials reported HBV genotype of some or all participants, including 69/156 (44.2%) trials with registration ID. HBV genotype was reported for 14,060 (24.5%) participants

Table 1. Characteristics of included trials (N = 287).

	Trials (column %)* Total = 287
Participants (median, IQR)	102 (60.0–185.0)
Study size	
≤150	58 (20.2)
151–300	81 (28.2)
301–450	40 (13.9)
>450	108 (37.6)
Number of countries†	
Single country	235 (81.9)
Multinational	52 (18.1)
2–5	24
6–10	10
11–15	6
>15	5
Countries not stated	7
Recruiting countries (among single country trials)	
Africa	0 (0.0)
Northern Africa	0
Sub-Saharan Africa	0
Americas	8 (3.4)
Latin America and the Caribbean	0
Northern America	8
Asia	213 (90.6)
Central Asia	0
Eastern Asia	196
South-eastern Asia	7
Southern Asia	6
Western Asia	3
Europe	13 (5.5)
Eastern Europe	1
Northern Europe	0
Southern Europe	5
Western Europe	7
Oceania	1 (0.4)
Australia and New Zealand	1
Melanesia	0
Micronesia	0
Polynesia	0
Year of publication	
2010–2014	120 (41.8)
2015–2018	82 (28.6)
2019–2023	84 (29.3)
Interventions	
Nucleos(t)ide analogues	120 (41.8)
Interferons	59 (20.6)
Other drugs	41 (14.3)
Complementary and alternative medicines and extracts	61 (21.3)
Non-drug interventions	6 (2.1)
Trial design phase‡	
1	20 (9.1)
2	26 (11.9)
3	28 (12.8)
4	145 (66.2)
Funding sources	
Industry	114 (39.7)
Government	104 (36.2)
Academy	21 (7.3)
Hospital	14 (4.9)
Charity	4 (1.4)
None reported	74 (25.8)

*All data presented as number (column percentage) unless otherwise stated. Column percentages exclude unavailable data (*e.g.* none reported/not stated categories).
†Countries categorised per United Nations geographic regions.
‡Trial design phase for nucleos(t)ide analogues, interferons, and other drug interventions.

(Table S7). Of these, most participants had HBV genotype C (7,145, 50.8%) or B (4,205, 30.0%).

Only eight (2.8%) trials reported results considering age or sex, and four (1.4%) trials reported results by race and ethnicity groups (Table 2). No trial reported results stratified by HBV genotypes or recruitment regions.

Representation of clinical trial participants compared to the global population affected by CHB

The weighted average age of participants in clinical trials was similar to that of the global population with CHB (38.8 *vs.* 37.9 years) (Table S5). However, people of female sex were under-represented, with a representation ratio of 0.7, suggesting females are under-represented by 30% in CHB trials (Fig. 2A).

Although 31.0% of people affected by CHB are living in Africa, only five (0.01%) participants were recruited from Africa, demonstrating vast under-representation (representation ratio <0.001) (Fig. 2B, Table S5). People living with CHB in Asia were over-represented in trials by 40% (representation ratio 1.4), with even more over-representation of people living with CHB in Europe or Americas (representation ratio 2.5).

Similarly, although many people with CHB are living in low-income or lower-middle-income countries, they contributed very few participants to trials (representation ratios 0.0, 0.1) (Fig. 2B). Most participants were recruited from upper-middle-income countries and high-income countries, despite the relative low proportions of people affected by CHB (representation ratios 1.9, 5.5).

Disproportionate distribution was also observed on the country-level (Fig. 3), which highlights variations even within regions. For instance, over-representation within Asia was largely driven by China, with poor trial representation in Indonesia, which has a significant burden of CHB.

People with different HBV genotypes were not well represented in trials, with over-representation of genotype B and C (representation ratios 2.2, 1.9), and under-representation of the remaining genotypes (Fig. 2A, Table S7). This under-representation was particularly stark for genotype E, affecting 17.6% of the world population with CHB (representation ratio 0.04).

Exclusion criteria

Most trials excluded children (205, 71.4%), and many (119, 41.5%) excluded older adults (Table 2). A small number of trials (6, 2.1%) recruited children only, contributing 1.1% (621) of the total participants. No trials recruited older adults exclusively. More trials had eligibility restrictions related to female than male sex (157, 54.7% *vs.* 38, 13.2%) (*e.g.* excluding pregnant women). Seven trials with 1,186 (2.1%) participants recruited women (with pregnancy or in child-bearing age) only. Although no trials had race and ethnicity exclusion criteria, four trials recruited specific Asian ethnicity participants, and one trial recruited English-speaking participants only.

Concerningly, among more recently published trials (2019–2023), more trials reported exclusions related to age or

Table 2. Summary of included clinical trials (N = 287) by transparency of participants' demographics in recruitment and results reporting; and demographic-related eligibility criteria.

Transparency					
Trials*	**Age**	**Sex**	**Race and ethnicity**	**Region of recruitment**	**HBV genotype**
Reporting cohort characteristics	285 (99.3)	278 (96.9)	107 (37.3)†	254 (88.5)	84 (29.3)
Reporting results stratified by	8 (2.8)	8 (2.8)	4 (1.4)‡	0 (0.0)	0 (0.0)

Eligibility criteria			
Trials*	**Age**	**Sex**	**Race and ethnicity**
With inclusion criteria for	Children only: 6 (2.1) Older adults only: 0 (0.0)	Female only: 7 (2.4) Male only: 0 (0.0)	Specific ethnicities: 4 (1.4) English-speaking: 1 (0.3)
With exclusion criteria for	Children: 205 (71.4) Older adults: 119 (41.5)	Female-related§: 157 (54.7) Male-related¶: 38 (13.2)	Ethnicity-related: 0 (0.0)

*Data presented as n (%).
†Of 235 single-country trials, 57 (24.3%) of them reported participant race and ethnicity; of 52 multinational trials, 50 (96.2%) reported participant race and ethnicity.
‡Reporting categories were: (1) Chinese, Malay; (2) Chinese, non-Chinese East Asian; (3) Asian, non-Asian; and (4) Australian or European, Asian, Others.
§Exclusions included females who were pregnant, breastfeeding, and/or declined specific birth control measures.
¶Exclusions included males who declined specific birth control measures, and/or whose wife was pregnant or breastfeeding.

sex (Fig. 4). Trials not reporting any funding sources tended to report fewer age- or sex-based exclusions than those reporting industry, government, or other funding, which had broadly similar exclusion criteria and rates (Fig. S1). There were also fewer exclusions among phase III and IV trials than phase I and II trials, although over 50% still had female-related exclusions or exclusions of children, and over 25% still had exclusions of older adults. Exclusions related to intervention type were broadly concordant with expected risk–benefit profile, with the most exclusions among 'other drug' interventions, which included novel agents, fewest among non-drug interventions, and more exclusions based on age for interferon trials compared with nucleos(t)ide analogues.

Discussion

Key findings and contextualisation

We found recent RCTs for CHB have limited transparency in the reporting of participant race and ethnicity and HBV genotype, and under-representation of people of female sex and living in Africa. Children and older adults were frequently excluded, and this has increased over time. Such distorted population representation, combined with a near-absence of trial results stratified by demographic features, limit the generalisability of findings for existing and new interventions to key populations, particularly given the plausibility of differential effects for some groups (*e.g.* women). Targeting of these under-represented groups requires close attention in future trial design, recruitment, and reporting.

Limited transparency of reporting by race and ethnicity or HBV genotype

The interaction between race and ethnicity, geographic location, and HBV genotype remains an under-studied area of importance to CHB pathophysiology. For example, there are recognised variations in the natural history of CHB by ethnicity (leading to the stratification of hepatocellular carcinoma surveillance recommendations for people of Asian and African descent[25]) and regional differences in CHB treatment efficacy (*e.g.* lower rates of HBsAg loss in clinical trials in Asia [2%] compared with those in Europe and North America [20%][26]). HBV genotypes differ substantially genetically, affecting treatment response.[26,27] For example, genotype A and B might respond better than genotype C and D to interferons.[27] Yet, the biology of such differences in both natural history or treatment response are poorly understood and under-studied, including the relative contribution of the geographic variations in HBV genotype *vs.* host genetic differences. Our understanding of such factors, and their impact on treatment paradigms, will likely remain elusive without more diverse participation in and reporting of clinical trials.

There are likely to be multiple factors contributing to poor transparency. Although in contrast with recommendations to report information on race and ethnicity in trials,[28] how race and ethnicity are used in medical research remains debated.[29] Uncertainty about how to include these details in trial manuscripts could be a reason for the low proportion of trials reporting such information. Limited transparency regarding HBV genotypes may relate to limited testing, either owing to financial constraints or low HBV DNA levels among participants. Although we used country of recruitment in our analysis

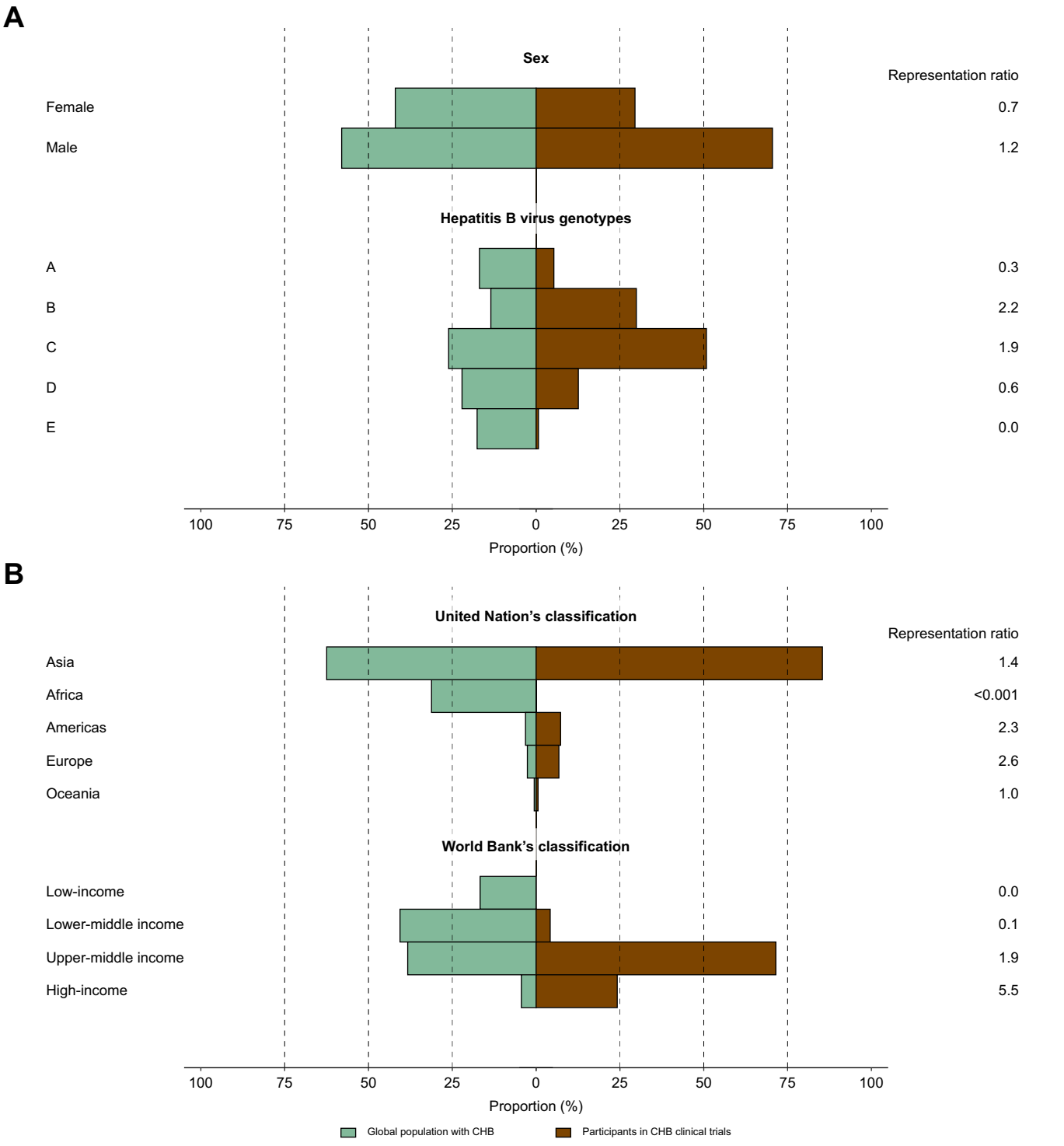

Fig. 2. Tornado plot demonstrating the proportions of the global population with CHB to those of participants in CHB clinical trials. (A) By sex* and hepatitis B virus genotype† and (B) by geographic regions of recruitment‡. Representation ratio defined as the proportion of people in CHB trials divided the proportion of people globally with CHB. *Included participants with reported sex from 278 trials (n = 56,111). †Included participants with reported HBV genotypes from 84 trials (n = 14,060). Genotypes with a global distribution less than 1.0% were not included. Global data adapted from: Velkov S, Ott JJ, Protzer U, Michler T. The global hepatitis B virus genotype distribution approximated from available genotyping data; Genes (Basel), 2018;9:495. ‡Included participants from 235 single-country trials and 19 multi-national trials with reported recruitment locations (n = 51,841). Geographic regions were classified per United Nations geographic regions and World Bank income classification. CHB, chronic hepatitis B.

to proxy these factors, a high proportion of multinational trials did not report recruitment numbers by geographic region, although this information is objective and readily available. This could certainly be easily remedied in future trial reporting.

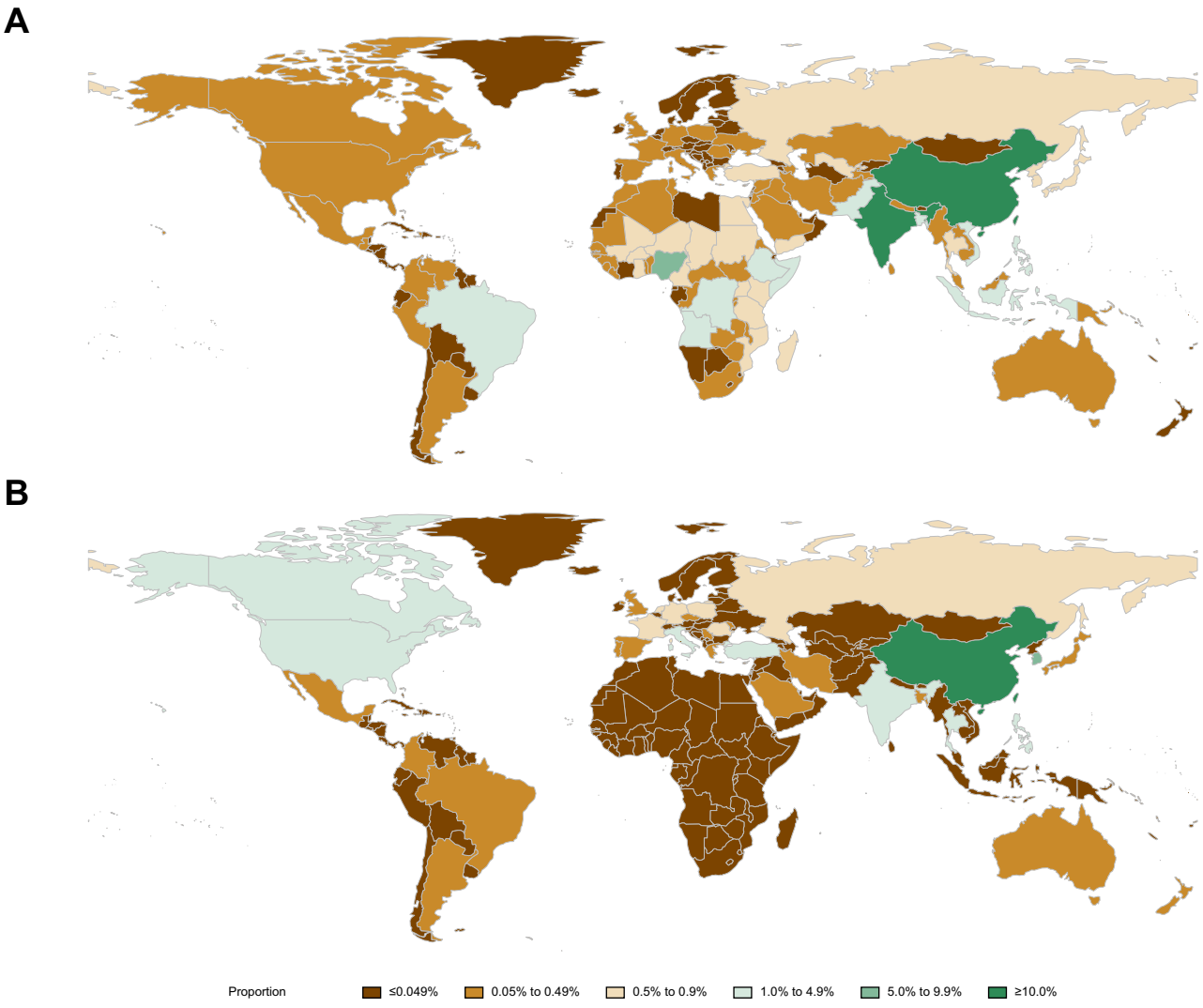

Fig. 3. Geographic distribution. (A) People living with chronic hepatitis B in 2021* and (B) total weighted number of participants included in trials (n = 51,841)†. *Data extracted from Global Burden of Disease Study 2021. Countries with no available prevalence data are shown in white. †Trials with no geographic information are not shown (n = 33).

Under-representation of people living in Africa in CHB trials

We found gross distortions in geographic representation of CHB trials, which may exacerbate existing global inequities in CHB outcomes, and lead to issue of distributive justice. Specifically, the low proportions of CHB trial participants recruited from Africa, of Black race or African ethnicity, or infected with HBV genotype E, is in stark contrast to Africa's high prevalence and incidence of CHB,[8] limited access to existing treatments,[30] and more aggressive disease phenotypes.[31] Although limited trial activity in Africa represents one reason for the under-representation of people of Black race or African ethnicity in global trials, Mitchell *et al.*[32] have demonstrated that this population remains inadequately represented in CHB trials conducted in high-income countries, pointing to broader structural inequalities in clinical research participation. Sub-Saharan Africa has a much higher proportion of people aged under 20 years (36.4% *vs.* 17.6% globally),[8] and genotype E, exclusively found in Africa in high prevalence, is associated with young onset of CHB-associated hepatocellular carcinoma.[31] Given limited access to current models of care, African people likely have the most to gain from the development of curative therapies for CHB being studied in ongoing clinical trials.[30] Intersectionally, with more young people afflicted by CHB,[8] higher fertility rates,[18] and younger onset of CHB-related liver cancer,[8,31] Africans affected by CHB are more likely to benefit from inclusive research considering the benefits of treatment for CHB at younger ages or during pregnancy, as well as adverse events associated with life-long treatment.

How can we remedy such poor CHB trial recruitment from Africa? Although most countries in Africa are of low-income or lower-middle-income,[13] the large number of HIV clinical trials in Africa has demonstrated that a regional-level lack of financial resources alone should not be regarded as the primary reason for this under-representation.[14,33] This highlights needs for building support for clinical triallists in lower-income countries

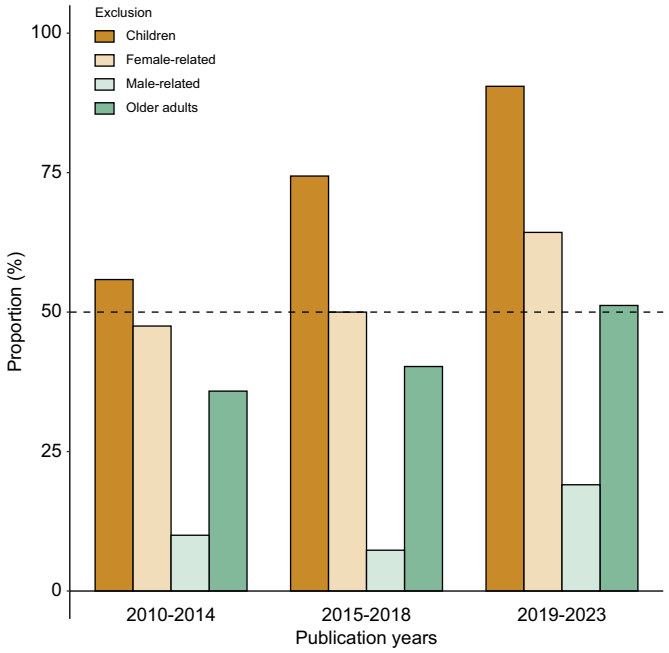

Fig. 4. Exclusion criteria in CHB clinical trials (N = 287) by publication year. The dashed line indicates 50%.

to conduct more CHB trials, as has been seen in trials for HIV, such as increased infrastructure funding, and by addressing ethical and logistical barriers.[14,33] Where multinational trials are implemented in developing countries, there are likely to be additional costs and set-up time, but the necessity has been emphasised, and relevant frameworks outlined, in global health documents.[34–36]

Sex disparities in CHB trial representation

The under-representation of people of female sex in CHB trials may relate to the high frequency of sex-based trial exclusions. WHO guidelines for clinical trials illustrated that the exclusion of pregnant and lactating women is justified if 'they are at very low risk of the health issue the trial seeks to address'.[37] Pregnancy-based trial exclusions for CHB may be arguably justified in risk–benefit analysis given the safety of current antivirals therapy to both pregnant women and foetus and the low risk of vertical transmission.[38] However, trial exclusions often extend beyond the pregnancy period to all females of 'child-bearing potential'. International guidelines for clinical trial practices have been established to enable clinical trials to include pregnant and lactating women and women of child-bearing age.[37,39] Other issues contributing to differential enrolment of women were beyond the scope of this study, but have been described elsewhere. For instance, in other disciplines, non-sex-based exclusions have been shown to disproportionately affect women.[40] Bias in medical care provision is well-recognised, and seen in CHB in with inequitable treatment prescription for women;[41] this bias may extend to clinical trial recruitment differences. Compounding the effects of under-representation, while the Sex and Gender Equity in Research guidelines also urge researchers to report results by sex where differences in treatment effects are likely,[42] we found this was lacking. Female representation and result reporting in CHB trials is important given sex hormones impact both the pathophysiology of CHB and pharmacokinetics of drug treatments.[10,11,26] Female sex is associated with lower rates of antiviral treatment response.[41] To address female under-recruitment, it is essential for triallists to address issues of equity and justice, and provide justification on female-based exclusion criteria.

Lack of data for children and older adults

The frequency and persistency of age-based exclusions as well as lack of age-stratified results are concerning, even if the median age of trial participants correlated with the global burden. There are known differences in CHB at the extremes of age. For instance, the frequent exclusion of older adults from CHB is a missed opportunity to generate relevant evidence for the age group with highest morbidity from CHB.[8] As such, CHB treatment guidelines tend to have laxer criteria for treatment with advancing age.[25] The generalisation of evidence to older adults from trials that exclude them is problematic, because of differences in physiology, increased rates of other chronic illness, and polypharmacy.[8] The necessity of inclusion of older adults in trials where they form a key part of the target population is well-recognised,[43] and CHB triallists must focus on removing unnecessary age-based exclusions, and improving the reporting of results by age so specific harms can be identified.

Children with CHB not only have differences in human and disease biology, but face potential life-long consequences of a chronic disease and/or complications from long-term treatment. International guidelines for treatment of children with CHB vary given the lack of evidence (*e.g.* entecavir only recommended at age 16 years in European [2017] and Asian Pacific [2016] guidelines, but from age 2 years in American [2018] and age 12 years in WHO [2024] guidelines[38,44–46]). Key questions remain regarding when to start treatment;[9] for instance, the possibility that antiviral initiation among infants could lead to high rates of functional cure is tantalising.[47] Specifically designed trials for children may be warranted to answer such questions. The inclusion of children in broader clinical trials is complex, and triallists must weigh potential benefits *vs.* long-term consequences of unknown risks of new treatments. In addition, trial complexity increases with challenges regarding informed consent and administrative requirements.[5] However, where drugs are likely to be applied to their context in clinical practice, especially phase IV studies with existing guideline-based treatment indications, the routine exclusion of children without specific justification is another missed opportunity to generate relevant evidence.[5,43]

Strengths and limitations

This is the first study to quantitatively investigate the transparency and representation of global CHB clinical trials at the participant level. Our study design is systematic and prospectively registered. The coverage of trials was maximised by including all types of interventions without language

exclusions. We supplemented bibliographic information with supplementary material and registry data, and homogenised demographic and result reporting formats. In addition, we compared the findings to accepted and most recent global CHB prevalence data, and followed international standard definitions.[8]

Limitations include the number of trials with no reported clinical trial ID, which may mean the true number of exclusions is under-reported where trials have additional unpublished criteria. Representation results are limited to those studies which reported demographics (as denoted by transparency percentages), although we had robust data available for comparison for age, sex, and recruitment country (>90%), genotype data are limited to 24.5% (14,060) of participants. This limited genotype data introduced constraints in our representation ratio analysis, and hindered our ability to draw definite conclusions about the representation by HBV genotypes. The exclusion of trials with coinfections may have biased results given the prevalence of coinfection with HIV in Africa; among the three trials excluded for coinfections, only 106 participants are from Africa, with the remainder from Asia and Europe, where over-representation occurs. In addition, while we focused on race and ethnicity, HBV genotype, and geographic representation, we recognise that numerous other vulnerable populations (*e.g.* migrants, individuals experiencing homelessness) living with CHB may also face barriers to trial participation, and these structural barriers should be addressed. Understanding and addressing health inequities for these populations requires specific contextual analysis of local healthcare systems, social determinants of health, and structural barriers, which beyond the scope of our current study.

Implications of research

Although the ongoing pace of research in CHB is admirable, there remains scope for improvement in the trial landscape to improve care equitably. This is a global imperative, according to UN SDG.[30] We suggest the need for increased inclusion of older adults and children in trials, where other inclusion and exclusion criteria can be met, and no specific age-based exclusion is justified. Focused trials on specific needs of under-represented populations may redress overall inequities. Targeted recruitment of children, women, and those living in Africa should be a key consideration for those designing and funding future trials, as well as building mechanisms to support triallists to conduct more trials where the needs are the most. These changes are likely to require additional time, cost and trial complexity which needs consideration from the outset. Relevant stakeholders, including researchers, publishers, and funders, must also be aware of the failure to report basic demographics and stratify results by subgroups, where the potential influences in the biology of CHB and differential effectiveness of treatments for different groups could have practical impacts on disease outcomes.

Conclusions

There is an under-representation of people of female sex and people living in Africa in clinical trials for CHB, limited transparency regarding participant HBV genotype and race and ethnicity, and frequent exclusion of children and older adults. It is crucial for researchers, funders, and publishers to actively consider equity and inclusion when designing, conducting and reporting CHB trials.

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Abbreviations

CHB, chronic hepatitis B; GBD, Global Burden of Disease; HBV, hepatitis B virus; PRISMA, Preferred Reporting Items for Systematic Review and Meta-Analysis; PROSPERO, International Prospective Register of Systematic Reviews; RCTs, randomised controlled trials; SDG, Sustainable Development Goals; UN, United Nations; WHO, World Health Organization.

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Authors' contributions

Contributed to the concept development: XH, KW, SM, AW. Performed the literature search: XH. Data abstraction: XH, KW. Statistical analysis: XH. Data interpretation: XH, KW. Prepared the draft manuscript: XH. Critical review of the draft manuscript: SM, AW. Critical review: KW. Supervision: KW. Commented on the draft manuscript and approved the final manuscript for submission: all authors.

Data availability statement

Data are available upon request to the corresponding author.

Supplementary data

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References

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[1] Sheena BS, Hiebert L, Han H, et al. Global, regional, and national burden of hepatitis B, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Gastroenterol Hepatol 2022;7:796–829.

[2] Seaman CP, Luong P, Xiao Y, et al. A global investment case for hepatitis B elimination: a modelling study. Lancet Gastroenterol Hepatol 2023;8:932–942.

[3] Knottnerus JA, Tugwell P. Heterogeneity and clinical reality. J Clin Epidemiol 2013;66:809–811.

[4] National Academies of Sciences. Engineering, and medicine; policy and global affairs; committee on women in science, engineering, and medicine; committee on improving the representation of women and underrepresented minorities in clinical trials and research. Why diverse representation in clinical research matters and the current state of representation within the clinical research ecosystem. Washington, DC: National Academies Press; 2022.

[5] Versavel S, Subasinghe A, Johnson K, et al. Diversity, equity, and inclusion in clinical trials: a practical guide from the perspective of a trial sponsor. Contemp Clin Trials 2023;126:107092.

[6] World Medical Association. World medical association declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013;310:2191–2194.

[7] World Health Organization. WHO statement on public disclosure of clinical trial results. https://cdn.who.int/media/docs/default-source/medicines/regulatory-updates/who_statement_results_reporting_clinical_trials.pdf?sfvrsn=805357d7_5#:~:text=Negative20and20inconclusive20as20well,trials20conducted20in20the20past. [Accessed 18 June 2024].
[8] Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2021 (GBD 2021) Results. Seattle, United States: Institute for Health Metrics and Evaluation (IHME), 2022. Available from https://vizhub.healthdata.org/gbd-results/. [Accessed 20 June 2024].
[9] **Indolfi G**, **Easterbrook P**, Dusheiko G, et al. Hepatitis B virus infection in children and adolescents. Lancet Gastroenterol Hepatol 2019;4:466–476.
[10] Matthews PC, Brown R, Goulder P. Sexual dimorphism in chronic hepatitis B virus (HBV) infection: evidence to inform elimination efforts. Wellcome Open Res 2022;7:32.
[11] Wang S-H, Chen P-J, Yeh S-H. Gender disparity in chronic hepatitis B: mechanisms of sex hormones. J Gastroenterol Hepatol 2015;30:1237–1245.
[12] Velkov S, Ott JJ, Protzer U, et al. The global hepatitis B virus genotype distribution approximated from available genotyping data. Genes (Basel) 2018;9:495.
[13] World Bank. No. 7528 the World Bank's classification of countries by income. Washington, DC: World Bank; 2016.
[14] Delphin M, Mohammed KS, Downs LO, et al. Under-representation of the WHO African region in clinical trials of interventions against hepatitis B virus infection. Lancet Gastroenterol Hepatol 2024;9:383–392.
[15] Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.
[16] Murad MH, Wang Z. Guidelines for reporting meta-epidemiological methodology research. Evid Based Med 2017;22:139–142.
[17] Veritas Health Innovation. Covidence systematic review software. www.covidence.org.
[18] United Nations Department of Economic and Social Affairs, Population Division. World population prospects 2022: summary of results. (UN DESA/POP/2022/TR/NO. 3), 2022. https://population.un.org/wpp/publications?year=previous. [Accessed 1 September 2023].
[19] United Nations Department of Economic and Social Affairs, Statistics Division. Methodology. Standard country or area codes for statistical use (M49), 2023. https://unstats.un.org/unsd/methodology/m49/. [Accessed 1 September 2023].
[20] Flanagin A, Frey T, Christiansen SL, et al. The reporting of race and ethnicity in medical and science journals: comments invited. JAMA 2021;325:1049–1052.
[21] Flanagin A, Frey T, Christiansen SL, AMA Manual of Style Committee. Updated guidance on the reporting of race and ethnicity in medical and science journals. JAMA 2021;326:621–627.
[22] RStudio Team. RStudio: integrated development environment for R. Boston, MA. 2020.
[23] Wickham H. ggplot2: elegant graphics for data analysis. New York, NY: Springer; 2016.
[24] South A. rworldmap: a new R package for mapping global data. R J 2011;3:35.
[25] Lubel JS, Strasser SI, Thompson AJ, et al. Australian consensus recommendations for the management of hepatitis B. Med J Aust 2022;216:478–486.
[26] Peters MG, Yuen M-F, Terrault N, et al. Chronic hepatitis B finite treatment: similar and different concerns with new drug classes. Clin Infect Dis 2024;78:983–990.
[27] Raimondi S, Maisonneuve P, Bruno S, et al. Is response to antiviral treatment influenced by hepatitis B virus genotype? J Hepatol 2010;52:441–449.
[28] Chew M, Samuel D, Mullan Z, et al. The Lancet Group's new guidance to authors on reporting race and ethnicity. Lancet 2024;403:2360–2361.
[29] Schaefer GO, Tai ES, Sun SHL. Navigating conflicts of justice in the use of race and ethnicity in precision medicine. Bioethics 2020;34:849–856.
[30] United Nations. The sustainable development Goals report: special edition, 2023. https://unstats.un.org/sdgs/report/2023/The-Sustainable-Development-Goals-Report-2023.pdf. [Accessed 1 September 2023].
[31] Ingasia LAO, Wose Kinge C, Kramvis A. Genotype E: the neglected genotype of hepatitis B virus. World J Hepatol 2021;13:1875–1891.
[32] Mitchell T, Nayagam JS, Dusheiko G, et al. Health inequalities in the management of chronic hepatitis B virus infection in patients from sub-Saharan Africa in high-income countries. JHEP Rep 2023;5:100623.
[33] **González-Alcaide G**, **Menchi-Elanzi M**, Nacarapa E, et al. HIV/AIDS research in Africa and the Middle East: participation and equity in North-South collaborations and relationships. Glob Health 2020;16:83.
[34] World Health Organization. Strengthening clinical trials to provide high-quality evidence on health interventions and to improve research quality and coordination. https://apps.who.int/gb/ebwha/pdf_files/WHA75/A75_R8-en.pdf 2022. [Accessed 1 September 2023].
[35] CESCR. General comment No. 14 (2000) on the right to the highest attainable standard of health. Philadelphia: University of Pennsylvania Press; 2006. p. 359–376. Article 12).
[36] Pratt B. Research for Health Justice: an ethical framework linking global health research to health equity. BMJ Glob Health 2021;6:e002921.
[37] World Health Organization. Guidance for best practices for clinical trials. Geneva: WHO; 2024.
[38] Sarin SK, Kumar M, Lau GK, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol Int 2016;10:1–98.
[39] ICH Final Concept Paper. E21: inclusion of pregnant and breast-feeding individuals in clinical trials. Geneva, ICH. 2023.
[40] Stanton RJ, Aziz YN, Sucharew H, et al. Clinical trial exclusion criteria affect trial inclusivity by race and sex. J Am Heart Assoc 2024;13:e035102.
[41] **Kudaravalli S**, **Huang DQ**, Yeh M-L, et al. Sex and ethnic disparities in hepatitis B evaluation and treatment across the world. J Hepatol 2024;81:33.
[42] Heidari S, Babor TF, De Castro P, et al. Sex and gender equity in research: rationale for the SAGER guidelines and recommended use. Res Integr Peer Rev 2016;1:2.
[43] National Institutes of Health. Revision: NIH policy and guidelines on the inclusion of individuals across the lifespan as participants in research involving human subjects. https://grants.nih.gov/grants/guide/notice-files/NOT-OD-18-116.html; 2017. [Accessed 1 September 2023].
[44] Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 2018;67:1560–1599.
[45] Lampertico P, Agarwal K, Berg T, et al. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2017;67:370–398.
[46] World Health Organization. Guidelines for the prevention, diagnosis, care and treatment for people with chronic hepatitis B infection. Geneva: WHO; 2024.
[47] Wang F-S, Li J, Zhang C. Why is the functional cure rate of young children with chronic hepatitis B receiving antiviral therapy considerably high? Hepatol Int 2024;18:296–298.

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