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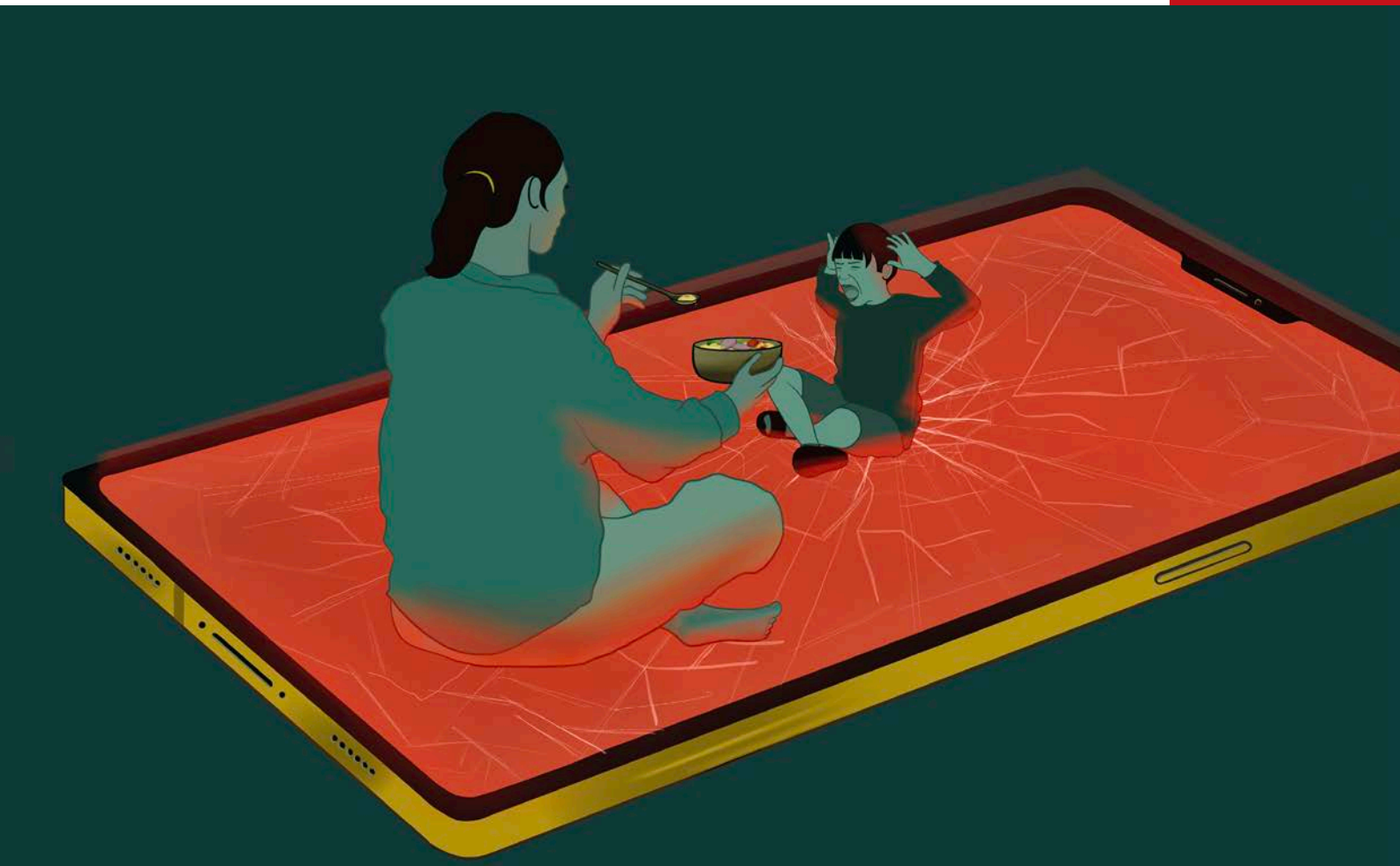

Screen time and social-emotional skills in preschoolers with developmental, behavioural or emotional issues in Singapore

New study reveals that children with developmental, behavioural or emotional issues are exposed to screen time earlier than in recommended guidelines. This early exposure is linked to increased inattention, aggression and behavioural concerns in toddlers. (See full article, p.410)

Illustration by Ladyfingers Co.

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EDITORIAL

Balancing screen time: Insights and impact on preschool children

Daisy Kwai-Lin Chan[1,2] *MMed (Paed)*

Over the past decade, the exposure of young children to screen devices at home and preschool has become increasingly common. Screen viewing time (SVT) has risen alongside the surge in ownership of screen devices such as television, smartphones, tablets and laptops worldwide.[1] In many countries, screen time and digital technology is utilised as tools to support young children's development of practical skills in creativity, problem-solving, curiosity, and expanding their knowledge to new topics, cultures and ideas. However, screen time can be a double-edged sword.[2]

In this issue of the *Annals*, Kiing et al. are to be congratulated for conducting a cross-sectional study of preschool children (0–5 years old) who were referred for developmental, behavioural or emotional (DBE) issues.[3] The study aimed to investigate patterns of SVT in children with DBE issues, including changes over time and reasons for SVT introduction, and to evaluate the relationship between SVT and social-emotional development using the Devereux Early Childhood Assessment-Clinical (DECA-C) questionnaire.[3] The authors found that among 225 children with a mean age of 32.4 months, the mean SVT was 138.1 minutes per day.[3] This duration exceeds the recommendation of expert guidelines from the World Health Organization,[4] American Academy of Paediatrics,[5] Canadian Paediatric Society,[6] Asia-Pacific experts[7] and the Singapore Ministry of Health (MOH).[8] The 2023 MOH Guidance on Screen Use in Children advises that sedentary screen time is not recommended for toddlers younger than 18 months, except for interactive video-chatting.[8] For children aged between 18 months and 3 years, screen time should be limited to less than 1 hour per day.[8] The study reported a mean age of 13.8 months for the introduction of screen time,[3] which is also earlier than recommended.[4]

Parents of study subjects admitted that introducing screen time in the first 12 months was often to facilitate easier feeding during mealtimes.[3] This is commonly observed in Singapore, where infants may be seen engrossed in a smartphone while being spoon-fed. The study's cross-sectional design means that an observed association does not always imply causation. Some children with attentional issues may rely on screens to stay seated long enough for caregivers to complete feeding. The relationship between screen viewing time and socio-emotional development is complex and interlinked.

Of greater concern is the downstream effect of excessive SVT on the health and well-being of developing pre-school children, which can be divided into 4 categories—socio-emotional and language development, physical health, sleep quality, and quality parent-child interaction. Using the standardised DECA-C questionnaire, Kiing et al. revealed an association between higher past SVT and lower social-emotional skills,[3] reflected as limited self-regulation, poor attentional skills, more aggression, and total behavioural concerns. Offering a screen device to distract or calm the upset child may preclude self-soothing strategies, lead to emotional instability and over-dependence on screens for emotion regulation, with missed opportunities for learning anger management. Excessive screen time is also associated with expressive language delay at 18 months,[9] poor attention control in toddlers, and lower cognitive development and executive function.[10] A systematic review of 42 studies showed that greater screen time was associated with lower language skills, while better-quality screen use was associated with stronger language skills.[11] Later onset of screen use was also linked to stronger language skills.[11]

Excessive screen viewing, except for physically engaging videos like yoga or dance, is associated with poorer physical heath. Although SVT had not been strongly correlated with weight gain in preschoolers, the risk of becoming sedentary persists into later life, leading to obesity and associated cardiovascular disease.[12] Viewing commercial advertisements can induce children to choose unhealthy food and encourage snacking on junk food, increasing overall intake.[13] Prolonged

[1] Department of Neonatal & Developmental Medicine, Singapore General Hospital, Singapore
[2] Department of Child Development, KK Women's & Children's Hospital, Singapore
Correspondence: Associate Professor Daisy Kwai-Lin Chan, Department of Neonatal & Developmental Medicine, Singapore General Hospital, Academia Level 3, College Road, Singapore 169856.
Email: daisy.chan.k.l@singhealth.com.sg
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screen time, near viewing and limited outdoor activities are linked to the onset and progression of myopia, especially during school closures when digital device use increases.[14]

The presence of screen devices in a child's bedroom is strongly associated with less sleep due to arousal from viewing, melatonin suppression and sleep displacement. This can lead to shorter night-time sleep, more daytime napping, later bedtimes, delayed sleep onset and greater sleep resistance.[15] Although a digital screen cannot replace quality parent-child interaction, it is often used to keep children occupied, similar to a nanny's role. This "techno-ference" displaces quality, face-to-face interaction, depriving children of interactive storytelling, shared book reading, problem-solving and building shared memories with parents. Parents in Singapore have voiced serious concerns for their child's digital media use, including addiction, poor eyesight, inappropriate content, lack of parent-child interaction, poor sleep and lack of physical activity. Yet, they did not seem to enforce changes to limit screen use.[16]

How can healthcare providers minimise excessive SVT in preschool children?

Child-centred approaches

- For children younger than 18 months, screen time should be avoided, except for interactive video-chatting with caring adults.
- For toddlers (18 months to 3 years old) and preschoolers (3–5 years old), limit sedentary screen time to less than 1 hour per day.
- Maintain screen-free times around meals and an hour before bedtime. Establish bedtime routines to help preschoolers fall asleep.

Parent/caregiver-centred approaches

- Co-view screen content with children to encourage digital media literacy by helping them recognise and question advertising messages, stereotyping and inappropriate content.
- Support self-regulation without screen use by discussing alternative strategies for managing anger and emotional lability.
- Curate appropriate playlists and limit exposure to advertising content.

Family-centred approaches

- Encourage families to prioritise shared media use, such as watching movies or playing video games together, over solitary use by children.
- Promote activities unrelated to screens, such as shared book reading, outdoor play, board games and crafts.

Future studies on screen viewing in young children should consider parental screen viewing patterns, as parents are often the first role models children emulate. This study underscores the need for similar research in neuro-typical population, emphasising the collective responsibility of parents, caregivers, healthcare providers and early childhood educators to ensure the holistic well-being of children, including their digital health.

Declaration

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Keywords: *children, developmental paediatrics, emotional regulation, language expression, preschool, screen time, toddlers*

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EDITORIAL

The alcohol flushing syndrome: A risk factor for cancer

Meng Sha*[1] *PhD*, Jia-qian Sun*[2] *PhD*, Qiang Xia[1] *PhD*

Globally, alcohol consumption is responsible for an estimated 3 million deaths annually and contributes to over 740,000 new cancer cases each year.[1] Acetaldehyde, a byproduct of alcohol metabolism, has been designated as first-class carcinogens by the International Agency for Research on Cancer.[2] In East Asian countries such as China, Japan and Korea, approximately 36% of the population cannot effectively metabolise alcohol due to an inherited deficiency in the enzyme aldehyde dehydrogenase 2 (ALDH2).[3] This deficiency leads to the accumulation of acetaldehyde in the blood, causing alcohol flushing syndrome (AFS), characterised by facial flushing, palpitations and nausea.[4] AFS is a predictor of inactive ALDH2 and is associated with a higher risk of cancer development.

To date, numerous studies have confirmed the relationship between AFS and esophageal squamous cell carcinoma (ESCC).[5] However, evidence remains inconclusive for many other cancers such as those of the pancreas, stomach and lung. Additionally, the impact of different drinking patterns, including frequency and quantity, on cancer risk has not been thoroughly investigated. Previous studies have been limited by the types of cancers studied, single-centre designs and relatively small sample size.[6] Therefore, a comprehensive analysis of the impact of AFS on cancer risk is urgently needed, particularly in East Asia where hereditary factors, drinking patterns and cancer types differ significantly from those in the West.

In an article published in this issue of the *Annals*, Sim et al. respond to this need through a systematic review and meta-analysis, which investigated the risk of cancers associated with AFS and examined the presence of a dose-response relationship.[7] The analysis included 18 studies from East Asian countries, encompassing 387,521 participants across various types of cancers. The results showed that AFS was associated with an increased risk of all cancers, with the most significant relationships observed in ESCC, gastric adenocarcinoma and male flushers. These findings align with global research on alcohol consumption, which has revealed that 4.1% of all new cases over a 10-year period are attributable to alcohol consumption. Males accounted for more than 500,000 (76.7%) of total alcohol-attributable cancer cases, with esophageal and liver cancers contributing the most cases.[8]

Subgroup analysis based on alcohol consumption levels showed that flushers who drank more than 200 g of pure ethanol/week had a higher risk of cancer compared to those who drank less than 200 g of pure ethanol/week. Furthermore, the increase in cancer risk for flushers was more pronounced at higher levels of regular alcohol consumption compared to non-flushers who drank the same amount. These results provide evidence of a dose-response relationship between alcohol intake and cancer risk, suggesting that certain drinking patterns exacerbate the risk. Additionally, the findings confirm the biological mechanism whereby the East Asian-specific ALDH2 loss-of-function mutation leads to acetaldehyde accumulation, causing AFS and increasing cancer risk. This meta-analysis, based on large population-level data, supports the association between AFS and increased cancer risk, as well as a dose-response relationship.

The impact of AFS on cancer risk is particularly concerning in East Asian populations. Individuals often overcome the discomfort of flushing to continue drinking, developing some level of alcohol tolerance. One reason for this behaviour is the lack of knowledge about the causes of flushing and its potential outcomes. Without formal alcohol education in schools, changing long-standing attitudes towards drinking through social media promotion is essential. Providing accurate information about the cause of AFS and its associated risks could raise awareness and offer practical genetic feedback to drinkers.[9] Social pressures and relationship maintenance also contribute to continued drinking among flushers.

[1] Department of Liver Surgery, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China
[2] Department of Endocrine, Shanghai Ninth People's Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China
* Joint first authors
Correspondence: Prof Meng Sha and Prof Qiang Xia, Department of Liver Surgery, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200127, China.
Email: simonsha23@163.com

Heavy drinking occasions, particularly those involving celebrations, etiquette requirements and drinking goals, often override concerns for flushers. Developing motivational strategies to create social expectations for bystanders to assist friends who flush by reducing or stopping their drinking is crucial. An increasing number of young people, including college students, suffer from AFS and seek ways to hide the visible effects.[10] University professionals must increase students' awareness of the link between AFS and cancer risks. It is also important to remind students that taking allergy medications before drinking is problematic, as it raises blood alcohol levels without altering acetaldehyde metabolism. Internet-based interventions and reminders from friends are recommended to reduce or stop drinking.

In summary, AFS is associated with a higher cancer risk in East Asian male populations, particularly in ESCC and gastric adenocarcinoma. Certain drinking patterns, such as daily drinking and consuming more than 200 g of pure ethanol/week, further exacerbate the cancer risks in flushers. Based on the findings, a simple facial flushing questionnaire is suggested to quickly identify individuals at high risk of cancer. Moreover, education about the cause of AFS and its potential hazards from alcohol consumption is urgently needed to protect against chronic alcoholism and cancer risks. Public health support targeting flushers at high risk of cancer must be focused and integrated to reduce or stop their drinking.

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Declaration

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Keywords: *alcohol consumption, alcohol flushing syndrome, cancer, medical education, public health*

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EDITORIAL

How close are we from achieving demographic diversity in clinical trials? Insights from Singapore

Yueyang Yi[1] *MSc*, Thomas Yuen Tung Lam[1,2] *PhD*

Clinical trials are essential for assessing the efficacy and safety of new therapies. Because different patient subgroups may respond variably to treatments, it is important to emphasise diversity among participants. This approach ensures that the trial population accurately reflects the patients who will use the medication in real-world settings and helps generate broadly applicable evidence. Over half a century after Archie L. Cochrane's call for robust, impactful and equitable trials,[1] external validity remains a significant concern for clinicians when applying clinical trial results.

Results from clinical trials may not be universally applicable due to distorted demographic representativeness caused by trial recruitment criteria. Recent studies highlight this issue: for 302 cancer trials with 262,354 participants from the US conducted between 1994 and 2015, the median age of trial participants was on average 6.47 years smaller than the population median age for the disease site.[2] In 122 COVID-19 trials with 176,654 US participants, female representation was 48.9% in prevention trials and 44.6% in treatment trials, compared to 52.4%[3] in the general US population. Among 213 Pfizer-funded trials with 103,103 US participants conducted between 2011 and 2020, Asian participants exceeded census levels in 16.0% of trials, Native Hawaiian and Pacific Islander participants in 14.2%, and American Indian and Alaska Native participants in only 8.5% of trials.[4] The lack of diversity in clinical trials—manifested in age, sex and ethnic disparities—has long been considered a moral, scientific and medical issue that hinders innovation and accessibility.[5]

Singapore is renowned for its long-term commitment to fostering an inclusive society for its 4 major ethnic groups: Chinese, Malay, Indian and Others. Due to its island city-state nature, Singaporean participants are frequently involved in multiregional clinical trials. This issue of the Annals features one of the first systematic review that comprehensively examines the representativeness of participants in pharmaceutical randomised controlled trials conducted in Singapore. This review not only enhances our understanding of local clinical trials, but also highlights the importance of diversity representation in multiregional clinical trials.[6]

After reviewing 23 trials involving Singaporean adult participants conducted between 2017 and 2022, Bin WJJ et al. found that women, ethnic minorities and elder individuals were underrepresented.[6] It is crucial to prioritise the inclusion of women, minorities and the elderly when recruiting participants in Singapore, as is recommended in other countries.[7] Despite nearly half of the Singapore-only studies meeting census criteria for ethnic diversity, over one-third of trials did not fully disclose ethnic information. Most trials failed to detail recruitment strategies, analyse demographic representativeness and external validity, similar to issues observed in the US.[9] Inadequate demographic representation and insufficient reporting hinder the development of robust, impactful and equitable clinical trials. Furthermore, only one multiregional study provided details beyond the umbrella term "Asian", which suggests homogeneity and overlooks interethnic differences that can affect drug responses.[8] This ambiguity in reporting results from multiregio-nal clinical trials exacerbates the challenges faced by minorities living in small-to-medium-sized countries.

Since the turn of the millennium, demographic diversity in pharmaceutical clinical trials has steadily increased, especially in the US.[7] Historically, women of childbearing potential were excluded from Phase 1 and early Phase 2 research due to the risks associated with thalidomide use during pregnancy.[10] This restriction was lifted by the US Food and Drug Administration guidelines,[11] but even today, women of childbearing potential remain underrepresented in early-phase clinical trials compared to late-phase trials, reflecting remnants of these earlier regulations.[12] Governmental regulations significantly impact demographic diversity in clinical trials, highlighting the importance of regular updates. The National Institutes of Health Revitalization Act has been continuously updated to improve the inclusion of women and minorities in clinical

[1] Stanley Ho Big Data Decision Analytics Research Centre, The Chinese University of Hong Kong, Hong Kong SAR
[2] The Nethersole School of Nursing, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR
Correspondence: Professor Thomas Yuen Tung Lam, The Nethersole School of Nursing, Faculty of Medicine, The Chinese University of Hong Kong, Chung Chi Rd, Ma Liu Shui, Hong Kong SAR.
Email: thomaslam@cuhk.edu.hk

trials, requiring inclusion in all biomedical research projects and clarifying reporting guidance,[13] revising minimum standards of inclusion[14] and mandating disclosure on ClinicalTrials.gov.[13]

Despite regulatory advancements, minorities remain underrepresented in clinical trials compared to their proportions in the US populations.[9] In the US and globally, the pharmaceutical industry plays a key role in applied preclinical and clinical research, as well as in the production, marketing and distribution of new therapies.[15] Industry-funded trials have been shown to be associated with greater age disparities, unlike government initiatives.[2] This raises concerns among researchers that regulatory and financial incentives might indirectly reward homogeneity, reducing confounding risks due to patient-related factors, and resulting in a higher enrolment of White individuals.[9,12] Investigating demographic disparities among trial participants due to industry funding is crucial, especially given past concerns that industry sponsorship could introduce bias in result reporting.[16]

Beyond our critique of governments and the industry, we acknowledge the social factors contributing to the disparities. These include, but are not limited to, the accessibility of trial sites, leading to age disparities;[2] reduced willingness to participate, differences in prognosis, perceived symptoms and perceived greater risk of harm from interventions, resulting in gender disparities; and the location of trial sites, institutional and/or systematic racism, distrust of healthcare systems, low socioeconomic status and language and communication barriers, causing ethnical disparities.[3] Effective solutions that resonated with both participants and the healthcare system often involve active community engagement, thoughtful logistics planning and clear communication of the research process.[17] A significant barrier to diversifying participation among principal investigators, coordinators or site staff is the lack of demographic competency.[17] From a technical standpoint, failing to recognise demographic diversity can invalidate clinical trial outcomes. For instance, when a disease is more prevalent among elderly individuals, relying solely on census data for trial enrolment may be inadequate;[12] epidemiological data could serve as a more appropriate reference.

After analysing the current study populations in Singapore, the authors suggest that special attention should be given to female participants and individuals of Indian ethnicity.[6] Increasing transparency at each recruitment stage is also necessary to facilitate the assessment of bias and the determination of generalisability. For Singapore and multicultural societies, we recommend the following:

- Governments should lead in refining regulations and tailoring reporting formats for demographic diversity by thoroughly investigating the real-world issues faced by the underrepresented groups and frequently updating relevant policies.
- The industry, as the primary implementer of clinical trials, should take on more responsibility to help achieve equity.
- Communities serving as the mediator between patients and the healthcare system should excel in creating an environment of trust and facilitating effective communication.
- Trialists should consider the actual demographic diversity in their studies, taking disease prevalence into account for certain conditions.

To achieve the United Nations Sustainable Development Goal 3,[18] "ensure healthy lives and promote well-being for all at all ages", international collaborations are needed to establish regulatory guidelines for multiregional clinical trials that safeguard the well-being of minorities in small-to-medium-sized countries.

Trial participants should ideally reflect the diverse population that will receive the treatment. A robust, impactful and equitable clinical trial must ensure that safety and efficacy outcomes reliably indicate the investigational treatment's benefit-risk profile for general use. Embracing demographic diversity and collaboratively dismantling barriers are crucial steps towards a future where no one is left behind.

Declaration

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Keywords: *patient recruitment, pharmaceutical, randomised controlled trials, public health, study design, trial representativeness*

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ORIGINAL ARTICLE

Screen time and social-emotional skills in preschoolers with developmental, behavioural or emotional issues in Singapore

Jennifer SH Kiing[1,2] *MBBS*, Ying Qi Kang[1,2] *MMed (Paeds)*, Kalyani Vijaykumar Mulay[1,2] *MMEDSci (Child Health)*, Tammy SH Lim[1,2] *MMed (Paeds)*, Shang Chee Chong[1,2] *MMed (Paeds)*, Mae Yue Tan[1,2] *MMed (Paeds)*, Yiong Huak Chan[3] *PhD*, Alicia SY Lim[4] *MASc (OT)*, Ramkumar Aishworiya[1,2] *MMed (Paeds)*

ABSTRACT

Introduction: This study aimed to determine patterns of screen viewing time (SVT) in preschool children with developmental, behavioural or emotional (DBE) issues, and to identify its relationship with social-emotional development.

Method: This cross-sectional study involved children aged 0–5 years who were referred to a developmental paediatric clinic for DBE issues. Parents completed a screen time questionnaire, and the Devereux Early Childhood Assessment-Clinical (DECA-C) questionnaire which assessed the social-emotional competence of the children. Data were analysed using logistic regression, correlational analyses and tests of comparison.

Results: Among 225 children (mean age: 32.4 months), mean daily SVT was 138 minutes. More than half (51.1%) of the children had clinical features of language delay, while 26.6% had features suggestive of autism spectrum disorder. Screen time was first introduced at a mean age of 13.8 months, with 32.4% of children previously experiencing higher SVT. Compared to SVT introduction after 1 year of age, SVT in the first 12 months was primarily to facilitate feeding ($P<0.05$). Children with higher past SVT had poorer attention, more aggression, and increased behavioural concerns. Children with DBE issues have significantly more screen time than same-aged peers.

Conclusion: Children with DBE issues are exposed to SVT at a very young age and have significantly more screen time than their peers. It is crucial to guide parents to reduce SVT in early childhood, particularly around mealtimes.

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Keywords: developmental concerns, preschool, public health, screen time, social-emotional skills

CLINICAL IMPACT

What is New

- This study reveals that children with developmental, behavioural or emotional (DBE) issues are exposed to screen time earlier than in recommended guidelines.
- The primary reason for early screen time introduction in children with DBE is to aid in feeding during infancy. This early exposure is linked to increased inattention, aggression and behavioural concerns in toddlers.

Clinical Implications

- Clinicians and child health professionals should actively inquire about both current and past screen time practices during screenings and routine surveillance.
- Anticipatory guidance on reducing screen time exposure, particularly around mealtimes, should begin as early as the antenatal period.

INTRODUCTION

Preschool children, particularly those with developmental, behavioural or emotional (DBE) issues, are highly vulnerable to the negative effects of excessive screen viewing time (SVT) on their social and emotional development.[1,2] Singapore, an island nation with a declining birth rate,[3] places significant emphasis on human potential, particularly the social and emotional development of its young children.[4] There has been a noticeable increase in the number of young children in

[1] Child Development Unit, Khoo Teck Puat-National University Children's Medical Institute, National University Hospital, Singapore
[2] Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[3] Biostatistics Unit, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[4] Women's Emotional Health Service, Department of Psychological Medicine, National University Hospital, Singapore
Correspondence: Dr Ying Qi Kang, Child Development Unit, Khoo Teck Puat-National University Children's Medical Institute, National University Hospital, National University Health System, 5 Lower Kent Ridge Road, Singapore 119074.
Email: ying_qi_kang@nuhs.edu.sg
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Singapore experiencing excessive SVT. The Singapore Longitudinal Early Development Study (SG LEADS) reported that nearly 50% of children under 3 years of age engage in SVT for entertainment purposes at least once a week.[5] SVT is also used for learning, games[5] and during mealtimes.[6] Excessive SVT impacts children's development, including cognition, executive function, and social-emotional regulation.[2,7,8] Children with neurodevelopmental disorders such as autism spectrum disorder (ASD), speech language delay (SLD), and attention deficit hyperactivity disorder (ADHD) already struggle with social and emotional regulation and are particularly prone to increased SVT and its adverse effects.[2,9-11] Research has shown that SVT is higher in children with neurodevelopmental disorders compared to the general population.[9] Additionally, SVT at 1 year of age has been linked to autism symptoms at 3 years of age.[12]

In response to these global trends, many SVT guidelines have been established.[1] The Ministry of Health in Singapore has implemented public health messages, including a 24-hour activity guideline and a screen use guideline, emphasising the importance of limiting SVT exposure in young children.[13,15] We investigated whether such messages were effectively reaching the public in Singapore and whether SVT management in young children had improved. Our study aimed to: (1) examine patterns of SVT in children with DBE issues, including changes in SVT over time and reasons for its introduction; and (2) explore the relationship between SVT and social-emotional development in these children. We hypothesised that SVT might still be introduced too early to keep children occupied and would be associated with poorer social-emotional development, particularly in terms of attention and emotional regulation.

METHOD

Study participants

Data for this cross-sectional study was obtained from an ongoing study titled "Clinical Correlates, Contributions and Characteristics of Children with Developmental Issues in the Child Development Unit (5C Study)" conducted at the developmental paediatric clinic of the Child Development Unit at the National University Hospital, Singapore from September 2019 to August 2021. Inclusion criteria were: (1) children from birth up to age 4 years 11 months visiting the clinic for any DBE concerns; and (2) recruitment at first clinic visit before the commencement of any diagnostic assessment or intervention. The exclusion criterion was parents/caregivers who could not read English. Ethics approval was obtained from the National Healthcare Board Domain Specific Research Board for all study-related procedures (DSRB reference 2019/00132-SSR6).

Measures

Short SVT questionnaire

A descriptive screen time questionnaire was developed by consensus of the authors, comprising 9 questions to gather details on when SVT was first introduced, reasons for its introduction, details of device use including content, current and past SVT duration, and background television information. This questionnaire was completed by parents or the caregiver accompanying the child (Supplementary Appendix S1).

The Devereux Early Childhood Assessment-Clinical (DECA-C)

The DECA-C is a standardised behaviour rating scale for children aged 2–5 years with behavioural difficulties in a clinical setting.[16,17] It consists of 3 protective factor scales (initiative, self-control and attachment) contributing to a total protective factor (TPF) score, and 4 behavioural concerns scales (attention problems, aggression, withdrawal/depression, and emotional control problems) contributing to a total behavioural concern (TBC) scale. For protective factors, the initiative subscale measures the ability of the child to independently act to meet their needs. The self-control subscale reflects the child's ability to act and speak appropriately to express thoughts and feelings. The attachment subscale refers to the specific 2-way relationship between the child and a significant caregiver, such as a parent. The TPF score denotes the cumulative strength of these 3 protective factors, with higher scores representing better social-emotional development. For behavioural concerns, the attention problems subscale evaluates the child's ability to sustain focus on a task. The aggression subscale measures hostile or destructive acts aimed at other people or things. The withdrawal/depression subscale reports behaviours where a child is preoccupied with their thoughts or play, rather than engaging with others. The emotion control problems subscale explores a child's difficulties in moderating the expression of negative emotions to reach their goals. The TBC score represents a composite of these 4 scales, indicating the magnitude and severity of the child's behavioural problems, with higher scores denoting greater problems.

Demographic questionnaire

Parents completed a demographic questionnaire to provide information on their qualifications, the child's age, and their preschool grade level. Details of comorbid medical illnesses, the family's need for financial subsidies, and family history of developmental disabilities were retrieved using a standardised data extraction form from medical records. Information on parents' ethnic background was not collected.

Statistical analyses

Data were analysed with SPSS version 28.0 (IBM Corp, Armonk, NY, US); statistical significance was set at $P<0.05$ (2-sided). Descriptive statistics for numerical variables are presented as mean ± SD for continuous variables or n (%) for categorical variables. The average SVT (in minutes) was derived using the following formula: (weekday screen time /day x 5) + (weekend screen time /day x 2)] / 7. Logistic regression was performed to determine the association for the reasons for first introducing SVT within a year of age. Odds ratios with 95% confidence intervals were computed. Correlational analysis was used to determine the strength of association between numerical screen time variables and numerical DECA-C scores. The analyses were adjusted for demographic and family variables.

RESULTS

Study cohort and screen time data

Data were obtained from 225 participants who completed the questionnaires. One parent returned an incomplete questionnaire. The mean ± SD age of children was 32.4±11 months (range 10.8–58.8 months). The average daily SVT was 138.1±109.2 minutes, which is over 2 hours. SVT was first introduced at a mean age of 13.8±8.9 months. The longest past daily SVT, at mean 262.6±140.7 minutes, exceeded 4 hours. The mean background television viewing duration was 3 hours 54 minutes (234.8±174.6 minutes). Demographic information is summarised in Table 1. One hundred and fifty-one (67.1%) of children were boys, and 151 (67.4%) were enrolled in preschool. Among the parents, 104 (46.2%) mothers and 98 (43.6%) fathers had educational qualifications of university or higher. Sixty-seven (29.8%) children lived with grandparents, and 32 (14.2%) had a live-in domestic helper (Table 1). One hundred and fifteen children (51.1%) had clinical features of SLD, while 60 (26.6%) had features suggestive of ASD (Table 1). One in 5 parents (n=47, 20.8%) reported a family history of either mental health conditions (5 mothers and 1 grandparent with depression) or DBE conditions, including siblings with autism (n=10; 4.4%), speech or developmental delay (n=6, 2.7%). A minority (n=28; 12.4%) of children had other chronic medical conditions.

Table 1. Demographics and descriptive data of study participants (n=225).

Demographic	n (%)
Sex	
Male	151 (67.1)
Female	74 (32.9)
DBE diagnosis	
SLD	115 (51.1)
ASD	60 (26.6)
Behavioural dysregulation[a]	19 (8.4)
GDD	17 (7.6)
Others[b]	13 (5.8)
Child's school enrolment status	
In school	151 (67.1)
Not in school	73 (32.4)
Data not provided	1 (0.5)
Child's school grade level	
Playgroup (PG) /Nursery 1 (N1)	47 (20.9)
Nursery 2 (N2)	87 (38.7)
Kindergarten	17 (7.6)
Child has siblings	
Yes	140 (62.2)
No	83 (36.9)
Data not provided	2 (0.9)
Mother's highest educational level	
Primary to post-secondary	60 (26.7)
Diploma	51 (22.7)
Degree/post-graduate	104 (46.2)
Data not provided	10 (4.4)
Father's highest educational level	
Primary to post-secondary	70 (31.0)
Diploma	48 (21.3)
Degree/post-graduate	98 (43.6)
Data not provided	9 (4.1)

Table 1. Demographics and descriptive data of study participants (n=225). (Cont'd)

Demographic	n (%)
Other information	
Living with immediate family	202 (89.8)
Household includes domestic helper	32 (14.2)
Household includes grandparents	67 (29.8)
Child has medical issues	28 (12.6)
Child has existing developmental issues	29 (13.1)
Family history of mental health or DBE conditions	47 (20.9)

ASD: autism spectrum disorder; DBE: developmental, behavioural or emotional issues; GDD: global developmental delay; SLD: speech language delay
[a] Includes inattention and hyperactivity.
[b] Includes chronic medical conditions or syndromes such as ex-premature, coordination disorders, etc.

Patterns of SVT

The top 3 reasons for first introducing SVT were for keeping children occupied, to facilitate mealtime routines, and for play (Table 2). Fifty-four (24.0%) children had their screen devices, with 35 (64.8 having a tablet and 26 (48.1%) having a mobile phone. One hundred and thirty-eight (61.3%) children watched television, and 137 (60.9%) could change the screen content themselves. One hundred and sixteen (51.6%) viewed entertainment suitable for children, while 62 (27.6%) viewed educational content as indicated by parents. Seventy-three (32.4%) had more SVT in the past, and a further 78 (34.7%) had SVT in the first year of life. There was no significant age difference between children using SVT as entertainment compared to education (mean age 2.69 vs 2.87 years; *P*=0.61). Only 11 children (4.9%) played video games, and they were slightly older at 2.94 years. The quality of screen time was not evaluated.

Table 2. Patterns of SVT as reported by parents/caregivers (n=225).

SVT pattern	n (%)
Reason(s) for SVT introduction	
Meal time	103 (45.8)
Play	97 (43.1)
Keep child calm	68 (30.2)
Keep child occupied	120 (53.3)
Education	89 (39.6)
Others	15 (6.7)
Child has own device	
Yes	54 (24.0)
Tablet	35 (64.8)
Mobile phone	26 (48.1)
Others	2 (3.7)
No	167 (74.2)
Data not provided	4 (1.8)
Device child uses most often	
TV	138 (61.3)
Mobile phone	50 (22.2)
Tablet	39 (17.3)
Child is able to change device programming	
Yes	137 (60.9)
No	82 (36.4)
Data not provided	6 (2.7)
Screen time content	
Entertainment for child	116 (51.6)
Educational content	62 (27.6)
Playing games	11 (4.9)
Entertainment for parents	10 (4.4)
History of more SVT in the past	
Yes	73 (32.4)
No	147 (65.3)
Data not provided	5 (2.3)
SVT introduced in the first year of life	
Yes	78 (34.7)
No; introduced after 1 year	147 (65.0)

SVT: screen viewing time

SVT associations

When SVT was first introduced under 1 year of age, it was predominantly for mealtime purposes (adjusted odds ratio [AOR] 2.6, 95% confidence interval [CI] 1.3–5.1, *P*=0.005, Table 3). Children who had SVT on mobile phones were more likely

to be introduced to screen time at a younger age (mean±SD 10.6±5.4 vs 14.3±9.2 months, *P*=0.026), after adjusting for parental and demographic variables shown in Table 1. A higher level of parental education appeared predictive of lower SVT in children. Higher maternal education (i.e. degree and above) was associated with lower SVT per day, compared to diploma and primary to post-secondary (mean±SD time of 114±99 vs 161±112 vs 168±113 minutes, *P*=0.003). Similarly, higher paternal education (i.e. degree and above) was also associated with lower SVT per day, compared to diploma and primary to post-secondary (mean time of 115±102 vs 129±91 vs 177±124 minutes, *P*=0.001). Children enrolled in preschool had less SVT compared to those who were not (84±90 vs 150±192 minutes, *P*=0.001). Children who lived with grandparents were less likely to have SVT to keep them occupied (41.8% vs 58.2%; AOR 0.4, 95% CI 0.2–0.9, *P*=0.018). Children who live with siblings compared to those who were only children were more likely to use television for SVT (71.2% vs 51.9%; AOR 2.4, 95% CI 1.2–4.7, *P*=0.013).

Screen time and social emotional measures on the DECA-C

Table 4 shows the results of analysis of DECA-C scores against SVT patterns. Higher initiative scores were associated with later age of SVT introduction (*r*=0.156, *P*=0.02). In addition, longer weekend SVT was associated with poorer emotional control scores (2.8±2.6 vs 2.1±1.9, adjusted *P*=0.04) and poorer TBC scores (2.7 vs 2.1, unadjusted *P*=0.040 and adjusted *P*=0.388). Children who had more SVT in the past had poorer attention scores compared to those who did not (mean±SD: 58.7±10.4 vs 55.6±11.6; *P*=0.030); higher aggression scores (mean±SD: 50.3±11.5 vs 47.2± 10.3; *P*=0.016); and, higher TBC scores (mean±SD: 56.6±10.4 vs 53.0±11.8; *P*=0.032) (Table 5).

Population, age and COVID-19 pandemic comparisons

There was no significant difference in mean SVT between the 0–2 and 3 and above age groups (*P*=0.563 for SVT involving television, and *P*=0.472 for SVT involving other electronic devices; regardless of weekday or weekend) (Table 6). There was also no significant difference in mean weekday (*P*=0.23) and weekend (*P*=0.18) SVT before and during the pandemic when comparing children enrolled before (n=55) and after March 2020 (n=170) during which pandemic-related work-from-home measures were applied.[18] When compared to a typical preschool population from another study,[19] children with DBE conditions in our cohort have significantly more SVT (*P*<0.05; Table 6).

DISCUSSION

Children in this study received SVT exposure much earlier than is recommended by international guidelines, which advise no screen time for children under 2 years old.[20] This pattern is also reported globally and aligns with existing studies in Singapore.[5,20] In our study, almost a quarter of children had their own screen devices, such as tablets (65%) or mobile phones (48%). Similar numbers were reported in the SG LEADS study, with up to 21% of children under 3 years and 32% of children over 3 years using electronic devices for entertainment daily.[5] However, children in our study with DBE concerns had significantly higher SVT than those in the SG LEADS study, which represents a typical preschool population (Table 6). This finding is consistent with data

Table 3. Reasons for first introduction of SVT.

Reason	SVT introduction, n (%)		Unadjusted odds		Adjusted odds[a]	
	Within a year (n=78)	After a year (n=147)	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Meal time	44 (56.4)	59 (40.1)	**1.9 (1.1–3.4)**	**0.020**	**2.6 (1.3–5.1)**	**0.005**
Play	29 (37.2)	68 (46.3)	0.7 (0.4–1.2)	0.191	0.7 (0.3–1.2)	0.185
Keep child calm	23 (29.5)	45 (30.6)	0.9 (0.5–1.7)	0.861	0.9 (0.5–1.8)	0.751
Keep child occupied	42 (53.8)	78 (53.1)	1.0 (0.6–1.8)	0.911	1.0 (0.5–1.8)	0.970
Educate	30 (38.5)	59 (40.1)	0.9 (0.5–1.6)	0.807	0.9 (0.5–1.8)	0.873

OR: odds ratio; SVT: screen viewing time
[a] adjusted for all variables in Table 1.
Values in bold are significant at *P*<0.05.

Table 4. Correlations between SVT variables and DECA-C scores.

DECA-C scales	When SVT was first introduced (months)	Average SVT per day (hours)	Average SVT on weekends (hours)
Initiative	0.156	0.112	0.123
Self-control	0.021	0.025	0.022
Attachment	-0.022	0.004	0.066
TPF	0.050	0.072	0.098
Withdrawal	-0.084	0.031	0.056
Emotional control	0.052	0.087	0.138
Attention	-0.099	0.081	0.109
Aggression	0.038	0.009	0.051
TPC	-0.019	0.059	0.113

DECA-C: Devereux Early Childhood Assessment-Clinical; SVT: screen viewing time; TBC: total behavioural concern; TPF: total protective factor
Values in bold are significant at *P*<0.05.

Table 5. Association between higher SVT exposure in the past and DECA-C scores.

	Ever have more SVT in the past, mean ± SD		Unadjusted Odds	Adjusted Odds*
DECA-C scores	No (n=147)	Yes (n=73)	*P* value	*P* value
Initiative	36.2±8.1	36.7±7.7	0.596	0.923
Self-control	40.9±9.9	41.1±8.6	0.920	0.868
Attachment	39.6±11.6	40.9±9.6	0.403	0.387
TPF	36.1±8.4	36.8±8.0	0.556	0.749
Withdrawal	57.2±12.1	59.1±11.3	0.271	0.407
Emotional control	51.8±12.3	54.9±10.9	0.069	0.072
Attention	55.6±11.6	58.7 ±10.4	0.056	0.030
Aggression	47.2±10.3	50.3±11.5	0.043	0.016
TBC	53.0±11.8	56.6±10.4	0.030	0.032

DECA-C: Devereux Early Childhood Assessment-Clinical; SVT: screen viewing time; TBC: total behavioural concern; TPF: total protective factor
* adjusted for all variables in Table 1.
Values in bold are significant at P<0.05.

in Singapore showing that children with DBE conditions have higher SVT.[21] Pandemic-related restrictions did not result in significant differences in SVT, possibly due to the already high levels of use.

We found that SVT was introduced to children under 12 months of age to facilitate easier feeding during meal times, representing a novel and important finding in Singapore. Children with DBE concerns may experience more feeding difficulties than typically developing children. Atypical eating behaviours and feeding difficulties are more common in children with ASD,[22] where another preschool study suggested an association between hyperactivity, authoritarian feeding style, and feeding difficulties in children with ASD.[23] This could explain the use of SVT during feeding. We also speculate that the use of SVT for feeding may be cultural and occur even among typically developing children in Singapore, although this

Table 6. Comparison of data between SG LEADS study[19] and the current study.

Study	Source of screen time, weekday/ weekend	Duration of screen time		*P* value (comparing children under 2 years vs those over 3 years in current study)	*P* value (SG LEADS vs current study)
		Children aged 0–2 years old	Children aged 3–4 years old		
SG LEADS	TV, weekday	42 minutes	50 minutes	0.563	<0.05[a]
Current study		2 hours	1 hour 45 minutes		
SG LEADS	TV, weekend	51 minutes	1 hour 18 minutes	0.563	<0.05[a]
Current study		2 hours 11 minutes	2 hours 48 minutes		
SG LEADS	Other electronic devices, weekday	12 minutes	21 minutes	0.472	<0.05[a]
Current study		1 hour 54 minutes	1 hours 48 minutes		
SG LEADS	Other electronic devices, weekend	16 minutes	30 minutes	0.623	<0.05[a]
Current study		2 hours 18 minutes	2 hours 42 minutes		

SG LEADS: Singapore Longitudinal Early Development Study
[a] One sample t-test

was not directly evaluated in this study. Findings from another study on food parenting practices in typically developing preschoolers supports the observation that Singaporean parents use more coercive control practices compared to Western counterparts, putting more pressure on a child to eat, and using bribes and threats for a child to finish meals quickly.[24] Differential expectations related to feeding could potentially contribute to parents in our study using SVT to expedite feeding through distraction rather than encouraging independent eating. The use of SVT during meals has also been reported in other countries.[25] In Thailand, more than half (58%) of typically developing toddlers had SVT for meals.[6] This highlights the need for education on developmentally appropriate mealtime routines to reduce the need for screen-based distractions for both children with DBE conditions and typically developing children.

Unsurprisingly, school enrolment reduced screen time as children spend less hours at home and more time in a largely screen-free environment. Children under the care of grandparents had less screen time, possibly because grandparents can engage more with children than domestic workers. However, no significant difference was found between domestic worker care and screen time. Domestic workers are employed by many households in Singapore to take on caregiving responsibilities amid other household duties.[26] The presence of siblings increased the likelihood of SVT due to television sharing. Similarly, an Australian study found that having 1–2 siblings increased SVT, but having more siblings encouraged other activities to displace SVT.[27] While the distribution of educational qualifications within our sample is consistent with national norms,[28] our finding that parents with higher educational levels gave their children less SVT is similarly described in other studies.[29,30] A past history of higher SVT use was present in about one-third of children, suggesting that parents reduced SVT by the time of the first specialist consultation. However, reasons for this reduction were not elicited. Asking whether a child "ever" had more SVT in the past may be a useful measure, as parents' reports of current SVT exposure may not always be reliable compared to real-time measures.[31]

We found that earlier SVT introduction was associated with lower initiative scores on the DECA-C. Initiative, the ability to take independent action to achieve a goal, is a key component of social emotional regulation. Studies have shown that excessive SVT can negatively impact the development of initiative and self-regulation.[32,33] However, the children in this study with DBE issues could have started with lower initiative scores. Longer weekend SVT was associated with poorer emotional control, but this was not observed with longer weekday SVT. This may be due to children being solely in parents' care on weekends, compared to weekdays when other caregivers are involved, leading to more accurate reporting of SVT history. Emotional control, managing one's emotions and behaviours in different situations, is crucial for social-emotional development. Excessive SVT in children has been linked to negative effects on emotional control.[34] SVT can be overstimulating, altering brain chemistry;[35] it may disrupt the development of social skills like communication and empathy;[36] and lead to

a sedentary lifestyle, which is linked to poorer emotional control.[37] The content and quality of SVT can also impact emotional control, as educational programmes and interactive games may positively influence cognitive development and social skills, indirectly improving emotional control.[1] A past history of "ever" having more SVT correlated with higher aggression scores, poorer attention and more total behavioural concerns. This likely reflects that prolonged SVT exposure can impact a child's ability to self-regulate. Excessive SVT in early childhood has been associated with increased aggression and other behavioural problems.[1] The children in our study have poorer initiative scores, emotional control, higher aggression scores, poorer attention, and more total behavioural concerns related to early and excessive SVT use. These findings could be influenced by multiple confounding factors, including underlying developmental delay, obesity,[38] parental income and educational level, number and type of devices in the home, and number of older siblings using devices.[39,40] Nonetheless, our findings emphasise the need to continue public health education efforts to improve awareness of healthy screen time practices, understand reasons for its use and delay the early introduction of SVT to children.

The finding of SVT introduction in infancy for mealtime routines among children with DBE concerns requires special attention. Healthcare professionals need to be aware of the higher likelihood of SVT use during feeding in children with DBE conditions, particularly ASD, and provide appropriate counselling and support. Furthermore, parents and caregivers of all children require knowledge and explicit coaching about developmentally appropriate mealtime routines even before an infant is weaned. Anticipatory guidance for mealtime habits could be provided for all children during the first postnatal visit at 8 weeks of age and subsequent well-child visits. The reasons why one-third of parents had reduced SVT by the time of the first tertiary clinic visit need to be explored to understand what influenced their decision. Parents can better understand and practise developmentally appropriate ways to engage children without relying on electronic and media devices. However, they cannot do this alone and require the support of a well-integrated public health approach with a central message on delaying and limiting SVT in young children, and engagement of all stakeholders to improve outcomes for both "at risk" and typically developing children in Singapore. Further research on parents and caregivers' knowledge of guidelines would be useful for reviewing public health efforts in disseminating childcare and health information, identifying the gaps, and instituting enhancing measures.

One of the key limitations of the study is the lack of a comparative sample of typically developing children without DBE issues. Hence, our findings on SVT patterns and their relation to socio-emotional development may not be generalisable to the broader population. This limitation was partially addressed by comparing our data with a separate study in Singapore on typically developing children to understand which findings were potentially more generalisable. Further studies should apply similar measures of socio-emotional development to typically developing children to better understand this topic. We also did not collect data on potential study participants who declined to participate, which may have introduced a selection bias and limit the wider applicability of the results. Lastly, the setting of study recruitment within a tertiary clinic may not have been ideal for parents experiencing indirect stress associated with the visit; this could have affected their reported SVT history, which was based on parent recall rather than objective measures,[31] and may be subject to reporting bias. We sought to mitigate this by providing a child-friendly environment and ample time as needed for questionnaires completion.

Our study shows that in children with DBE concerns, SVT is introduced too early and remains excessive. Early introduction in the first year of life is related to mealtime routines. Early and excessive SVT is associated with poorer social emotional regulation related to initiation, emotional control, and attention. Public health messaging on SVT needs to be well-integrated, and delivered as early as possible in a child's life, i.e. antenatally, and can benefit both children with DBE conditions and those who are typically developing. Parents have demonstrated that they can change the behaviour and reduce SVT in their children; reasons for this should be explored further. The findings of this study contribute to the well-being and success of preschool children with DBE issues in Singapore and may hold lessons for similar cultures.

Declaration

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ORIGINAL ARTICLE

Association between alcohol flushing syndrome and cancer: A systematic review and meta-analysis

Wilson Sim[1] *MBBS*, Jason Timothy Pan[1] , Cheryl Wan Xuan Chua[1] *MBBS*, Khi Yung Fong[1] *MBBS*, Sunny H Wong[2,3] *FRCP*, Bernett Lee[*4,5,6] *PhD*, Hazel H Oon[*1,7] *MD*

ABSTRACT

Introduction: Alcohol flushing syndrome (AFS) is experienced by up to 46% of East Asians. This study aimed to review the risk of cancers in AFS patients, elucidate an exposure-response relationship, and understand risk associated with alcohol intake and cancer.

Method: An electronic database search of PubMed, Embase, Scopus and Cochrane Library was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines. Observational studies on AFS' effects and all cancers risk were included. Studies including patients with existing malignancy were excluded. Dichotomous variables were pooled using the Mantel-Haenszel method with a random effects model. Sensitivity and subgroup analyses were performed. PROSPERO (CRD42023392916) protocol was followed.

Results: A total of 18 articles were included in the final analysis with a total of 387,521 participants. AFS was associated with an increased risk of all cancers (odds ratio [OR] 1.19, 95% confidence interval [CI] 1.06–1.34), esophageal squamous cell carcinoma (OR 1.47, 95% CI 1.05–2.05) and gastric adenocarcinoma (OR 1.40, 95% CI 1.14–1.72). Men with AFS exhibited an increased risk of all cancers (OR 1.34, 95% CI 1.13–1.59). However, this was not observed in women. All cancers risk was associated with AFS in those who consumed drink (i.e. consumed alcohol) more than 200 g of pure ethanol/week (OR 1.68, 95% CI 1.20–2.37) but not those who consumed less than 200 g of pure ethanol/week (OR 1.27, 95% CI 0.90–1.79) or non-drinkers (OR 0.99, 95% CI 0.67–1.47).

Conclusion: AFS is associated with an increased risk of all cancers, particularly esophageal squamous cell carcinoma and gastric adenocarcinoma.

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Keywords: alcohol, alcohol dehydrogenase, alcohol flushing syndrome, aldehyde, cancer

CLINICAL IMPACT

What is New

- Alcohol flushing syndrome (AFS) is observed to be associated with an increased risk of cancer incidence.
- The risk of cancer increases with the amount of alcohol consumed by those with AFS, providing preliminary evidence of an exposure-response relationship that was not consistently observed in previous studies.

Clinical Implications

- It is important for clinicians to educate and increase public awareness of the association between AFS and increased risk of cancer.

INTRODUCTION

Alcohol flushing syndrome (AFS) is characterised by intense facial flushing, often accompanied by palpitations, headache and nausea shortly after the consumption of alcohol. This phenomenon occurs in up to 46% of East Asians and to a much lesser extent Caucasians, due to the accumulation of acetaldehyde, a metabolic byproduct of catabolism of alcohol. This results from a combination of increased production by fast metabolising alcohol dehydrogenase (ADH) enzyme and reduced clearance due to a slow metabolising or inactive aldehyde dehydrogenase (ALDH) enzyme.[1] Despite the discomfort associated with drinking (i.e. consume alcohol), many people with AFS continue to consume alcohol with societal pressures as one reason.[2-4]

[1] Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[2] Centre for Microbiome Medicine, Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore
[3] Department of Gastroenterology and Hepatology, Tan Tock Seng Hospital, Singapore
[4] Centre for Biomedical Informatics, Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore
[5] Singapore Immunology Network, Agency of Science Technology and Research, Singapore
[6] Infectious Disease Labs, Agency for Science, Technology and Research, Singapore
[7] National Skin Centre and Skin Research Institute of Singapore, Singapore
* Joint last authors
Correspondence: Dr Hazel H Oon, National Skin Centre, 1 Mandalay Road, Singapore 308205.
Email: hazeloon@nsc.com.sg

To date, the relationship between AFS and esophageal squamous cell carcinoma (ESCC) is the most well-studied association in previous systematic reviews. In a review of 7 studies, Andrici et al. reported a positive association between AFS and ESCC.[1] This increase in risk of cancer for flushers, compared to non-flushers who consumed the same amount of alcohol, was even more pronounced at higher levels of regular alcohol consumption and indicated preliminary evidence of a dose relationship.[1] More recently in 2017, Zhang et al.[5] found a similar positive association between AFS and cancer; however, subgroup analyses did not demonstrate a significant association for women and a dose-response relationship could not be elucidated due to lack of granularity on alcohol consumption amounts.[5] Apart from the lack of well-defined association between AFS and non-ESCC cancers such as gastric carcinomas, 8 new studies have also emerged reporting the association of AFS with other cancers such as pancreatic cancer,[6] bladder cancer[7] and lung cancer.[8]

This study aimed to systematically review the risk of all cancers associated with AFS and to examine for the presence of an exposure-response relationship.

METHOD

The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines was used in the synthesis of this review, with the PRISMA checklist completed (Supplementary Appendix S1). An electronic database search of PubMed, Embase, Scopus and Cochrane Library was performed on 18 January 2023 using keywords and terms synonymous with "alcohol flushing syndrome" and "cancer". An example of the search strategy has been included in Supplementary Appendix S2. The references of included articles were also assessed for suitability for inclusion. A re-run of the search was also performed across all databases on 17 August 2023 with no new relevant studies identified.

The inclusion criteria comprised observational studies, including cohort studies and case-control studies, reporting on the effect of AFS and the risk of all types of cancer. Exclusion criteria include grey literature, studies that were not in English, or studies with participants with a current or history of malignancy.

Article selection was performed by 2 authors based on the inclusion and exclusion criteria. Any discrepancy was resolved based on consensus with a third author. Data extraction was performed by the blinded pair of authors, where blinded details include author, year of publication, title, country of origin, study design, clinical setting, patient population, comparators, number of participants, mean age, and odds ratios comparing the risk of cancer in patients who flush and those who do not.

Data analysis was performed using Revman version 5.4 (The Cochrane Collaboration, 2020) and R studio version 1.3.1093 (R Foundation for Statistical Computing, 2020) in accordance with statistical approaches laid out by the Cochrane Handbook. Dichotomous variables were pooled using the Mantel-Haenszel with a random effects model and adjusted ratios were used whenever available. Sensitivity analysis using only adjusted outcomes was performed. Next, subgroup analyses were performed based on the location of cancer, alcohol consumption status and sex. Statistical significance was considered at a P value of ≤ 0.05. Heterogeneity was assessed with Cochran Q test and I^2 test, with a significance value at $P \leq 0.10$ or $I^2 \geq 40\%$, respectively. Publication bias was assessed by visual inspection of funnel plots when sufficient studies were available (n>10).

Risk of bias for observational studies was assessed by the 2 authors in the blinded pair using the Newcastle-Ottawa Scale, which grades studies as having a high (<5 stars), moderate (5–7 stars) or low (≥8 stars) risk of bias. Studies with a high risk of bias were excluded from data synthesis. This systematic review was submitted to PROSPERO (CRD42023392916) on 18 January 2023 prior to its commencement.

RESULTS

The search strategy yielded 1853 potentially relevant articles. After the titles and abstract were screened, 111 full-text articles were reviewed, of which 18 were included in the final analysis (Fig. 1). Studies that investigated the association between AFS and cancer but contained strong confounders were excluded; for example, Harada et al.[9] was excluded after full-text reviews due to the presence of strong confounders, as the study evaluated patients with oral and pharyngeal squamous cell carcinoma. Four studies by Yokoyama et al. have been included based on differences in recruitment methodologies, outcomes of interest, time periods and study designs leading to a low likelihood of data overlap.[10-13] Of the 18 included articles, 14 were from Japan,[6,7,10-21] 3 were from China[8,22,23] and 1 was from Taiwan,[24] with a collective total of 387,521 participants. Eight new studies[6-8,19-21,23,24] were included and were not previously analysed by Zhang et al.[5] The characteristics of included studies including patient demographics, smoking percentages, alcohol consumption amounts and

quality assessment are in Table 1.

AFS was associated with an increased risk of all cancers (OR 1.19, 95% CI 1.06–1.34) (Fig. 2), with pooled adjusted OR (OR 1.43, 95% CI 1.12–1.82) (Supplementary Fig. S1). Alcohol consumption was associated with an increased incidence of ESCC (OR 1.47, 95% CI 1.05–2.05) (Fig. 3) and gastric adenocarcinoma (OR 1.40, 95% CI 1.14–1.72) (Fig. 3). There was no significant association found between drinking alcohol and oral and pharyngeal squamous cell carcinoma (OR 1.00, 95% CI 0.77–1.29) (Fig. 3).

Flushing was associated with increased risk of all cancers in men (OR 1.34, 95% CI 1.13–1.59) (Fig. 4) but this association was not seen in women (OR 1.00, 95% CI 0.88–1.14) (Fig. 4). A further subgroup analysis was supportive of an increased risk of ESCC in male flushers (OR 2.06, 95% CI 1.19–3.56) (Supplementary Fig. S2).

In the subgroup analysis based on alcohol consumption levels, flushers who consumed more alcohol than 200 g of pure ethanol/week (OR 1.68, 95% CI 1.20–2.37) (Fig. 5) had a higher risk of cancer compared to those who consumed less than 200 g of pure ethanol/week (OR 1.27, 95% CI 0.90–1.79) (Fig. 5). Flushers who were non-drinkers were not observed to have an increased risk of cancer (OR 0.99, 95% CI 0.67–1.47) (Supplementary Fig. S3).

Another subgroup analysis based on flushing status did not show a significant difference in risk of all cancers among current (OR 0.98, 95% CI 10.56–1.72) and former (OR 1.49, 95% CI 0.77–2.87) flushers (Supplementary Fig. S4).

The largely symmetrical funnel plot of the 18 studies did not indicate publication bias (Supplementary Fig. S5).

DISCUSSION

With the rising prevalence of alcohol consumption, notably in Asian countries, it is salient to inspect the health impacts of AFS, which reportedly affect 36% of East Asians[25] or around 610,000,000 people. Our analysis of 18 studies involving 387,521 participants supported the association between AFS and cancer, consistent with previous studies. Additionally, subgroup analyses also delineated an increased risk of ESCC and gastric adenocarcinoma while newly emerged studies on bladder[7] and pancreatic[6] cancers were also included in our analysis.

Acetaldehyde increases the risk of cancer through several mechanisms including the alteration of deoxyribonucleic acid (DNA) replication, formation of DNA adducts that may trigger replication errors or mutations, and impairment of DNA repair.[26] These mechanisms require the exposure of tissues to elevated levels of acetaldehyde, which accounts for the strong association of flushing with upper aerodigestive tract cancers.[5] ADH is mainly expressed in the liver and gastrointestinal tract such as the esophagus and the stomach, whereas expression in the oral cavity may be lower.[27] While most of the alcohol ingested is processed by class I ADH in the liver, class IV ADH such as ADH7 is expressed in the esophagus and stomach[28] and is responsible for the first-pass metabolism of alcohol[29] contributing to the local aldehyde exposure.[28] The differential expression of ADH in various tissues may explain the different associations of AFS with various cancers. Importantly, while squamous cell carcinomas are well known to be associated with smoking and alcohol consumption, the relationship for adenocarcinomas are less defined. This study delineated the increased risk of gastric adenocarcinoma with facial flushing, and their association is also likely due to the local toxic effect of acetaldehyde that has similarly been reported by other studies.[30]

The gut microbiome may also have a role to play in the pathogenesis of cancer by affecting the local exposure to acetaldehyde, thereby modulating the risk of cancers at different sites. For example, microbial formation of acetaldehyde can occur in the oral cavity due to the presence of certain bacteria and yeasts,[31] while *Helicobacter pylori* in the stomach can oxidise ethanol into acetaldehyde,[32] demonstrating how dysbiosis can lead to an increased risk of cancer.[31,33-35] Additionally, genetic mutations can further contribute to the aldehyde-mediated risk of cancer by causing DNA damage and potentially triggering the carcinogenesis of BReast CAncer gene 2 (*BRCA2*) cancers.[36] Furthermore, it has also been shown that acetaldehyde concentrations are increased in gastric contents among those with ALDH2 deficiencies,[37] which may account for the strong associations in upper aerodigestive tract cancers compared to cancers of other sites, such as the breast, endometrium and bladder.[30]

Interestingly, in a subgroup analysis of 10 studies[6-8,10,13-16,21] using unadjusted data (Fig. 5), a consumption level of ≥200 g of pure ethanol/week (estimated based on US National Institute of Alcohol Abuse and Alcoholism guideline for moderate consumption of more than 14 drinks/week, which is approximately 196 g of pure ethanol/week[38]) was associated with increased risk of all cancers in flushers, but there was no increased risk observed when consumption amounts are <200 g of pure ethanol/week. This preliminary evidence of an exposure-response relationship was also previously reported by Oze et al. for

Table 1. Characteristics of included studies.

Study	Year of study	Country	N (flushers/ non-flushers)	N (male/female)[a]	Type of cancer (e.g. esophageal squamous cell carcinoma [ESCC], lung etc.)	Mean age (SD), years[a]	Smoking/ drinking alcohol/ physical activity/ reproductive details	Mean alcohol consumption[b]	Green leafy vegetable intake/ daily consumption of hot or burning hot tea	Newcastle-Ottawa score
Yokoyama[12]	2003a	Japan	271 (71/200)	All males	ESCC	Case: 56.7 (7.1) Control: 54.9 (8.9)	Smoking, % Case: 93.8 Control: 92.1	Cases/control, mean (SD) 10.2 (0.8)/10.4 (0.4) drinks per day		7
Yokoyama[13]	2003b	Japan	843 (469/374)	All males	ESCC	Case: 61.7 (7.9) Control: 58.9 (7.1)	Smoking, % Case: 91 Control: 71.9	Drinking <196 g/week, % Case: 12.5 Control: 58.1 ≥196 g/week, % Case: 82 Control: 40.2 Ex-drinker, % Case: 5.6 Control: 1.7	**Vegetable intake, %** (1–2 days/week) Case: 90.5 Control: 96.7	7
Yokoyama[10]	2006a	Japan	655 (120/535)	All males	Upper aerodigestive tract and ESCC	Age group: no. 40–49: 221 50–59: 250 60–69: 153 70–79: 31	No. (%) of drinkers based on age groups <20: 246 (37.6) 20–29: 234 (35.7) ≥30: 175 (26.7)	Drinking ≤99 g/day, % Case: 46.6 Control: 52.3 ≥100 g/day Case: 53.4 Control: 47.7		8
Yokoyama[11]	2006b	Japan	457 (199/258)	All females	ESCC	Case: 63.0 (8.8) Control: 58.7 (7.6)	Drinking, % Case: 42.3 Control: 17.5	Drinking <196 g/week, % Case: 67.3 Control: 88.8 ≥196 g/week, % Case: 25 Control: 8.5 Ex-drinker, % Case: 7.7 Control: 2.7	Vegetable intake, % (1–2 days/week) Case: 88.5 Control: 98 Hot tea consumption, % (likes very much or likes somewhat) Case: 48.1 Control: 31.2	7

Table 1. Characteristics of included studies. (Cont'd)

Study	Year of study	Country	N (flushers/ non-flushers)	N (male/female)[a]	Type of cancer (e.g. esophageal squamous cell carcinoma [ESCC], lung etc.)	Mean age (SD), years[a]	Smoking/ drinking alcohol/ physical activity/ reproductive details	Mean alcohol consumption[b]	Green leafy vegetable intake/ daily consumption of hot or burning hot tea	Newcastle-Ottawa score
Asakage[14]	2007	Japan	738 (352/386)	All males	Oral cavity and pharynx	Overall: 59.1 (7.3)	Drinking, % Case: 95.1 Control: 72.1	Drinking, % ≤196 g/week Case: 18.8 Control: 54.2 >196 g/week Case: 69.8 Control: 43.4 Ex-drinkers Case: 11.5 Control: 2.5	Vegetable intake, % (1–2 days/week) Case: 88.5 Control: 96.1 Hot tea consumption, % (likes very much or likes somewhat) Case: 27.1 Control: 25.4	6
Hosono[17]	2008	Japan	1527 (800/727)	All females	Endometrial	Median (min–max) Case: 56.0 (26–79) Control: 56.0 (23–80)	Drinking, % Case: 16.2 Control: 16.5 Regular exercise, % Case: 68.2 Control: 71.6 Age and reproductive details, cases/ control Age and menarche, median (min–max), years 14.0 (10–20)/ 14.0 (10–21) Duration of menstruation, years (quartiles) 37.0 (0–49)/ 36.0 (11–43)			7

Table 1. Characteristics of included studies. (Cont'd)

Study	Year of study	Country	N (flushers/ non-flushers)	N (male/female)[a]	Type of cancer (e.g. esophageal squamous cell carcinoma [ESCC], lung etc.)	Mean age (SD), years[a]	Smoking/ drinking alcohol/ physical activity/ reproductive details	Mean alcohol consumption[b]	Green leafy vegetable intake/ daily consumption of hot or burning hot tea	Newcastle-Ottawa score
							Parity, median (min–max) 2 (0–4)/ 2 (0–6) Contraceptive usage, % 5.4/5.0 Hormone replacement usage: 10.1% / 6.8%			
Ishiguro[15]	2009	Japan	44994 (23360/21634)	All males	ESCC	Overall: 51.4 (7.9)	Drinking, % Case: 52.1 Control: 53.2	Regular drinkers, % (>3 days/month) Flushing: 59.7 Non-flushing: 69.1	Vegetable intake, % (≥3 days/week) Case: 57.8 Control: 56.4 Hot tea consumption, % Case: 25.3 Control: 23.3	6
Oze[16]	2010	Japan	1721 (842/879)	1755 (1461/294)	Upper aerodigestive tract cancers: oral cavity and oropharynx, hypopharynx, oral cavity-oropharynx-hypopharynx not otherwise specified, larynx, and esophagus (C15)	Age group: no. (%) <40: Case: 20 (3.42) Control: 42 (3.59) 40–49: Case: 46 (7.86) Control: 101 (8.63) 50–59: Case: 186 (31.79) Control: 355 (30.34) 60–69: Case: 217 (37.09) Control: 460 (39.32) ≥70 Case: 116: (19.83) Control: 212 (18.12)	Drinking, no. (%) Never Case: 94 (16.07) Control: 361 (30.85) Moderate Case: 89 (15.21) Control: 332 (28.38) High-moderate Case: 134 (22.91) Control: 287 (24.53) Heavy Case: 253 (43.25) Control: 170 (14.53)		Vegetable intake, no. (%) Lowest tertile Case: 243 (41.54) Control: 372 (31.79) Middle tertile Case: 189 (32.31) Control: 370 (31.62) Highest tertile Case: 138 (23.59) Control: 411 (35.13)	7

Table 1. Characteristics of included studies. (Cont'd)

Study	Year of study	Country	N (flushers/ non-flushers)	N (male/female)[a]	Type of cancer (e.g. esophageal squamous cell carcinoma [ESCC], lung etc.)	Mean age (SD), years[a]	Smoking/ drinking alcohol/ physical activity/ reproductive details	Mean alcohol consumption[b]	Green leafy vegetable intake/ daily consumption of hot or burning hot tea	Newcastle-Ottawa score
							Smoking, no. (%) Pack-years (PY)<5: Case: 103 (17.61) Control: 448 (38.29) 5<PY<20: Case: 67 (11.45) Control: 164 (14.02) 20<PY<40: Case: 161 (27.52) Control: 258 (22.05) 40≤PY: Case: 249 (42.56) Control: 288 (24.62)		Hot tea consumption, no. (%) ≥3/day Case: 250 (42.74) Control: 472 (40.34) <3/day Case: 317 (54.19) Control: 671 (57.35)	
Suzuki[18]	2010	Japan	47681 (13803/23878)	All females	Breast cancer	Overall mean: 52 Non-drinkers: 52.8 (8.1) Occasional: 48.7 (6.7) ≤150 g/week: 49.2 (7.4) 151–299 g/week: 48.8 (7.1) 300 g/week: 48.2 (6.2)	Overall drinking, % Non-drinkers: 5.7 Occasional: 11.5 1≤150 g/week: 5.8 151–299 g/week: 37.9 300 g/week: 46.1	Mean alcohol consumption g/ week (SD) ≤150 g/week: 57.0 (38) 151–299 g/week: 212.8 (45) ≥300 g/week: 496.4 (183)		8
Song[22]	2014	China	397 (186/211)	All males	Gastric adenocarcinoma and ESCC	Overall: 61.7 (8.4)	Smoking, PY, mean (SD) Gastric cardia adenocarcinoma: 23.1 (25.9) ESCC: 26.4 (22.0) Control: 11.0 (17.9)	Overall: 1740.9 (2397.3) g-year		8

Table 1. Characteristics of included studies. (Cont'd)

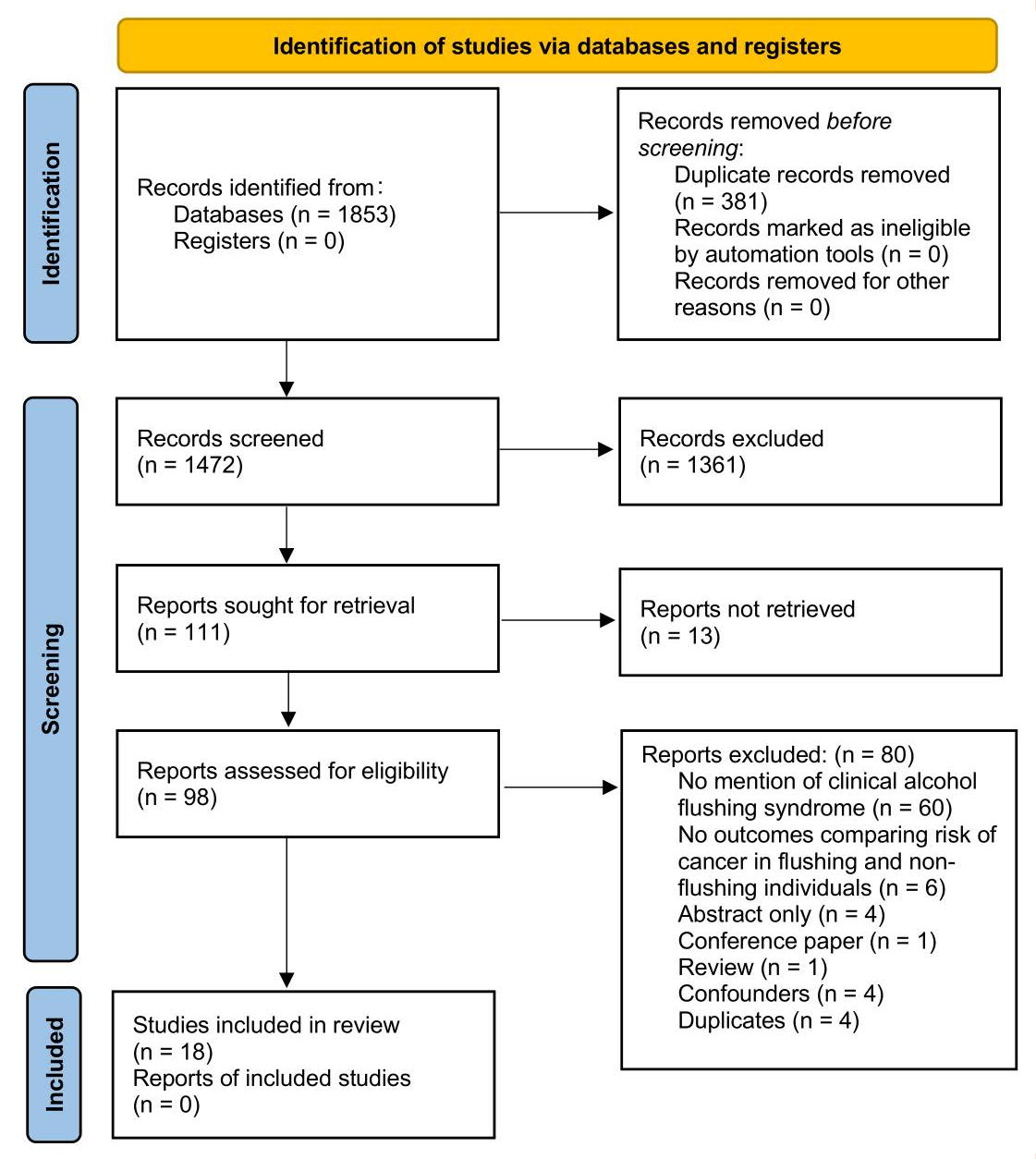
Study	Year of study	Country	N (flushers/ non-flushers)	N (male/female)[a]	Type of cancer (e.g. esophageal squamous cell carcinoma [ESCC], lung etc.)	Mean age (SD), years[a]	Smoking/ drinking alcohol/ physical activity/ reproductive details	Mean alcohol consumption[b]	Green leafy vegetable intake/ daily consumption of hot or burning hot tea	Newcastle-Ottawa score
Hirata[19]	2017	Japan	1776 (341/1435)	All males	Upper aerodigestive tract squamous cell carcinoma	Overall: 56.7 (10.1)	Overall drinking, %: 89.8	Overall: 121.9 (80) g/day		7
Masaoka[7]	2017	Japan	41,422 (23,454/ 17,968)	All males	Bladder cancer	Overall: 51.9 (7.8)	Overall drinking, %: 83.3	Overall: 292.0 (313.6)		8
Lu[20]	2018	Japan	Total: 71,038 (41,000/ 30,308)	Males: 40,696 (23,092/17,604) Females: 30,342 (17,908/12,434)	Oral and Pharyngeal	Flushing: 53.6 (8.1) Non-flushing: 52.1 (7.9)	Drinking, % Flushing: 6.4 Non-flushing: 8.8	Heavy consumption ≥300 g/week, % Flushing: 4 Non-flushing 8.3	Hot tea consumption, % Flushing 33.3 Non-flushing: 34	7
Yu[23]	2018	China	28,756 (15,989/ 12,767)	All males	ESCC	Overall: 50.9 (10.6)	Smoking, % Flushing: 24.9 Non-flushing: 25.7 Drinking, % Flushing: 86.4 Non-flushing: 87.6 Physical activity, %: Flushing: 24.3 Metabolic equivalent of task (MET)-hour/day Non-flushing: 23.8 MET-hour/day	Flushing: 69.6 g/day Non-flushing: 71.2 g/day	Vegetable intake, mean Flushing: 6.8 days/ week Non-flushing: 6.8 days/week Hot tea consumption, % Flushing: 35.3% daily Non-flushing 33.9% daily	7

Table 1. Characteristics of included studies. (Cont'd)

Study	Year of study	Country	N (flushers/ non-flushers)	N (male/female)[a]	Type of cancer (e.g. esophageal squamous cell carcinoma [ESCC], lung etc.)	Mean age (SD), years[a]	Smoking/ drinking alcohol/ physical activity/ reproductive details	Mean alcohol consumption[b]	Green leafy vegetable intake/ daily consumption of hot or burning hot tea	Newcastle-Ottawa score
Chuang[24]	2019	Taiwan	2920/5215	4050/4085	ESCC	Age group: no. 20–49: 3122 50–69: 3872 70–97: 1141	Drinking, % Case: 70.5 Control: 32.8	Any type of alcohol ≥1 per week		7
			2920/5215	4050/4085	Gastric adenocarcinoma	Age group: no. 20–49: 3122 50–69: 3872 70–97: 1141	Drinking, % Case: 30 Control: 34.2	Any type of alcohol ≥1 per week		
Ono[21]	2020	Japan	24,133/32,757 All males: 13,153/13,152 All females: 10,980/19,605	Males + females: 56,890 All males: 26,305 All females: 30,585	All cancers: mouth, pharynx and larynx, ESCC, stomach cancer, colorectal cancer, liver cancer, and breast cancer	Overall: 53.0 (8.9) All males: 52.7 (8.8) All females: 53.3 (8.9)	Overall smoking %: 28.1 Smoking, % All males: 52.4 All females: 7.2 Overall physical activity, %: 20.4 Physical activity, % All males: 20.2 All females: 20.5	Overall: 244.2 (286.5) All males: 277.2 (297.8) g/week All females: 109.2 (179.9) g/week	Overall vegetable intake, %: 22.6 Vegetable intake ≥5 times/week, % All males: 18.8 All females: 25.9	8
Im[8]	2021	China	12,492/57,252	69,734 (all males)	All cancers	Overall: 51.2 (10.8)	Overall drinking, %: 71.8			7
Okita[6]	2022	Japan	6900/1536 (non-drinker <1 day/month)	8436 (all males)	Pancreatic	Overall: 51.9 (7.9)	Overall drinking, %: 75.7 Overall physical activity, %: 19.5	Overall: 291.5 (300.8) g/week		7

Superscript numbers: refer to REFERENCES
[a] Unless otherwise specified.
[b] In grams of pure ethanol.

Fig. 1. PRISMA flow diagram of included studies.

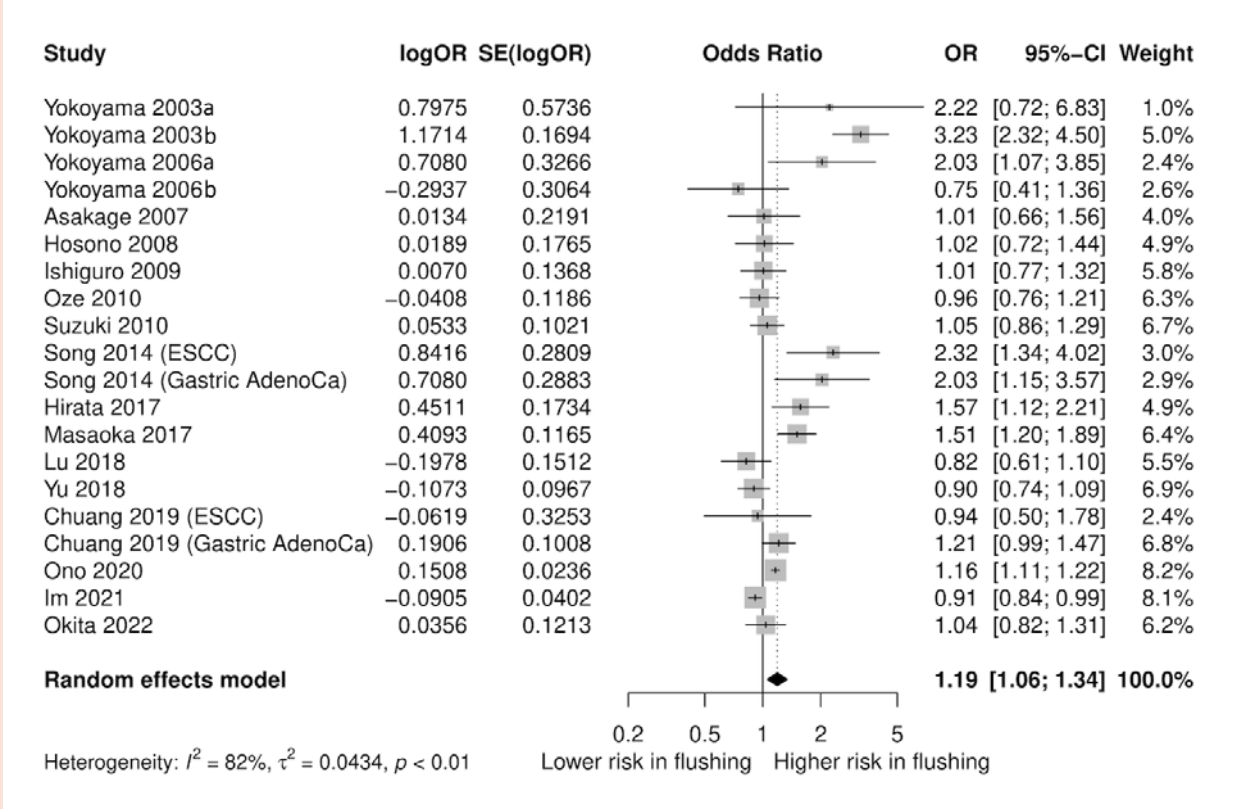


Adapted from: Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n271.

ESCC[16] and by Asakage et al.[14] for oral cavity and pharyngeal cancers, although both studies did not demonstrate an association between AFS and cancer. Importantly, this study did not observe an increased risk of cancers in flushers who do not consume alcohol, thus alleviating concerns of elevated cancer risk due to environmental sources of aldehyde such as in the air, foods and beverages we consume.

The effect sizes in this study may have been underestimated due to several reasons. First, the heterogeneity in the definition of facial flushing resulted in participants who flush quickly, after some time, currently flush or used to flush being analysed as a single entity. The accumulation of acetaldehyde in the body depends on the combination of alcohol and ALDH polymorphisms. A fast-metabolising ADH paired with an inactive ALDH will lead to the fastest accumulation of acetaldehyde and the soonest flushing response, which has been reported by Yu et al.[23] to increase the risk of cancer by up to 48 times compared to non-flushers. With further granularity on the speed of flushing after drinking, risks of cancer can be

Fig. 2. Forest plot of risk of all cancers.



CI: confidence interval; ESCC: esophageal squamous cell carcinoma; Gastric AdenoCa: gastric adenocarcinoma; OR: odds ratio; SE: standard error

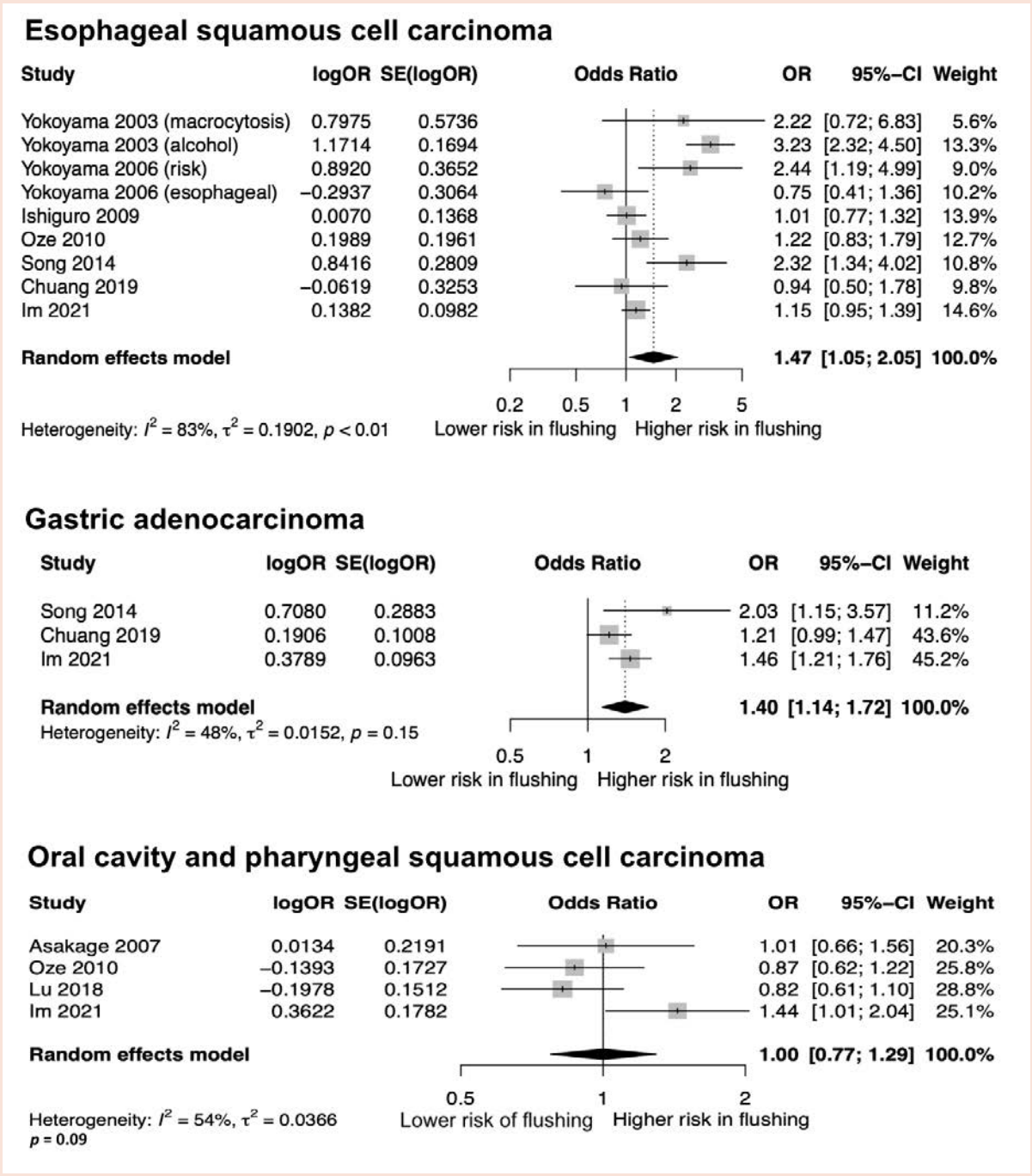
sharply delineated especially for those who are most susceptible. Additionally, as heterozygotes for ALDH polymorphisms may retain some function of the enzyme and may experience reduced flushing with prolonged alcohol consumption,[39] there is value to categorise participants based on current or past flushing to investigate the risks of cancer in all subgroups. Second, the definition of flushing that quizzes only on the presence of facial redness could include patients with rosacea as flushers though they do not possess defective ALDH polymorphisms responsible for increased cancer risk, potentially leading to underestimated effect sizes. Third, while the jury is still out on the net effect of wine on our health, some studies have shown reduction in cancer risk,[40] and therefore, it could be interesting to analyse subgroups based on the type of alcohol consumed.

Globally, there is growing interest in products that reduce facial flushing, such as the use of topical alpha-adrenergic brimonidine gel,[41] patches, antihistamines and traditional remedies. While such products may mask the flushing response, they have not been evidenced to reduce the adverse relations of flushing to cancer and instead, can lead to higher levels of alcohol consumption among those with AFS. With growing evidence supporting the association between AFS and cancers, the flushing response can be potentially used as part of a predictive tool to identify at-risk patients to screen for alcohol-related cancers in a cost-effective manner. It is salient for clinicians and the public to be cognisant of the ramifications of alcohol consumption for individuals who flush.[4]

Limitations

This study is limited by heterogeneity across studies attributable to differences in study design, method of assessment and definition of flushing, and differences in patient baseline characteristics such as alcohol consumption amounts and smoking status which were not always reported. To account for such heterogeneity, a random effects model was utilised in analysis and sensitivity analyses were further performed using only adjusted ratios. Subgroup analyses were also performed based on sites of cancer, alcohol consumption amounts and sex leading to reductions in heterogeneity in several subgroups. While no association was observed in the female subgroup, the subgroup analysis of studies on women was dominated by

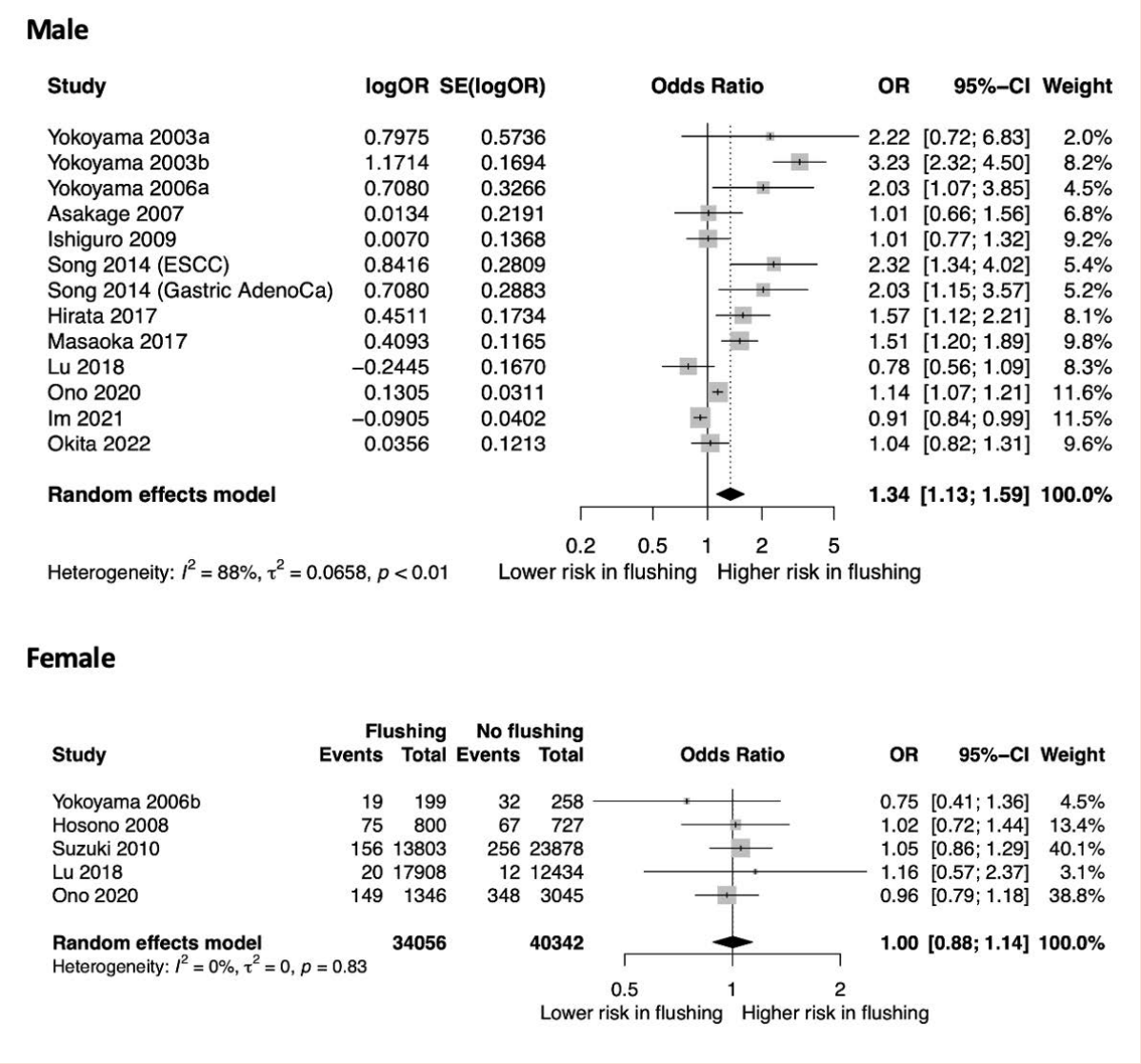
Fig. 3. Forest plot of risk of cancers by site: esophageal squamous cell carcinoma, gastric adenocarcinoma and oral cavity and pharyngeal squamous cell carcinoma.



CI: confidence interval; OR: odds ratio; SE: standard error

1 study showing a negative association between flushing and cancer and that a low level of alcohol consumption in women who flush may mask the association between flushing and cancer.[21] This has similarly been reported for patients with rs671 ALDH2 mutations in whom esophageal cancers are less common as patients avoid alcohol due to the intense flushing response.[42] The study may also be limited by the presence of confounders, as adjusted effect sizes were not always available and raw numbers were used for analysis (female subgroup, Fig. 5 and Supplementary Fig. S3). Additionally, the lack of uniformity in the stratification of alcohol consumption amounts resulted in difficulty analysing all the studies in an all-inclusive manner. There is a need for more high-quality prospective studies with control of major confounders such as smoking status, alcohol consumption amounts

Fig. 4. Forest plot of risk of all cancers in male and female patients.



CI: confidence interval; ESCC: esophageal squamous cell carcinoma; Gastric AdenoCa: gastric adenocarcinoma; OR: odds ratio; SE: standard error

(based on recommended alcohol guidelines such as 14 and 7 drinks per week for men and women, respectively[38]) and speed of flushing after drinking.

CONCLUSION

In summary, our findings support the association between AFS and increased risk of cancer. Significant associations were similarly observed in our ESCC and gastric adenocarcinoma but not in the oral cavity and pharyngeal cancers subgroup. Preliminary evidence is supportive of a dose response relationship between alcohol consumption and risk of cancer in flushers. However, high-quality prospective studies comparing cancer risk between flushers and non-flushers at different alcohol consumption levels will provide value in confirming this association.

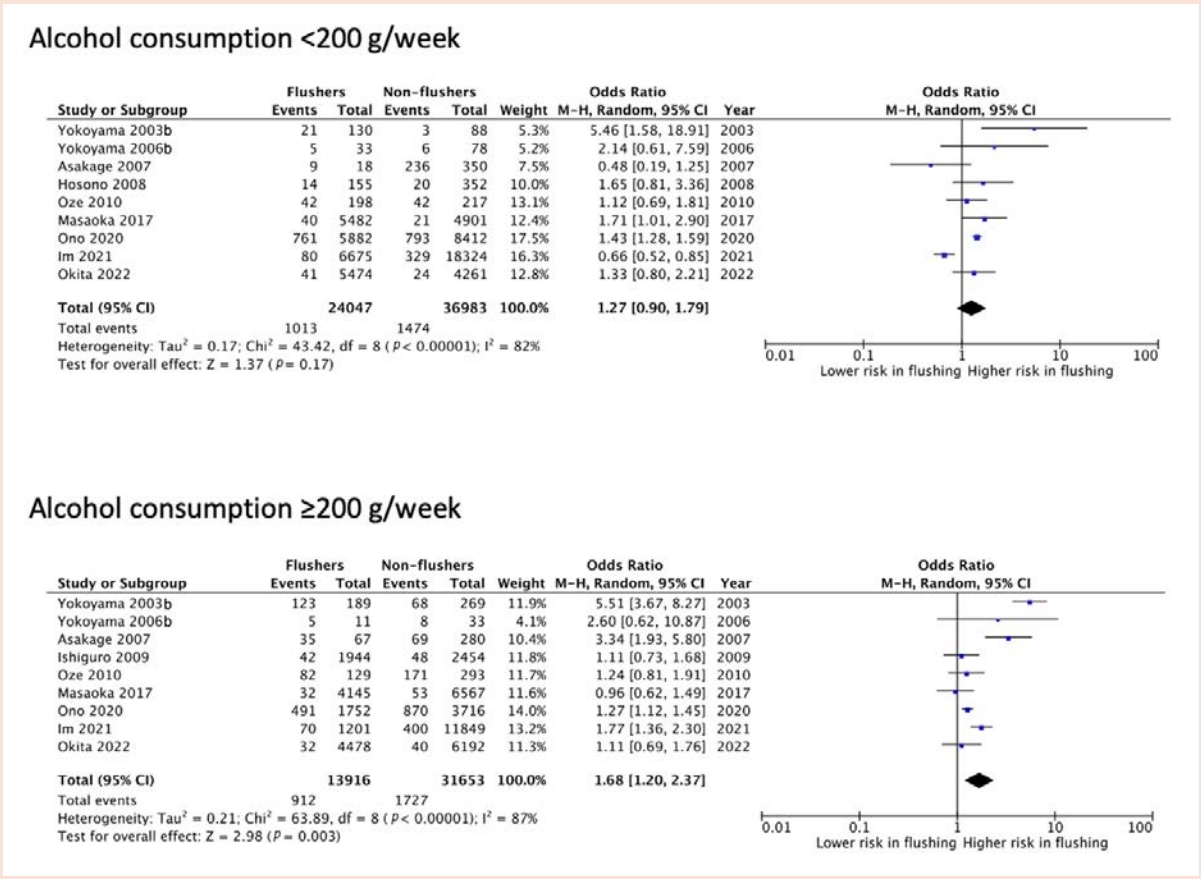
Supplementary materials

Fig. S1. *Forest plot of pooled adjusted odds ratios for all cancers.*
Fig. S2. *Forest plot of risk of ESCC in males.*
Fig. S3. *Forest plot of risk of all cancers in non-drinkers.*
Fig. S4. *Risk of all cancers in current and former flushers.*
Fig. S5. *Funnel plot of included studies.*
Appendix S1. *PRISMA checklist.*
Appendix S2. *PubMed search strategy.*

Declaration

Hazel H Oon is a speaker, advisory board member and researcher for AbbVie, Galderma, Janssen and Novartis. She has also been a clinical investigator for Pfizer, advisory board member

Fig. 5. Forest plot of risk of all cancers at an alcohol consumption level below and above 200 g of pure ethanol/week.



CI: confidence interval
Alcohol consumption in grams of pure ethanol.

for Amgen, speaker and advisory board member for Boehringer Ingelheim and Eli Lilly. The remaining authors disclose no conflicts. No financial support was received for this work.

Data transparency statement

The data that support the findings of this study are available from the corresponding author, Hazel H Oon, upon reasonable request.

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ORIGINAL ARTICLE

Trends in fluid overload-related hospitalisations among patients with diabetes mellitus The impact of chronic kidney disease

Joshua Kuan Tan[1] *MSc*, Hanis Abdul Kadir[1] *MSc*, Gek Hsiang Lim[1] *MSc*, Julian Thumboo[1] *FAMS*, Yong Mong Bee[2] *FRCP*, Cynthia Ciwei Lim[3] *FRCP*

ABSTRACT

Introduction: Fluid overload is a known complication in patients with diabetes mellitus, particularly those with cardiovascular and/or chronic kidney disease (CKD). This study investigates the impact of fluid overload on healthcare utilisation and its association with diabetes-related complications.

Method: Electronic medical records from the SingHealth Diabetes Registry (2013–2022) were analysed. Hospitalisations due to fluid overload were identified using International Classification of Diseases, 10th Revision (ICD-10) discharge codes. Trends were examined using Joinpoint regression, and associations were assessed with generalised estimating equation models.

Results: Over a period of 10 years, 259,607 individuals treated at primary care clinics and tertiary hospitals were studied. The incidence of fluid overload-related hospitalisations decreased from 2.99% (n=2778) in 2013 to 2.18% (n=2617) in 2017. However, this incidence increased from 2.42% (n=3091) in 2018 to 3.71% (n=5103) in 2022. The strongest associations for fluid overload-related hospitalisation were found with CKD stages G5 (odds ratio [OR] 6.61, 95% confidence interval [CI] 6.26–6.99), G4 (OR 5.55, 95% CI 5.26–5.86) and G3b (OR 3.18, 95% CI 3.02–3.35), as well as with ischaemic heart disease (OR 3.97, 95% CI 3.84–4.11), acute myocardial infarction (OR 3.07, 95% CI 2.97–3.18) and hypertension (OR 3.90, 95% CI 3.45–4.41). Additionally, the prevalence of stage G5 CKD among patients with fluid overload increased between 2018 and 2022.

Conclusion: Our study revealed a significant increase in fluid overload-related hospitalisations and extended lengths of stay, likely driven by severe CKD. This underscores an urgent need for initiatives aimed at slowing CKD progression and reducing fluid overload-related hospitalisations in diabetes patients.

Ann Acad Med Singap 2024;53:435-45

Keywords: chronic kidney disease, diabetes mellitus, fluid overload, healthcare utilisation, heart failure

CLINICAL IMPACT

What is New

- There has been an increasing trend in the number of patients with diabetes mellitus experiencing at least 1 hospital admission due to fluid overload within the SingHealth system in Singapore. This trend correlates with a growing healthcare burden.
- Our analysis indicates that the progression to end-stage chronic kidney disease (CKD) is a significant factor contributing to these trends.

Clinical Implications

- There is an urgent need for interventions to slow the progression of CKD and to reduce fluid overload-related hospitalisations among patients with diabetes mellitus.

INTRODUCTION

Diabetes mellitus (DM) is a major global health problem, contributing to significant clinical disease burden, healthcare expenditure and societal costs.[1] In Singapore, DM accounts for 2.9% of disability-adjusted life years and 4.3% of years lived with disability.[2,3] By 2030, it is projected to cost approximately USD 1.89 billion in healthcare spending.[4] The burden and costs of DM are expected to worsen due to the rising prevalence of diabetes-related macrovascular and microvascular complications, particularly cardiovascular disease (CVD) and chronic kidney disease (CKD).[5,6] Furthermore, type 2 DM (T2DM) is a major risk factor for cardiorenal syndrome (CRS),[7] a condition where CVD and CKD interact, leading to worsening dysfunction of both systems.[8] Decompensated

[1] Health Services Research Unit, Singapore General Hospital, Singapore
[2] Department of Endocrinology, Singapore General Hospital, Singapore
[3] Department of Nephrology, Singapore General Hospital, Singapore
Correspondence: Dr Cynthia Ciwei Lim, Department of Renal Medicine, Singapore General Hospital, Academia Level 3, 20 College Road, Singapore 169856.
Email: cynthia.lim.c.w@singhealth.com.sg

CVD, CKD and CRS often present as symptomatic fluid overload and/or acute decompensated heart failure,[9] necessitating hospitalisation.[10–12] Severe fluid overload increases the risk of ventilatory support in the intensive care unit, prolonged hospitalisations, or recurrent hospitalisations,[13] thus contributing significantly to morbidity, mortality and healthcare costs.

As CVD and CKD become more prevalent among individuals with DM,[5] the occurrence of CRS and fluid overload is expected to lead to higher healthcare expenditure and productivity losses,[14] a trend observed in the US.[15] Between 2018 and 2021, we noted an increase in hospitalisations due to fluid overload among individuals with diabetes in Singapore.[12] However, the healthcare utilisation characteristics related to fluid overload in these patients have not been fully described. Fluid overload is a potentially avoidable and ambulatory-sensitive cause of unplanned hospitalisations. Understanding the trends and drivers of healthcare utilisation for fluid overload can inform targeted interventions and resource allocation to reduce hospitalisations and healthcare costs associated with diabetes. Therefore, we aimed to examine the long-term trends in hospitalisations due to fluid overload and explore the plausible reasons for these trends.

METHOD

Study design and population

We utilised data from the multi-institutional SingHealth Diabetes Registry (SDR), a comprehensive repository from the Singapore Health Services (SingHealth) Regional Health System in Singapore. We examined trends of fluid overload in the registry cohort from 2013 to 2022. The SDR includes data from electronic medical records and clinical databases, covering primary to tertiary care. It encompasses all individuals aged 18 and above diagnosed with DM, excluding those with pre-diabetes. Cases are annually identified using criteria that incorporate diagnosis codes (International Classification of Disease, 9th Revision [ICD-9] and 10th Revision [ICD-10]), prescription records and laboratory test records.[16]

Outcome ascertainment

Hospitalisations due to fluid overload were determined using ICD-10 diagnosis codes (E877, I50, I500, J81, N04 and R601) for fluid overload, heart failure, congestive heart failure, pulmonary oedema, nephrotic syndrome and generalised oedema, respectively. Fluid overload could be the principal cause of hospitalisation (coded as primary discharge diagnosis) or could occur alongside another condition (coded as secondary discharge diagnosis). Thus, we analysed trends and associations for fluid overload both as the "principal diagnosis" (i.e. primary discharge diagnosis) and the "discharge diagnosis" (i.e. either the primary or secondary discharge diagnosis). To evaluate the healthcare burden attributable to fluid overload, we analysed the proportion of individuals who had 1 or more hospitalisations due to fluid overload each calendar year. We also examined the total number of hospitalisations caused by fluid overload and the total length of stay (LOS) for all fluid overload-related hospitalisations within a year. The total LOS was calculated as the sum of the LOS of all hospitalisations in a calendar year where fluid overload was either the principal or discharge diagnosis. The average LOS per patient with fluid overload was determined by dividing the total LOS by the number of patients with fluid overload-related hospitalisations.

Explanatory variables

A total of 17 sociodemographic and clinical variables related to diabetic complications were evaluated. These included age, sex, housing type (used as a surrogate measure of socioeconomic status), smoking status, mean HbA1c over 1 year, estimated glomerular filtration rate (eGFR) category, hypertension, hyperlipidaemia, and diabetes-related macrovascular and microvascular diseases. The macrovascular diseases included ischaemic heart disease (IHD), peripheral arterial disease, stroke (both ischaemic and haemorrhagic). The microvascular diseases included lower extremity amputation (both major and minor), diabetes-related eye complications, and diabetic foot complications. eGFR was calculated using the last serum creatinine value of the calendar year and the CKD EPI 2021 equation.[17] eGFR categories were aligned with the Kidney Disease: Improving Global Outcomes (KDIGO) nomenclature.[18] The criteria for ascertaining these macrovascular and microvascular diseases have been described previously.[5]

Statistical analyses

The analysis was conducted for 4 age bands; 18–44 years (age band 1), 45–64 years (age band 2), 65–74 years (age band 3), and 75 years and older (age band 4) to control for age effects on trend estimates. When calculating event rates, the denominator included all patients present in the registry each year, while the numerator consisted of those who experienced the outcome. Patients who died but experienced specific outcomes

within their year of death were included in the analysis for that year but excluded from the registry in subsequent years. Joinpoint regression methodology[19] was used to analyse trends in the event rates of fluid overload hospitalisations, allowing a maximum of 1 Joinpoint based on the 10 years of observations. Generalised estimating equation (GEE) models were employed to evaluate the associations between fluid overload and explanatory variables. Multivariable GEE regression models were constructed to assess the association between explanatory variables and the occurrence of fluid overload-related hospitalisation, the number of such hospitalisations, and the LOS for these hospitalisations. The covariables were determined a priori, including all 17 sociodemographic and clinical variables in the multivariable GEE regression models. We used the binomial family with a logit link for the occurrence of at least 1 fluid overload-related hospitalisation (a binary outcome) within the calendar year, and Poisson family with a log link for the number of hospitalisations for fluid overload or total LOS. All GEE models included the calendar year as an independent variable and were adjusted for the confounding effect of age. Additional descriptive analyses were performed on variables identified by the GEE models as having the strongest associations. All analysis were performed using Stata version 14.0 (StataCorp, College Station, TX, US) or Joinpoint Regression Program version 5.02 (Statistical Methodology and Applications Branch, Surveillance Research Programme, National Cancer Institute, US). The study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist (Supplementary Table S1).

Ethics approval

The SingHealth Centralised Institutional Review Board (CIRB) determined that an ethics review was not required for the use of de-identified data obtained during routine clinical care (SingHealth CIRB reference number: 2022/2133). Since all participant data were de-identified, a waiver for participant consent was also granted.

RESULTS

This study included 259,607 unique patients. The characteristics of the registry are detailed in Table S2. Throughout the study period, the sex and ethnicity of the registry closely mirrored that of the Singapore population.[20] In 2022, nearly all patients in the registry (98.78%) had T2DM, with a small proportion (<1%) having type 1 or other types of diabetes (e.g. drug-induced, gestational, monogenic and secondary diabetes). The SDR is a dynamic cohort, and movement of the population in and out of the registry is illustrated in Fig. S1.

Trends in fluid overload

Over the study period, we observed an increase in the proportion of patients in the registry admitted for fluid overload (Table 1). In 2013, 0.94% of the registry (n=877) had at least 1 hospitalisation where fluid overload was the principal diagnosis. This prevalence decreased to 0.67% in 2017 but then sharply increased to 1.34% (n=1849) in 2022. A similar trend was seen for fluid overload as a discharge diagnosis, where the prevalence decreased from 2.99% (n=2778) in 2013 to 2.18% (n=2618) in 2017 and increased to 3.71% (n=5103) in 2022. The total LOS for all patients with fluid overload, whether as the principal diagnosis or discharge diagnosis, also increased over the study period. After adjusting for the number of patients with fluid overload in the registry, it was found that the average LOS per patient increased over time, indicating that patients spent longer durations in the hospital in the later years of the study.

Fig. 1 and Table S3 demonstrate that older adults in age bands 3 and 4 experienced event rates of at least 1 fluid overload-related hospitalisation that were 2 to 5 times higher than those of younger adults in age band 1. Additionally, Fig. 1 shows that older adults in age band 4 exhibited the steepest increase in the rates of fluid overload-related hospitalisation for both principal and discharge diagnoses.

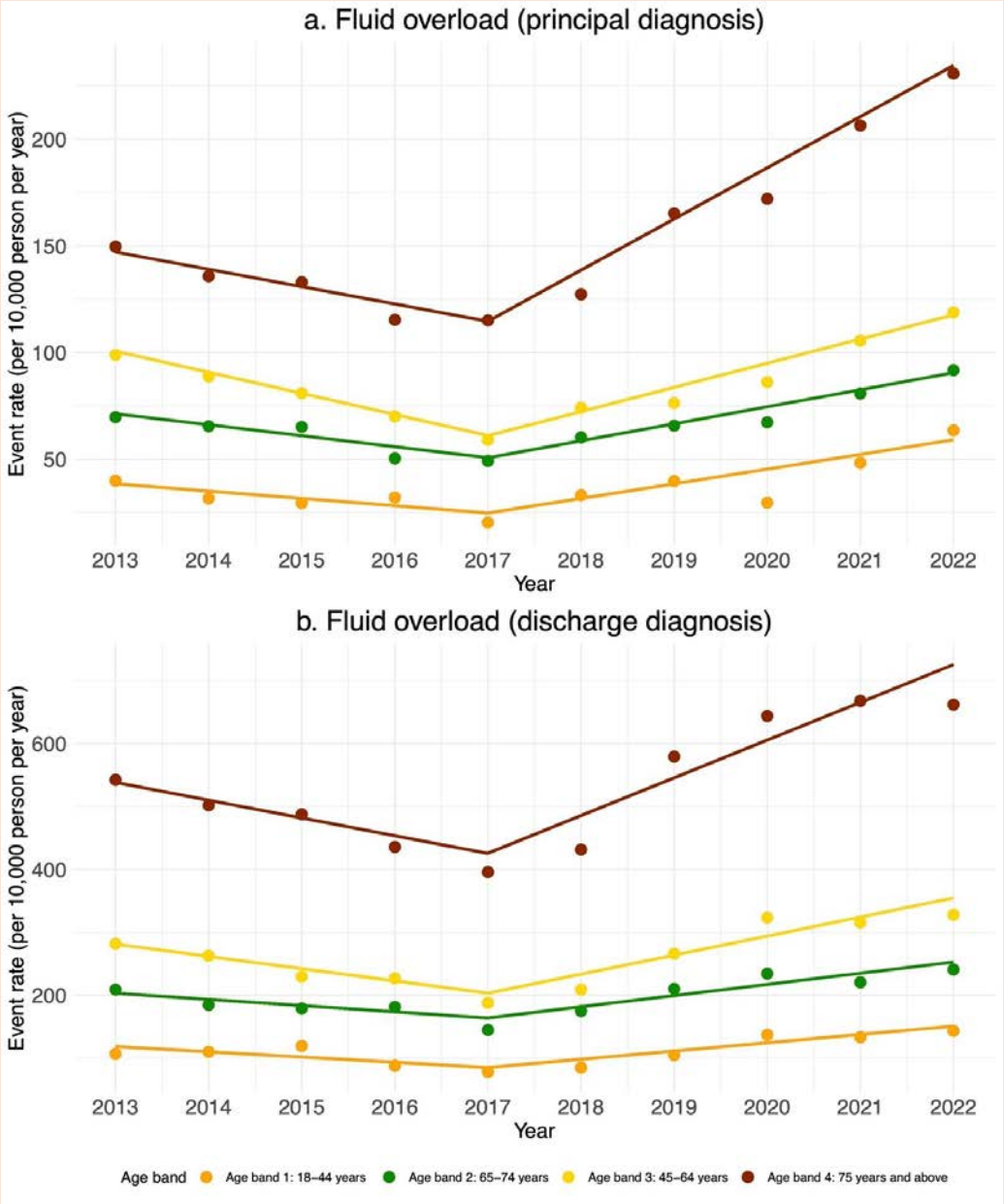
Joinpoint regression (Fig. 1) revealed that there was a statistically significant change in trends for fluid overload across all age bands, for both principal and discharge diagnoses. There was an initial decline from 2013 to 2017, followed by an increase from 2017 to 2022. Table S3 shows that in all Joinpoint models indicated a positive and statistically significant annual percentage change (APC) for the segments from 2017 to 2022. In age band 4, the APC was 15.39% (95% confidence interval [CI] 12.39%, 20.37%) for fluid overload as the principal diagnosis and 11.26% (95% CI 6.39%, 24.81%) for fluid overload as the discharge diagnosis. The dynamic nature of the SDR cohort (Fig. S1) added complexity to the analysis of fluid overload hospitalisation trends. To address this, we examined the flow of patients with fluid overload. Fig. S2 showed the trends in the annual inflow of patients. Between 2013 and 2017, there was a decrease in the absolute number of new patients admitted for fluid overload, while the number of patients with fluid overload already

Table 1. Utilisation characteristics of patients with fluid overload-related hospitalisations.

			Fluid overload as principal diagnosis				Fluid overload as discharge diagnosis			
Year	**SDR population**	**SDR year-on-year growth rate (%)**	**No. of patients (% of registry)**	**Unadjusted year-on-year growth rate (%)**	**Total LOS (days)**	**Average LOS per patient (days)**	**No. of patients (% of registry)**	**Unadjusted year-on-year growth rate (%)**	**Total LOS (days)**	**Average LOS per patient (days)**
2013	92,990	-	877 (0.94)	-	7820	8.92	2778 (2.99)	-	41,544	14.95
2014	96,846	4.15	839 (0.87)	-4.33	7577	9.03	2678 (2.77)	-3.60	41,616	15.54
2015	105,181	8.61	882 (0.84)	5.13	7338	8.32	2771 (2.63)	3.47	40,366	14.57
2016	111,963	6.45	792 (0.71)	-10.20	5828	7.36	2802 (2.50)	1.12	41,159	14.69
2017	120,221	7.38	810 (0.67)	2.27	6408	7.91	2617 (2.18)	-6.60	35,319	13.50
2018	127,989	6.46	1011 (0.79)	24.81	8302	8.21	3091 (2.42)	18.11	43,191	13.97
2019	134,670	5.22	1236 (0.92)	22.26	9939	8.04	4194 (3.11)	35.68	62,298	14.85
2020	140,859	4.60	1356 (0.96)	9.71	13,035	9.61	5008 (3.56)	19.41	78,597	15.69
2021	137,584	-2.33	1610 (1.17)	18.73	16,288	10.12	4868 (3.54)	-2.80	78,914	16.21
2022	137,627	0.03	1849 (1.34)	14.84	19,977	10.80	5103 (3.71)	4.83	83,471	16.36

LOS: length of stay; SDR: SingHealth Diabetes Registry

Fig. 1. Trends in fluid overload-related hospitalisations by age bands.



included in the previous year's registry remained relatively constant. Starting in 2018, there was a rise in the number of newly diagnosed patients with fluid overload, including both new entrants to the SDR and those already present in the SDR from the previous year, across both principal and discharge diagnosis categories.

Variables associated with fluid overload-related hospitalisations

Patients with stages G3b–G5 CKD, hypertension, IHD and acute myocardial infarction (AMI) had the highest odds of experiencing at least one hospitalisation for fluid overload, whether as the principal or the discharge diagnosis, throughout the study period (Table 2). These associations remained consistent when analysed using individual logistic regression models for each year (data not shown). Similarly, these factors were also most strongly associated with the number of fluid overload-related hospitalisations and total LOS.

Detailed trends in CKD and IHD

Given the strong association between CKD and IHD with fluid overload-related hospitalisations (Table 2), we further examined the trends in these variables in Figs. 2 and 3 and Table S4. Fig. 2 shows an increase in the proportion of stage G5 CKD between 2018 and 2022 among those with fluid overload-related hospitalisations (Figs. 2b and 2c),

with the most significant increase observed when fluid overload was the principal diagnosis (Fig. 2b). This trend was evident among patients newly added to the SDR each year (Figs. 3a and 3b) as well as those already present in the previous year's registry (Figs. 3c and 3d). Conversely, the proportions of CKD stages 3B, 4 and 5 remained unchanged over the years among the entire SDR population (Fig. 2a) and those without fluid overload-related hospitalisations (Figs. 2d and 2e).

We observed a gradual increase in the prevalence of IHD in the entire SDR cohort (Fig. S3a, Table S5), consistent with our earlier study.[5] Interestingly, there was no significant change in the prevalence of IHD among patients with fluid overload, whether as the principal or discharge diagnosis (Figs. S3b and S3c, Fig. S4).

DISCUSSION

In this study, we observed a rising rate of fluid overload-related hospitalisations among individuals with diabetes over the past decade. This increase was accompanied by a growing healthcare burden attributable to fluid overload, as evidenced by a rise in total inpatient bed days and average LOS. We found that stages G3b–G5 CKD, IHD, AMI and hypertension were most strongly associated with fluid overload, both as principal and discharge diagnoses. Furthermore, the prevalence of stage G5 CKD among patients with fluid overload had increased alongside the rise in fluid overload-related hospitalisations over the past five years. This study offers valuable insight into the epidemiology of fluid overload-related hospitalisations among individuals with DM. Joinpoint analysis revealed a decline in fluid overload rates from 2013 to 2017, followed by a significant increase from 2018 to 2022. The inflection point in 2017 across all Joinpoint models may be attributed to extrinsic factors. Notably, that year, the Ministry of Health restructured the public healthcare system, transferring two polyclinics previously managed by SingHealth to other healthcare clusters.[21] Consequently, we observed a significant outflow of more than 20,000 patients from the SDR in 2017 (Fig. S1). These patients may have sought care with other healthcare clusters if they experienced fluid overload. However, these changes cannot fully explain the sustained increase in fluid overload-related hospitalisations and LOS between 2018 and 2022.

Our analysis suggests that the changes in the prevalence of fluid overload-related hospitalisations may be attributed to the progression of CKD. Utilising GEE models, we found that stages G3b–G5 CKD, IHD, AMI and hypertension are associated with fluid overload, both as principal and discharge diagnoses. These associations remained strong in GEE models for the number of hospitalisations and LOS (Table 2). This indicates that G3b–G5 CKD, IHD, AMI and hypertension are linked not only to fluid overload but also to the increasing healthcare burden resulting from it. From 2013 to 2016, we observed an initial decline in the proportion of patients with stage G5 CKD, both with and without fluid overload (for both principal and discharge diagnoses; Figs. 2a, 2b and 2c, Table S4). This suggests that the initial decline in fluid overload may be partially due to the reduced number of patients with advanced CKD during the earlier years of the study. However, from 2018 to 2022, there was an increasing proportion of patients with stage G5 CKD, both with and without fluid overload (for both principal and discharge diagnoses) between 2018 and 2022 (Figs. 2a, 2b and 2c, Table S4), which aligns with the increasing trend in fluid overload-related hospitalisations (Fig. 1) This suggests that the progression to stage G5 CKD may be a significant driving factor.

This observation may also explain the sharp increase in fluid overload-related hospitalisations and LOS in older adults. In this population, the combination of diabetes, hypertension and obesity heightens the risk of CKD, IHD and possibly CRS. However, studying CRS is technically challenging because clinical codes for CRS and its four subtypes have not yet been defined. Additionally, creating and interpreting interaction terms between CRS, CKD and IHD in a GEE model can be complex. Future research could aim to model these interactions through causal modelling approaches. The increasing proportion of patients with stage G5 CKD and fluid overload within the existing SDR cohort (Figs. 3c and 3d) is worrisome. Despite evidence that guideline-directed medical therapy (GDMT) can slow CKD progression,[22] our findings suggest that the benefits of GDMT are not yet fully realised at the population level, possibly due to delays in its uptake.[12] Factors contributing to this delay include clinical inertia among patients and physicians,[23] low awareness of CKD among patients, multimorbidity, fragmented CKD care, and high drug prices.[24] Therefore, we welcome recent efforts to promote adherence to GDMT, including clinical practice guidelines by the Singapore Agency for Care Effectiveness[25] and drug subsidies.

Interestingly, the number of new SDR patients who experienced fluid overload-related hospitalisations and stage G5 CKD also increased (Figs. 3a, 3b and Table S4). This suggests that more patients who are not previously engaged with SingHealth's

Table 2. Factors associated with (a) any hospitalisation for fluid overload, (b) number of hospitalisations for fluid overload and (c) total length of stay for fluid overload hospitalisation, as principal and discharge diagnoses.

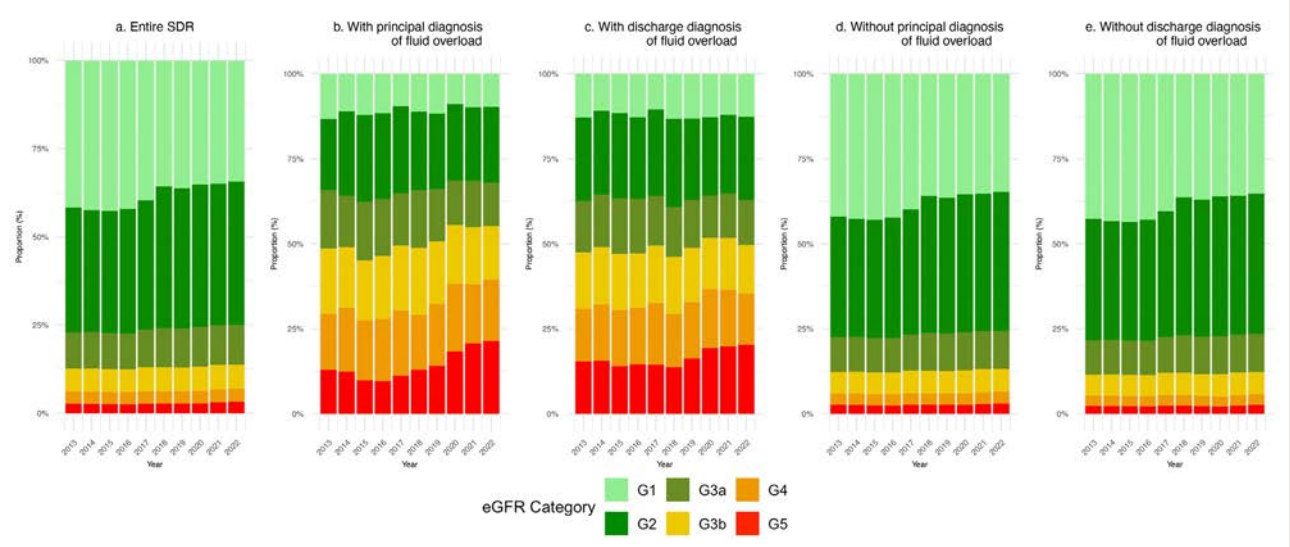
Variables	(a) Any hospitalisation for fluid overload				(b) No. of hospitalisations for fluid overload				(c) Total length of stay for fluid overload			
	Principal diagnosis		Discharge diagnosis		Principal diagnosis		Discharge diagnosis		Principal diagnosis		Discharge diagnosis	
	OR† (95% CI)	*P* value	OR† (95% CI)	*P* value	IRR‡ (95% CI)	*P* value	IRR‡ (95% CI)	*P* value	IRR‡ (95% CI)	*P* value	IRR‡ (95% CI)	*P* value
Female	Reference		Reference		Reference		Reference		Reference		Reference	
Male	0.96 (0.91–1.01)	0.118	0.85 (0.82–0.87)	<0.001	1.01 (0.97–1.06)	0.61	0.9 (0.88–0.92)	<0.001	0.86 (0.85–0.87)	<0.001	0.89 (0.88–0.91)	<0.001
Age (per year increase)	1.00 (1.00–1.00)	0.075	1.01 (1.01–1.02)	<0.001	1.00 (1.00–1.00)	0.041	1.01 (1.01–1.01)	<0.001	1.01 (1.01–1.01)	<0.001	1.00 (1.00–1.00)	<0.001
Housing type												
1- and 2-room flat	Reference		Reference		Reference		Reference		Reference		Reference	
3-room flat	0.73 (0.68–0.79)	<0.001	0.79 (0.75–0.83)	<0.001	0.64 (0.60–0.68)	<0.001	0.75 (0.72–0.77)	<0.001	0.85 (0.84–0.86)	<0.001	0.71 (0.70–0.73)	<0.001
4-room flat	0.68 (0.63–0.74)	<0.001	0.77 (0.73–0.80)	<0.001	0.61 (0.58–0.65)	<0.001	0.73 (0.70–0.76)	<0.001	0.79 (0.78–0.80)	<0.001	0.65 (0.64–0.67)	<0.001
5-room and executive flats	0.63 (0.58–0.68)	<0.001	0.71 (0.67–0.75)	<0.001	0.56 (0.53–0.60)	<0.001	0.68 (0.65–0.70)	<0.001	0.75 (0.74–0.76)	<0.001	0.61 (0.60–0.63)	<0.001
Condominium (Private)	0.48 (0.42–0.55)	<0.001	0.52 (0.48–0.57)	<0.001	0.42 (0.38–0.48)	<0.001	0.50 (0.47–0.54)	<0.001	0.52 (0.51–0.53)	<0.001	0.42 (0.40–0.44)	<0.001
Landed house (Private)	0.61 (0.54–0.70)	<0.001	0.63 (0.58–0.69)	<0.001	0.52 (0.47–0.58)	<0.001	0.59 (0.55–0.63)	<0.001	0.68 (0.66–0.69)	<0.001	0.58 (0.56–0.61)	<0.001
Smoking status												
Non-smoker	Reference		Reference		Reference		Reference		Reference		Reference	
Ex-smoker	1.85 (1.69–2.03)	<0.001	1.97 (1.85–2.09)	<0.001	1.58 (1.47–1.70)	<0.001	1.55 (1.48–1.61)	<0.001	1.73 (1.70–1.75)	<0.001	1.97 (1.92–2.03)	<0.001
Active smoker	1.32 (1.21–1.43)	<0.001	1.41 (1.34–1.48)	<0.001	1.25 (1.17–1.34)	<0.001	1.30 (1.25–1.35)	<0.001	1.20 (1.18–1.21)	<0.001	1.26 (1.22–1.29)	<0.001
Unknown	0.75 (0.71–0.79)	<0.001	0.87 (0.85–0.90)	<0.001	0.77 (0.74–0.80)	<0.001	0.78 (0.76–0.79)	<0.001	1.02 (1.01–1.03)	<0.001	0.86 (0.84–0.87)	<0.001
Comorbidities and complications												
Mean Hba1c (per 1% increase)	0.96 (0.94–0.97)	<0.001	0.96 (0.95–0.97)	<0.001	0.95 (0.93–0.96)	<0.001	0.95 (0.94–0.95)	<0.001	0.93 (0.93–0.93)	<0.001	0.91 (0.91–0.92)	<0.001
Hypertension	6.16 (4.67–8.12)	<0.001	3.90 (3.45–4.41)	<0.001	6.77 (5.26–8.71)	<0.001	4.03 (3.62–4.50)	<0.001	3.57 (3.47–3.68)	<0.001	10.67 (9.43–12.06)	<0.001
Hypercholesterolaemia	0.73 (0.63–0.84)	<0.001	0.68 (0.63–0.74)	<0.001	0.72 (0.64–0.82)	<0.001	0.73 (0.68–0.78)	<0.001	0.53 (0.53–0.54)	<0.001	0.63 (0.60–0.65)	<0.001

Table 2. Factors associated with (a) any hospitalisation for fluid overload, (b) number of hospitalisations for fluid overload and (c) total length of stay for fluid overload hospitalisation, as principal and discharge diagnoses. (Cont'd)

Variables	(a) Any hospitalisation for fluid overload				(b) No. of hospitalisations for fluid overload				(c) Total length of stay for fluid overload			
	Principal diagnosis		Discharge diagnosis		Principal diagnosis		Discharge diagnosis		Principal diagnosis		Discharge diagnosis	
	OR[†] (95% CI)	*P* value	OR[†] (95% CI)	*P* value	IRR[‡] (95% CI)	*P* value	IRR[‡] (95% CI)	*P* value	IRR[‡] (95% CI)	*P* value	IRR[‡] (95% CI)	*P* value
IHD	4.79 (4.52–5.07)	<0.001	3.97 (3.84–4.11)	<0.001	5.33 (5.06–5.60)	<0.001	4.27 (4.15–4.39)	<0.001	3.50 (3.47–3.53)	<0.001	5.08 (4.98–5.17)	<0.001
AMI	1.81 (1.71–1.91)	<0.001	3.07 (2.97–3.18)	<0.001	1.74 (1.66–1.82)	<0.001	2.39 (2.33–2.45)	<0.001	2.94 (2.91–2.96)	<0.001	1.82 (1.79–1.85)	<0.001
Peripheral arterial disease	1.41 (1.31–1.51)	<0.001	1.58 (1.52–1.66)	<0.001	1.46 (1.38–1.54)	<0.001	1.58 (1.54–1.63)	<0.001	2.04 (2.02–2.06)	<0.001	1.70 (1.67–1.74)	<0.001
Ischaemic stroke	0.96 (0.90–1.02)	0.184	1.21 (1.16–1.25)	<0.001	0.99 (0.94–1.05)	0.736	1.18 (1.14–1.21)	<0.001	1.46 (1.45–1.47)	<0.001	1.08 (1.06–1.10)	<0.001
Haemorrhagic stroke	1.05 (0.90–1.22)	0.536	1.41 (1.30–1.53)	<0.001	1.15 (1.02–1.30)	0.02	1.34 (1.27–1.42)	<0.001	1.86 (1.84–1.89)	<0.001	1.17 (1.12–1.22)	<0.001
Lower extremity amputation (major)	1.00 (0.79–1.25)	0.968	1.88 (1.63–2.15)	<0.001	0.89 (0.75–1.06)	0.187	1.23 (1.14–1.33)	<0.001	2.37 (2.34–2.41)	<0.001	1.03 (0.97–1.09)	0.372
Lower extremity amputation (minor)	0.96 (0.81–1.15)	0.67	1.25 (1.12–1.39)	<0.001	0.91 (0.79–1.05)	0.197	1.05 (0.98–1.13)	0.137	1.67 (1.65–1.70)	<0.001	1.18 (1.13–1.23)	<0.001
Diabetic foot and peripheral angiopathy	0.92 (0.87–0.97)	0.002	0.88 (0.85–0.91)	<0.001	0.95 (0.91–0.99)	0.018	1.04 (1.02–1.07)	<0.001	0.87 (0.87–0.88)	<0.001	0.78 (0.77–0.79)	<0.001
Diabetic eye disease	0.78 (0.74–0.82)	<0.001	0.81 (0.78–0.83)	<0.001	0.82 (0.79–0.86)	<0.001	0.86 (0.84–0.88)	<0.001	0.88 (0.87–0.88)	<0.001	0.90 (0.88–0.91)	<0.001
CKD stage												
Stage G1	Reference		Reference		Reference		Reference		Reference		Reference	
Stage G2	1.46 (1.35–1.58)	<0.001	1.27 (1.21–1.32)	<0.001	1.44 (1.35–1.54)	<0.001	1.34 (1.30–1.39)	<0.001	1.08 (1.07–1.09)	<0.001	1.38 (1.35–1.42)	<0.001
Stage G3a	2.59 (2.37–2.83)	<0.001	1.98 (1.88–2.09)	<0.001	2.59 (2.41–2.80)	<0.001	2.15 (2.06–2.24)	<0.001	1.66 (1.64–1.68)	<0.001	2.61 (2.53–2.68)	<0.001
Stage G3b	4.40 (4.02–4.81)	<0.001	3.18 (3.02–3.35)	<0.001	4.47 (4.15–4.81)	<0.001	3.28 (3.15–3.42)	<0.001	2.58 (2.55–2.62)	<0.001	4.74 (4.61–4.88)	<0.001
Stage G4	7.17 (6.55–7.85)	<0.001	5.55 (5.26–5.86)	<0.001	6.65 (6.17–7.17)	<0.001	4.84 (4.65–5.05)	<0.001	4.12 (4.07–4.17)	<0.001	7.98 (7.75–8.21)	<0.001
Stage G5	6.48 (5.90–7.13)	<0.001	6.61 (6.26–6.99)	<0.001	5.48 (5.06–5.93)	<0.001	4.91 (4.71–5.13)	<0.001	4.00 (3.95–4.05)	<0.001	5.93 (5.75–6.11)	<0.001

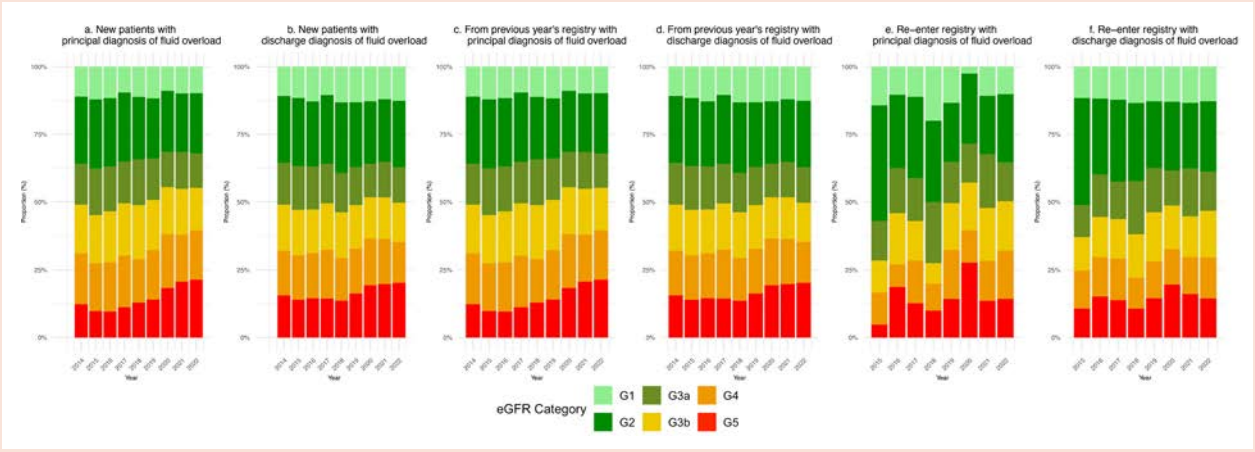
[a] Odds ratio
[b] Incidence rate ratio
AMI: acute myocardial infarction; CI: confidence interval; CKD: chronic kidney disease; IHD: ischaemic heart disease; IRR: incidence rate ratio; OR: odds ratio

Fig. 2. Characteristics of eGFR-defined CKD status among different subgroups of patients in the SingHealth Diabetes Registry (SDR).



CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate

Fig. 3. Characteristics of eGFR-defined CKD status among patients with fluid overload: (a) and (b) refer to new patients in the registry who were not in the registry in the previous calendar year; (c) and (d) refer to existing patients in the registry; and (e) and (f) refer to patients who had left the registry in the preceding calendar years then re-entered in that calendar year.



CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate

healthcare system were entering the SDR with late-stage CKD and in fluid overload in recent years. These individuals may have been receiving care at other healthcare settings before entering the SingHealth care system late in their CKD progression, or they may not have been diagnosed with CKD or receiving regular follow-up care. In both instances, our results highlight the urgent need for national-level programmes to identify individuals with CKD, ensure continuity of care across all healthcare settings, and facilitate advance care planning in anticipation of progression to kidney failure.[26] In this study, we conducted an extensive longitudinal analysis of fluid overload trends among a multiethnic cohort of individuals with diabetes. Our detailed analysis supports the Lancet Commission's call to action to improve diabetes care by identifying populations at risk of adverse health outcomes.[27] It offers valuable insights for public health interventions and future research as Singapore grapples with a rapidly ageing population. Based on these results, our hospital system is planning to implement or expand population health programmes to reduce fluid overload-related hospitalisations and slow the progression of CKD.[28] The issues identified by this study may also apply to other healthcare systems with ageing or super-ageing populations.

The limitations of our study arise from the dynamic nature of the SDR, particularly patients who exit the registry to seek clinical care at other healthcare institutions. The absence of data on fluid overload outcomes from other healthcare clusters or the private sector could influence our results. However, since the SingHealth cluster is the largest of the healthcare clusters in Singapore, the observed trends are likely similar in other clusters. Additionally, there may be bias related to outcome ascertainment as we used discharge codes that may be influenced by physician documentation and clinical coding practices. To minimise the bias, we considered fluid overload as both principal and discharge diagnoses and used a range of ICD codes (Table S6) to identify patients experiencing fluid overload in the context of DM and kidney disease, including those with unrecognised heart failure with preserved ejection fraction, which might not be included in studies focusing solely on heart failure.[29,30] Furthermore, while we analysed sociodemographic and clinical factors as potential explanatory variables, other drivers for the outcomes, such as socioeconomic determinants of health (e.g. personal income and educational level) and comorbidities (e.g. frailty and infection), were not included in this analysis. Interactions between the variables were not explored and should be considered in future analyses. Finally, our results may not be generalisable to other healthcare settings where the prevalence and risks of CKD and IHD differ.

CONCLUSION

This study highlighted an increasing occurrence of fluid overload-related hospitalisations within a significant and representative subsection of the Singapore population. Alarmingly, our findings suggest that the rising rates of fluid overload may indicate an impending surge in kidney failure cases across Singapore, with direct implications for healthcare utilisation. There is an urgent need for efforts to slow the progression of CKD and reduce fluid overload-related hospitalisations.

Supplementary materials

Table S1. STROBE Statement: Checklist of items for the reporting of observational studies.

Table S2. Population structure, demographics and comorbidities of the SDR population from 2013 to 2022.

Table S3. Event rates for fluid overload by age bands.

Table S4. Characteristics of patients by eGFR category and year.

Table S5. Characteristics of patients by IHD status and year.

Table S6. Counts and relative frequencies of ICD-10 codes used for outcome ascertainment.

Fig. S1. Progression of patients through the SDR from 2013 to 2022.

Fig. S2. Stock and flow diagram for patients with fluid overload in the SDR.

Fig. S3. Characteristic of IHD status among different subgroups of patients in the SDR.

Fig. S4. Characteristics of IHD status among patients with fluid overload.

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Declaration

All authors declare no relevant conflict of interest and no financial interest in this manuscript.

Ethics statement

SingHealth Centralised Institutional Review Board (2022/2133) approved the use of de-identified data and waiver of patient informed consent for this project.

Data availability statement

Data sharing is available and subjected to institutional data-sharing policies. Further enquiries can be directed to the corresponding author.

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REVIEW ARTICLE

Demographic diversity of participants in clinical trials conducted in Singapore

Bin Wen Jun Jerome[1] *MBBS*, Aloysius Chow[1] *BPsych (Hons)*, Helen Elizabeth Smith[1] *DM*, Lee Eng Sing[1,2] *PhD*

ABSTRACT

Introduction: The under-representativeness of participants in clinical trials limits the generalisability of results. This review evaluates the representativeness within pharmaceutical randomised controlled trials (RCTs) in Singapore.

Method: Four bibliographic databases were searched for papers on pharmaceutical RCTs which included Singapore adults (≥18 years old), published between 2017 and 2022. The demographic characteristics of study participants were compared against the population in the 2020 Singapore census. Recruitment strategies and authors' comments on the generalisability of their findings were reviewed.

Results: Thirty-three publications were included (19 Singapore-only studies and 14 multiregional trials which included Singapore). Where data were available, we found that females and Indians were under-represented compared to the census (41.3% versus [vs] 51.1%, $P<0.05$; 7.3% vs 9.0%, $P<0.05$). Ethnic diversity varied between individual studies, and almost half (46.2%) of Singapore-only studies achieved census levels. However, more than one-third of the trials provided no data (31.6%) or partial data (5.3%) on ethnicity. Half of the multiregional publications stated the number of participants recruited from Singapore, but only 1 reported any detail beyond Asian participants. Recruitment strategies were mentioned in fewer than half (42.4%), and less than a quarter (24.2%) commented on sample representativeness or the external validity of the evidence generated.

Conclusion: There is room for improvement regarding the recruitment of RCT participants in Singapore, with particular attention to female gender and Indian ethnicity. Demographic data should also be presented in full. RCTs should be designed and reported such that clinicians can ascertain the generalisability to the Singapore population and the potential benefits from the studied interventions in clinical practice.

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Keywords: ethnicity, external validity, generalisability, pharmaceutical, randomised controlled trials, real-world patients, recruitment

CLINICAL IMPACT

What is New

- This is the first review examining the representativeness of participants in pharmaceutical randomised controlled trials (RCTs) conducted in Singapore.
- Our analysis revealed significant under-representation of key demographics, including females and Indians, compared to the national census, highlighting many areas for improvement in RCT data reporting.

Clinical Implication

- The study underscores the urgent need for investigators to recruit a demographically diverse patient population that accurately reflects Singapore's population.
- We urge authors to ensure comprehensive data reporting to enhance the generalisability and relevance of trial findings for a wider audience.

INTRODUCTION

Randomised controlled trials (RCTs) and systematic reviews are the most reliable ways of relaying information on the most effective treatments for our patients in clinical practice. The careful design of trials to minimise the possibility of bias ensures that findings are internally valid, but this may threaten their clinical utility, as the results are not relevant to all the patients encountered in clinical practice—a concept known as external validity, applicability or generalisability of evidence. Over 50 years ago, Archie Cochrane commented that "Between measurements based on RCTs and benefit ... in the community, there is a gulf which has been much underestimated."[1] Today, external validity remains a frequent concern for clinicians when considering

[1] Family Medicine and Primary Care, Lee Kong Chian School of Medicine, Singapore
[2] National Healthcare Group Polyclinics, Singapore
Correspondence: Assistant Professor Lee Eng Sing, Director, Primary Care and Family Medicine Research Programme, Lee Kong Chian School of Medicine, 11 Mandalay Road, Singapore 308207. Email: eng_sing_lee@ntu.edu.sg

the results of RCT or systematic reviews, and the relevance of guidelines.

The result from a trial or the average result from pooled trials in a systematic review may not necessarily be applicable to all because the trial recruitment criteria distort representatives; for example, many RCTs exclude the elderly and occasionally females;[2] similarly they may not be attentive to ethnicity which can also influence the efficacy and safety of pharmaceutical interventions.[3] An analysis of 213 Pfizer-funded, interventional clinical trials, between 2011 and 2020 and involving 103,103 participants in the US, found that the involvement of minority ethnic groups was not uniform across trials, and they were often not represented at all.[4] More than half of the trials achieved population census levels for African–American, white and Hispanic/Latino participants, while Asian, Native Hawaiian or other Pacific Islander and American Indian or Alaska Native participants were commonly under-represented, achieving only census levels in 16%, 14.2% and 8.5% of trials, respectively.

Exclusion criteria may also prevent participation in trials of patients with comorbidities or multimorbidity, or those with more severe disease or illness of longer duration. A review of cardiology, mental health and oncology trials compared the baseline characteristics (i.e. demographic, socioeconomic and clinical) of trial participants with patients encountered in clinical practice.[5] It demonstrated that in 37 of 52 studies (71.2%), the population studied was not representative of real-world patients and thus limited the external validity of the RCT. The authors recommended that more appropriate evidence could be generated by tailoring trial design—including the recruitment of more representative patient samples—and carefully taking into account trade-offs made between internal and external validity.

There is a growing literature highlighting how the under-representativeness of research tpartici-pants in clinical trials may misinform clinical practice, and their inclusion in systematic reviews and meta-analyses may subsequently misinform health policies.[2,6] Singapore is a multiethnic nation, with 4 ethnic categories (i.e. Chinese, Malays, Indians and Others). In this study, we sought to review the representativeness of participants in pharmaceutical RCTs in Singapore. To the best of our knowledge, no such study had been conducted.

METHOD

Literature search

Searches were run in PubMed, Embase, Cochrane Library and Web of Science to identify pharmaceutical RCTs involving the Singapore population over 5 years from 1 January 2017 to 12 August 2022. The search strategy was developed in consultation with a medical librarian to ensure that the search strategies (Appendix S1) were optimal. All searches were run on 12 August 2022. Deduplication was initially performed using EndNote and then 2 authors (JB and AC) independently screened titles and abstracts on Covidence, manually removing duplicates and ineligible publications according to the inclusion and exclusion criteria listed in Table 1 (EndNote 21, Clarivate PLC, London, UK; Covidence software, Veritas Health Innovation, Melbourne, Australia). Potentially eligible full-text publications were retrieved, screened once more, with senior reviewers (LES or HES) resolving any disagreements on study selection.

Table 1. Inclusion and exclusion criteria.

Inclusion criteria
• Randomised controlled trial (RCT) • Adult patients (i.e. aged 18 years and older) • Only publications reporting pharmaceutical interventions as part of an RCT (placebo-controlled or active comparator) • Recruitment was, at least in part, conducted in Singapore • Published in English
Exclusion criteria
• Publications that undertook an analysis of patients who were recruited into an RCT compared to those that declined participation • Publications that involved patients younger than 18 years • Quasi-experimental RCTs • Conference abstracts, journal notes

Data extraction

A data extraction table was developed and tested on a sample of studies before being finalised. The data extracted from each publication included patient population and country of study, baseline demographic characteristics (i.e. ethnicity, sex and age), disease/therapy area (determined by study aims, authors' disciplines and journal) (Appendix S2). Recruitment strategies, inclusion and exclusion criteria, recruitment challenges and authors' comments on the generalisability of their studies were also extracted verbatim for inductive content analysis.[7]

Data analysis and interpretation

Descriptive statistics were used to summarise the demographic characteristics (i.e. sex, age and ethnicity) of trial participants. The study population demographics were compared with the 2020 Singapore Census of Population,[8] employing similar methodology used to assess demographic diversity in the US,[4] but adapted for Singapore and focusing on Chinese, Malay, Indian and Other ethnicities. When variables were reported only

for the treatment or the control population, the overall sample population was calculated to enable comparison with the census data. Comparison between the census population and the study population were made using the 2 proportion Z-tests.[9] When a specific trial is cited in the text, the first author's name follows in a bracket and in italics.

RESULTS

From the 932 potentially relevant articles retrieved from the databases searched, 33 publications had a Singapore footprint and were eligible for inclusion (Fig. 1). There were 19 Singapore-only-based trials and 14 multiregional studies, of which the US (n=7) was the most frequent collaborator (Fig. 2). Studies involving 5 regions were the most common, with a range from 2 (US and Singapore) (Szmulewittz et al.) to 17 (Latin America [2 countries], Europe [12 countries] and Others [3 countries: Singapore, Israel and Singapore]) (Reference 19 in Appendix S3). The data presented were often incomplete. In 24 publications (72.7%), demographic characteristics were described for treatment and control arms, but not reported in similar detail for the overall study population.

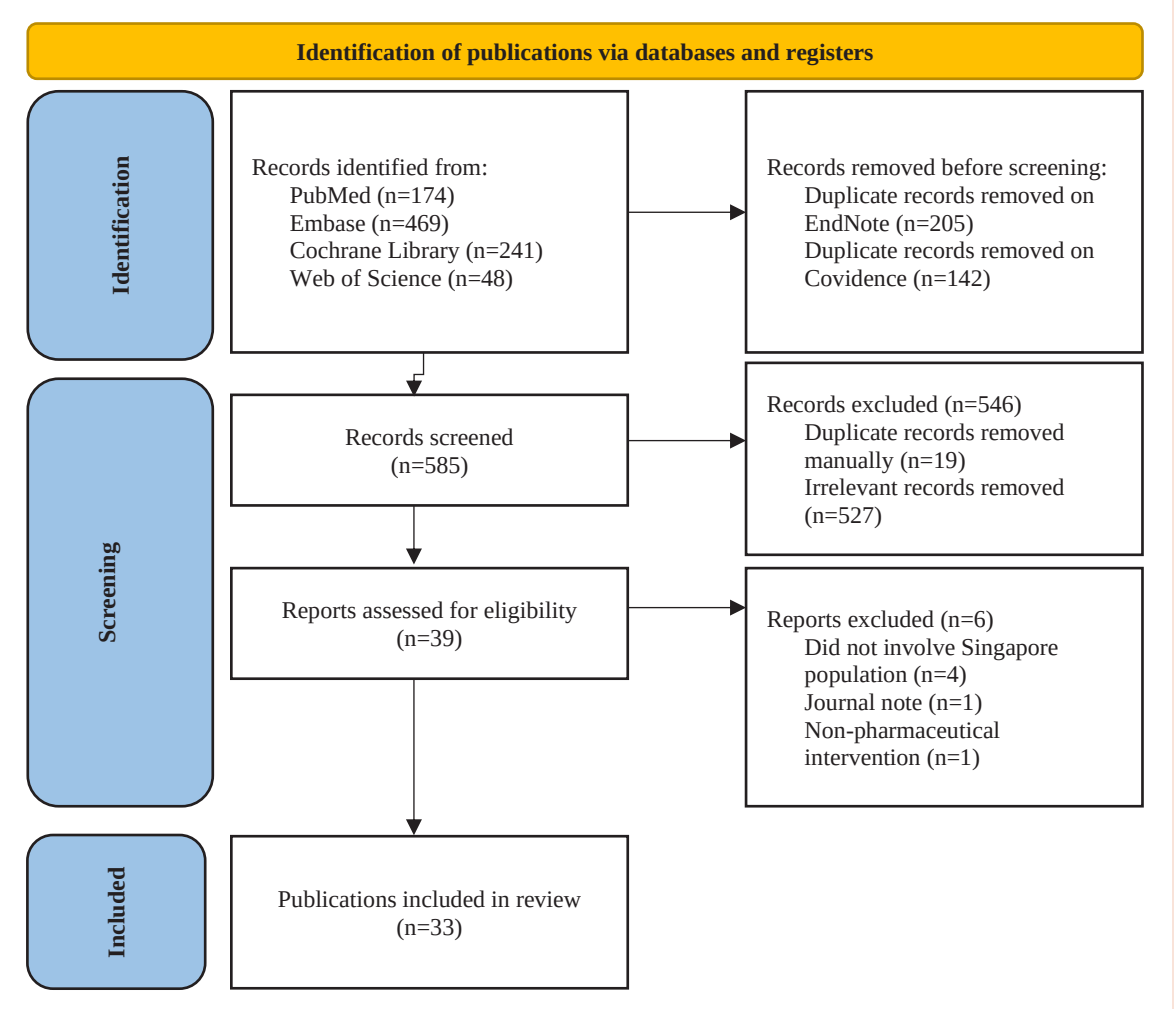
Fields of study

Infectious disease trials formed the greatest proportion of publications (9 trials, 7405 participants), with 5 relating to the management/treatment of COVID-19. Oncology trials (5 trials, 1242 participants) were the other major focus. The other fields of study were gastroenterology/hepatology (n=4 trials), cardiology (n=3), endocrinology (n=3), anaesthesia (n=2), dermatology (n=2), critical care (n=1), neurology (n=1), ophthalmology (n=1), psychiatry (n=1) and urology (n=1).

Multiregional publications

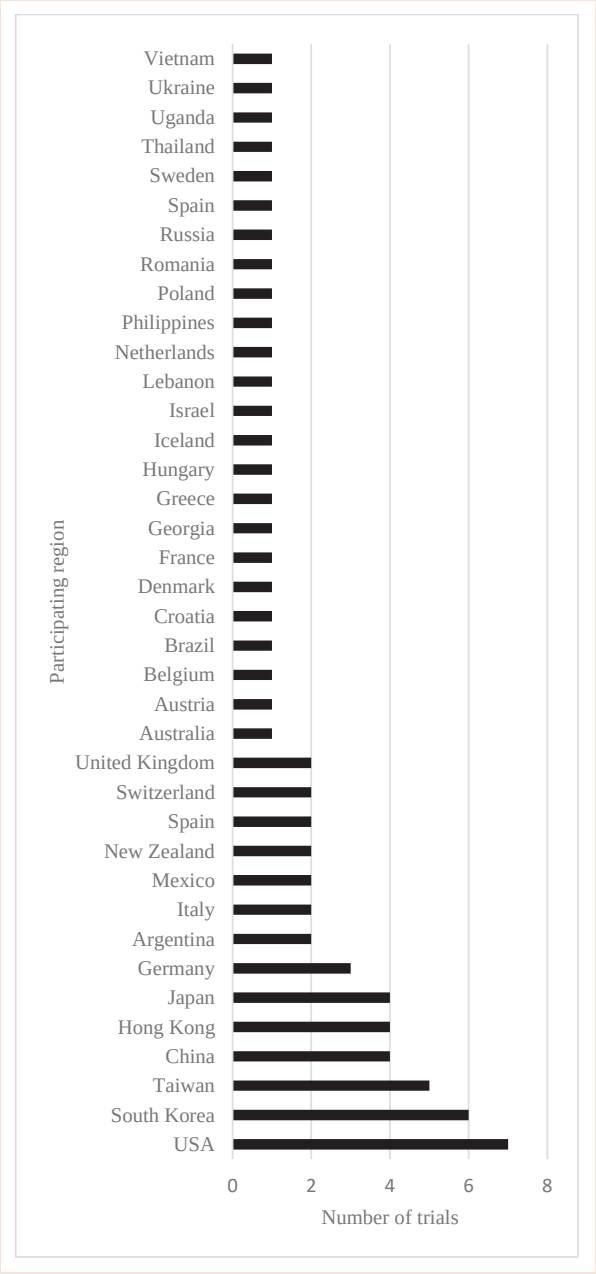
Seven of the 14 multiregional publications did not state the number of patients recruited from

Fig. 1. PRISMA flow diagram for the selection of manuscripts to explore the demographic diversity of participants in pharmaceutical trials in Singapore.



PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Fig. 2. Location of other centres which were part of the multiregional clinical trials that Singapore participated in.



Singapore. When the number of participants recruited from Singapore was listed, the percentage they contributed to the study ranged from <1.0% to 59.8%.

Age

The reporting of participants' age varied in format. Data were most commonly presented as mean/standard deviation, but others used mean/range, median/interquartile range and median/range. Unfortunately, due to the lack of country-specific data and the reporting of age in different ways, we were unable to conduct comparative analysis with Singaporean census data. Fourteen trials explicitly excluded older individuals, with upper age limits ranging from 45 to 85 years. There were 4 trials that excluded patients with common comorbidities (e.g. diabetes, hypertension) which were unlikely to be directly related to the intervention. Such exclusion criteria are more likely to apply to older people, as the prevalence of chronic disease and comorbidity increases with age. In Singapore, the mean number of chronic diseases among 45–64 year-olds is 1.68, and among those aged 65–84 years is 3.92.[10] Thus, even if the inclusion criteria seem older people-friendly, there is a possibility that they will not be eligible because of a co-existing health problem.

Ethnicity

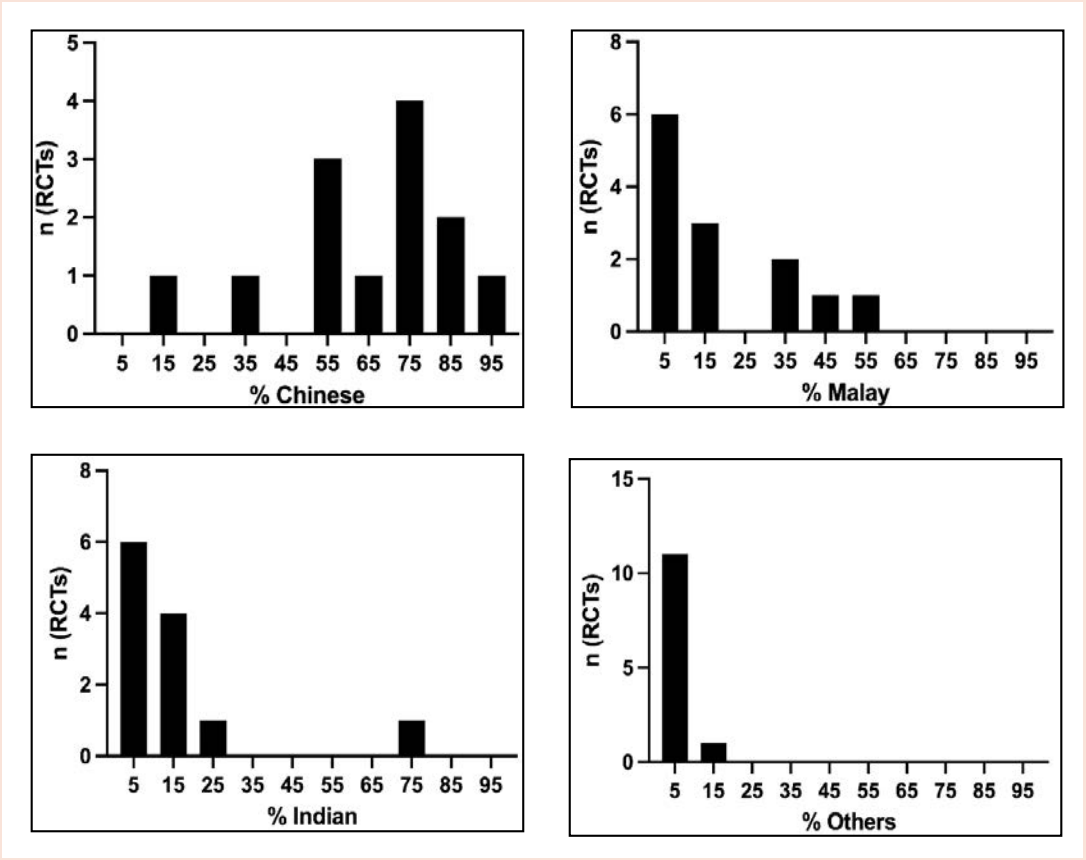
Thirteen of the 19 Singapore-only publications reported ethnicity in detail (Chinese/Malay/Indian/Others). In 1 publication, there was partial information, with only the number of Chinese and Malay participants reported, but nothing about the remaining participants. In 5 publications, there was no detail whatsoever. Only 1 of the multiregional studies (Reference 2 in Appendix S3) reported ethnic distribution in detail (Chinese/Malay/Indian/Others), when others did comment on ethnicity, they tended to use the broad descriptor of "Asian." When exploring the representativeness of ethnicity, 1 Singaporebased study (Reference 21 in Appendix S3) was excluded as it did not involve citizens or permanent residents, recruiting only temporary migrant workers from India and Bangladesh.

In the 13 studies where clinical trial population representativeness was compared with the real-world Singaporean population, we found that the proportion of the recruited population who were of Chinese and "Other" ethnicities was similar to the census, but there was an under-represen-tation of Indian participants (7.3% vs 9.0%, *P*=0.0217) and an over-representation of Malay participants (15.7% vs 13.5%, *P*=0.0124). Less than half (6 of 13; 46.2%) of the trials achieved census levels of ethnicity (Fig. 3).

Sex

The analysis of sex focused on Singapore-only trials, as there was insufficient Singapore-specific gender demographic data included in any multiregional studies. The analysis was relevant to 16 of the 19 studies, as 3 were single-sex, 2 exclusively male (focusing on erectile dysfunction [Reference 12 in Appendix S3] and COVID prophylaxis in migrant workers [Reference 21 in Appendix S3]), and 1 (Reference 24 in Appendix S3) was a female-only study that recruited women undergoing a

Fig. 3. Proportion of participants in RCTs by race.



Caesarean section. In Singapore-only trials (n=16) recruiting males and females, females were under-represented in comparison to the census (41.3% vs 51.1%, *P*<.0.00001) (Fig. 4). Females were under-represented significantly (*P*<0.05) in almost two-thirds of studies (62.5%); these were in the fields of infectious diseases, cardiology, endocrinology and psychiatry.

Recruitment strategies, recruitment challenges and generalisability of results

Fourteen of the 33 publications reviewed (42.4%) included some details of the recruitment strategies used. This was scanty but included information such as the number of recruitment centres, the status of patients (inpatient/outpatient) or mode of recruitment (e.g. advertisement, personal approach from study team). Fewer publications (24.2%) made comments on the applicability or generalisability of the study's findings, facilitating readers' assessment of external validity and real-world applicability.

DISCUSSION

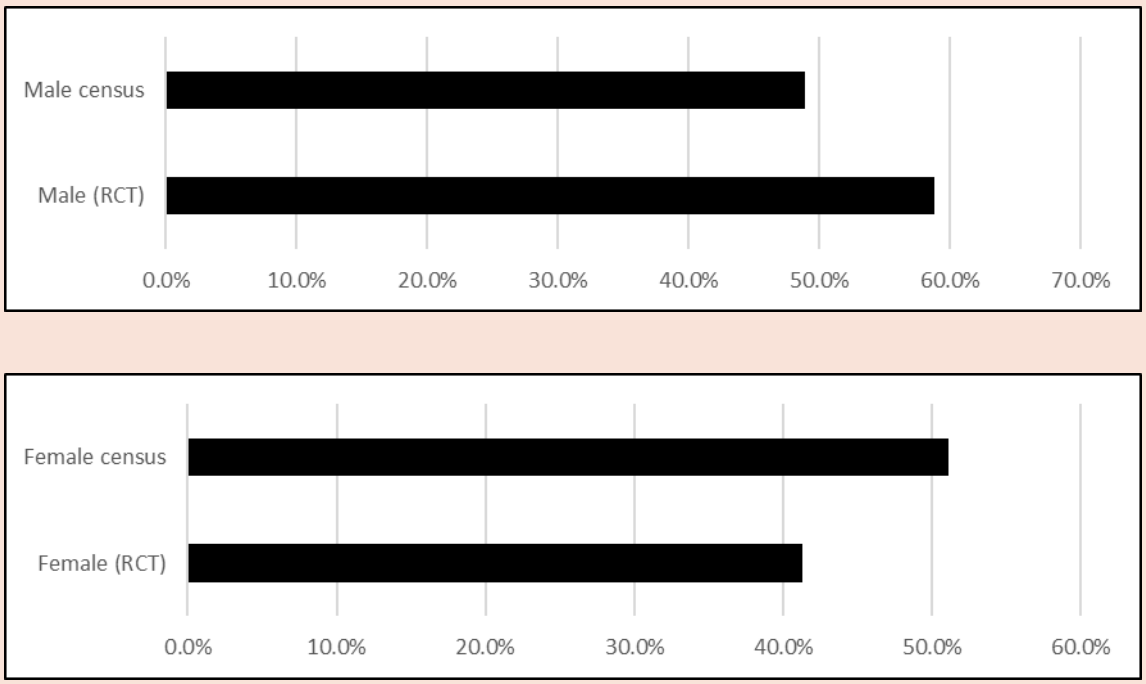
This review explored the representativeness of participants in pharmaceutical RCTs in Singapore over 5 years. This external validity analysis included 19 Singapore-only and 14 multiregional studies addressing studies in 12 clinical specialties.

Demographic diversity of participants in RCTs conducted in Singapore

When the data were collated, we found significant under-representation of women in 56.3% of trials in comparison to the 2020 Singapore census. Studies where women were under-represented were in the fields of infectious diseases, cardiology, endocrinology and psychiatry. Similar under-representation of women in these clinical areas has been reported by studies that analysed sample populations recruited in other countries, including the US.[11-13] Further research is needed to ascertain specific barriers to recruiting female participants, and if there are particular challenges that are specialty-specific.

Our analysis of ethnicity found significant under-representation of Indians and over-representation of Malays compared to the Singapore census; the number of Chinese and "Others" was similar to the census. Surprisingly, the absence of reporting of ethnic diversity was found in almost a third (31.6%) of Singapore-only publications, when Singapore commonly boasts its ethnic diversity in research. Detailed reporting of ethnic distribution

Fig. 4. Proportion of participants in Singapore-only RCTs by sex compared to Singapore census.



RCT: randomised controlled trial

in a multiethnic country, such as Singapore, is essential to enable the clinician or systematic reviewer to assess the external validity of the study's findings. One must wonder whether among those trials failing to publish data on ethnicity, there was a preponderance of over- and under-representation and an unwillingness to share. Many other countries have been challenged with improving the external validity of their trials. For example, a retrospective study showed that no data on race/ethnicity were reported by two-thirds of the clinical trials that informed the 2007 cardiovascular disease prevention guidelines of the American Heart Association.[14] This study was able to examine trends over 3 decades and found that the percentage including ethnic data has increased significantly, from 12.5% in the 1970s to 46.2% in the 2000s. The best improvement in reporting race/ethnicity as a baseline characteristic has been seen in trials funded by the National Institutes of Health. This illustrates how funding agencies can influence transparency and enable the consideration of external validity.

Multiregional clinical trials (MRCTs)

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use promotes worldwide development and approval of safe, effective and high-quality medicine in the most resource-efficient manner. It recommends that the regional allocation in MRCTs "should have a scientific basis (rather than arbitrary targets), should support the evaluation of consistency and should provide the information needed to support regulatory decisions," emphasising that no single region or regions should dominate enrolment, and therefore dominating the trial outcome.[15] Unfortunately, in our analysis, only half of multiregional publications reported the number of participants recruited from Singapore. Without precise reporting of sample size in different regions, it is impossible to assess the external validity and applicability to the country of interest.

The MRCTs reviewed did not only lack data on the number of participants from each country but also often had inadequate or incomplete data on ethnicity. When ethnicity was given, the broad descriptor "Asian" was used, and only 1 study reported the number of Chinese, Malay, Indian and Others recruited. The use of the term "Asian" suggests homogeneity and fails to recognise the heterogeneity of population within Asia, whose physical and biological differences influence their response to medication even for commonly used drugs.[16] For example, in Singapore, the mean weight-normalised maintenance warfarin dose in Indians is almost twice that for Singaporean Chinese and Malays, due in part to differences in the gene-encoding Vitamin K epoxide reductase complex 1.[17] The Asian Diversity Project and Pan-Asian Single nucleotide polymorphism study have demonstrated the extent of heterogeneity

between subgroups of Asians, concluding that the use of single-label "Asian" undermines genetic diversity within Asia, but at the same time could overstate its influence on differences in drug disposition and pharmacodynamics.[18] The awareness of inter-ethnic differences in pharmacokinetics and pharmacodynamics is a growing research field. The reporting of MRCTs needs to support the completeness and standardisation of participants' ethnicity.

Recruitment strategies, selection criteria and generalisability

In 2013, the Standard Protocol Items: Recommendations for Interventional Trials statement in 2013 recommended protocol descriptions of (1) where recruitment takes place, (2) who is the individual recruiting participants, (3) when participants are recruited and (4) how potential participants are informed of the trial.[19] Transparency in each stage of recruitment is key to the assessment of bias and generalisability by reviewers.[20,21] Only 14 included publications (42.4%) described recruitment strategies beyond detail on the location of recruitment. Further research is needed to identify potential barriers to publishing recruitment strategies. Two possible barriers include the perceived lack of importance by authors and word limit imposed by journals.

Study strengths and weaknesses

This is likely the first study on the demographic diversity of participants in clinical trials conducted in Singapore. We used a robust methodological approach, but our review was limited to adults and to pharmaceutical trials. Thus, the findings may be different for other healthcare interventions (e.g. psychological interventions, service delivery evaluations) or for trials involving children. The number of trials identified was relatively small, but boosting the number of included trials would have required increasing the search to earlier years, which was not desirable because we wanted our review to reflect contemporary, not historical, clinical trial practice.

We recognise that the COVID-19 pandemic disrupted in-person recruitment to trials, in-person data collection and follow-up.[22,23] Thus, when repeating this review, it would be valuable to look for trends over time and to examine whether the pandemic threatened the representativeness of trials.

Similar to studies conducted in other countries, we compared the demographic characteristics of patients recruited in these trials with population census data, but it would be preferable to make this comparison with the epidemiology (i.e. age, sex, race) of the specific disease under investigation. Such comparison would allow more meaningful detection of the disparity between participants recruited in RCTs and patients encountered in clinical practice.

CONCLUSION

By understanding current study populations, future clinical trials can be designed to improve the generalisability of findings, and evidence-based care can be better provided to our patients. There is some room for improvement regarding the recruitment of RCT participants in Singapore, with particular attention to female gender and Indian ethnicity. Attention must also be given to presenting demographic data in full. Even though Singapore prides itself on being multicultural, more than a third of publications did not describe the ethnic diversity of the patients studied. The reasons for incomplete data presentation are many, perhaps oversight or intentional (e.g. to detract from potential poor external validity) or constrained by medical journal word counts. Moving forward, we need to ensure that studies are designed and reported in such a way that allows the clinician to decide on the generalisability to the Singapore population and the benefit that will be derived from treatment in clinical practice.

Supplementary Materials

Appendix S1. Search strategies.
Appendix S2. Data extraction form.
Appendix S3. References of studies included.

Declaration

The authors declare there are no affiliations with or involvement in any organisation or entity with any financial interest in the subject matter or materials discussed in this manuscript.

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LETTER TO THE EDITOR

Using artificial intelligence as an ethics advisor

Kay Choong See[1] *MBBS*

Dear Editor,

Ethical dilemmas are common in the practice of medicine and can lead to an array of seemingly reasonable decisions unless policies or regulations mandate certain actions. Choosing the appropriate solution requires not only biomedical evidence, but also requires the balancing of possibly divergent preferences, values, contextual factors and ethical theories. These include utilitarianism, which aims to optimise happiness for the largest number of people; versus deontology, which promotes actions based on rules and duties even if these actions do not result in the greatest common good. The inability to find common ground can both delay appropriate care and trigger moral distress among health professionals.[1] However, training in ethical reasoning or obtaining ethics consultations may not be universally available. How then can frontline healthcare teams navigate ethical dilemmas?

Generative artificial intelligence (generative AI) is a form of artificial intelligence that can produce text in response to user prompts and includes large language model chatbots such as Chat Generative Pre-trained Transformer (ChatGPT, https://chat.openai.com/). To demonstrate how generative AI can act as an ethics advisor, the freely available ChatGPT version 3.5 was applied to 2 cases involving extracorporeal membrane oxygenation (ECMO)—a high-cost intervention fraught with ethical considerations[2]—from the *AMA Journal of Ethics* (Supplementary Material). In both cases, user prompts asked ChatGPT to provide answers to 5 queries:

1) "What should the clinician do for the case?" (A general, open-ended question to seek practical guidance on the appropriate action to be taken.)
2) "You mentioned ethical principles. Please elaborate." (A more specific question in response to ChatGPT's advice to consider ethical principles, seeking to clarify specific principles for the clinician's understanding.)
3) "What if no palliative care specialists or ethicists are available?" (A question for advice in the absence of specialist consultation, which is a real-world limitation that clinicians may encounter.)
4) "Should ECMO be continued or withdrawn?" (A specific question regarding withdrawing ECMO, aiming to elicit advice on a key course of action.)
5) "In retrospect, should the patient have received ECMO?" (A specific question regarding a counter-factual scenario, to help decision-making for future patients.)

ChatGPT's response provided a framework for ethical case analysis, complementing the general rules and practice recommendations provided by current ECMO guidelines,[3] and covered most of the common competencies of communications, ethics and professionalism for medical students and physicians[4] (Table 1). Although the general privacy, bias and explainability concerns[5,6] about artificial intelligence may still affect generative AI's role as an ethics advisor, generative AI does not require the input of confidential information and generates textual output that is transparent to human interpretation.

As demonstrated by the 2 case examples, generative AI like ChatGPT may be well-suited to provide ethical guidance to frontline clinicians. ChatGPT's responses can prompt clinicians to address critical aspects when navigating ethical dilemmas in healthcare. These include thorough information gathering; effective communication with family members and the multidisciplinary team; discussions about goals of care; ethical principles; consultation with specialist palliative care (where possible); seeking peer input; utilising online resources and guidelines; and maintaining clear documentation. Conceivably, such ethical challenges in healthcare can involve decision-making for the withholding or withdrawal of treatments across diverse fields of medicine.

Such support is not to replace the essential roles of humans during the process of ethical reasoning, as ChatGPT does not do the following: gathering information; communicating with patients, families and other clinicians; integrating ethical principles, human values, subjective judgements and

[1] Division of Respiratory and Critical Care Medicine, Department of Medicine, National University Hospital, Singapore
Correspondence: Dr Kay Choong See, Senior Consultant, Division of Respiratory and Critical Care Medicine, Department of Medicine, National University Hospital, Level 10 NUHS Tower Block, 1E Kent Ridge Road, Singapore 119228.
Email: kaychoongsee@nus.edu.sg
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Table 1. Common competencies of communications, ethics and professionalism.

Common competencies	Coverage by advice provided by ECMO guidelines[3]	Coverage by advice provided by ChatGPT
Values/ethics—appreciation of professional, legal and societal values to guide practice	Partially. Advised inclusion and exclusion criteria for ECMO, prognosis, possibility of bridging to advanced therapies. No mention of ethical principles.	Yes. Advised consideration of ethical principles (beneficence, non-maleficence, autonomy, justice), medical condition, prognosis, quality of life, goals of care, patient/family preferences and resource allocation.
Professional responsibilities—appreciation and manifesting these responsibilities	Yes. Advised assessment of the patient's condition and reviewing of treatment goals.	Yes. Advised continuous reassessment of the patient's condition, reviewing of treatment goals, and provision of emotional support to family members or surrogates.
Doctor-patient relationships—appreciation of the guiding principles, expectations and ability to nurture these relationships	Yes. Advised family education and discussions regarding possible discontinuation of ECMO support and provision of appropriate palliative care for cases where ECMO is unlikely to succeed.	Yes. Advised communication, information gathering, goals of care discussion, and shared decision-making with family members or surrogates.
Interprofessional team working	Yes. Advised involving palliative or supportive care teams, psychologic counsellors and ethics teams.	Yes. Advised involving a multidisciplinary team and palliative care consultation.
Ethical and legal responsibilities	Partially. Advised addressing ethical considerations, beyond merely providing treatment with ECMO. No mention of legal responsibilities.	Yes. Advised addressing ethical considerations, and good documentation of all discussions, decisions and care provided. Advised adherence to legal requirements and institutional policies.
Continuous learning and quality improvement	Yes. Advised that training and retraining be part of the ECMO programme.	Yes. Advised learning from external resources, online resources and colleagues.

ECMO: extracorporeal membrane oxygenation

contextual issues; balancing arguments and counterarguments.[7] Also, as ChatGPT's output has shown, generative AI does not provide binary "yes" or "no" answers to specific ethical questions. This limitation hinders its suitability for making quick decisions in urgent situations. Rather, by providing guidance on the essential areas for consideration, generative AI shows promise as a collaborative intelligence tool to augment human decision-making for ethical dilemmas.[8]

Declaration

There are no affiliations or financial involvement with any commercial organisation with a direct financial interest in the subject or materials discussed in the manuscript.

Keywords: *emergency medicine, internal medicine, mortality, palliative medicine, pneumonia, quality of life, respiratory medicine*

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LETTER TO THE EDITOR

Gaps in primary care management of urinary tract infections in Singapore

Terence Yi Song Liew[1,2] *MBBS*, Pey Gein Wong[2] *FCFP*, Justin Wee-Min Chong[2] *FCFP*, Hwee Ching Chung[2] *BSc*, Cynthia Kum Wai Cheong[2] *BSc (Hons)*, Sky Wei Chee Koh[2,3] *FCFP*

Dear Editor,

Urinary tract infection (UTI) is a common presentation in primary care, but gaps of care have not been well established in Singapore. UTIs are one of the most common bacterial infections worldwide,[1] constituting around 1% of all ambulatory clinic visits.[2] The healthcare burden of UTIs remains highly significant, with billions per year lost in societal costs (e.g. healthcare costs and time missed from work) alone.[2] In Singapore, genitourinary infections were the second most common group of conditions for which antibiotics were prescribed in 2021.[3]

Appropriate antibiotic prescribing is key to prevent resistance. Although international guidelines recommend clinical diagnosis of UTI based on typical symptoms of dysuria, urgency, frequency and the absence of vaginal discharge,[4] in Singapore, only 26% of UTIs were diagnosed clinically without the aid of urinary investigations.[5] With the potential for significant number of care gaps, we conducted a study to examine these gaps to improve practice, management and patient safety.

Random sampling of 280 adult patients with visit diagnosis of UTI from July to December 2021 was performed, with 40 patients selected from each of the 7 National University Polyclinics in Singapore. Case notes review was conducted by trained primary care physicians to identify and classify gaps in history, documentation, examination, investigations, diagnosis, labelling, management, follow-up and antibiotic prescriptions.

To determine antibiotic appropriateness, we reviewed international guidelines for acute uncomplicated cystitis, including the European Association of Urology (2022),[6] National Institute for Health and Care Excellence Guidelines (2018)[7] and Infectious Diseases Society of America Guidelines (2010).[8] This was paired with local antibiograms, expert opinions and published recommendations in Singapore. The list of antibiotics and doses considered appropriate were:

- Amoxicillin/clavulanate 625 mg 2 to 3 times a day (BD-TDS) for 3 to 7 days
- Cephalexin 500 mg 2 to 4 times a day (BD-QDS) for 5 to 7 days (while several guidelines recommend higher dosage, i.e. 500 to 1000 mg BD-QDS, newer studies suggest equal efficacy in twice-daily versus 4-times-daily dose)[9]
- Co-trimoxazole 2 tablets 2 times a day (BD) for 3 days
- Nitrofurantoin 50 to 100 mg 4 times a day (QDS) for 3 to 7 days

Statistical analyses were performed with IBM SPSS Statistics version 28.0 (IBM Corp, Armonk, NY, US). Descriptive statistics was used to showcase prevalence data, chi-square test to compare relationship between categorical variables and fixed effects Poisson regression to analyse factors affecting number of gaps per UTI visit.

A total of 280 patients were reviewed, with a mean age of 50.7 years (Table 1). Majority were female, largely premenopausal. Among patients with uncomplicated UTIs, 18.2% were recurrent. The most common cause of complicated UTIs were in males (69.5%). There were 12 patients (4.3%) who were inaccurately coded as UTI; 85% of patients had urine tests performed to guide diagnosis of UTI. The most common antibiotic prescribed is amoxicillin-clavulanate (50%). There were 41.4% of patients who had no gaps of care during their visit for UTI, with a mean number of gaps per patient at 0.81. The greatest number of gaps were present in history and documentation (31.6%). Significant number of gaps were also found in antibiotic prescriptions (22.4%), of which excessive antibiotic duration formed the majority (45.1%).

Patients who presented with uncomplicated UTIs were found to be significantly associated

[1] Department of Family Medicine, National University Health System, Singapore
[2] National University Polyclinics, National University Health System, Singapore
[3] Division of Family Medicine, Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
Correspondence: Dr Sky Wei Chee Koh, Family Medicine Department, National University Polyclinics, Corporate Office, 1 Jurong East Street 21, Singapore 609606.
Email: sky_wc_koh@nuhs.edu.sg
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Table 1. Characteristics of patients with visit diagnoses labelled as urinary tract infections (UTIs).

Study characteristics	Total (n=280)
Mean age, (SD), years	50.7 (18.8)
Sex, no. (%)	
Female	239 (85.4)
Pre-menopausal	133 (55.6)
Post-menopausal	106 (44.4)
Male	41 (14.6)
UTI type	
Uncomplicated UTIs	207 (73.9)
Episodic UTI	171 (82.6)
Recurrent UTI	36 (17.4)
Complicated UTIs	59 (21.1)
Male UTIs	40 (67.8)
Suspected pyelonephritis	8 (13.6)
Known urethral or bladder abnormalities	4 (6.8)
Partially treated UTI	4 (6.8)
Previous nephrolithiasis	3 (5.1)
Not UTIs	14 (5.0)
Urine microscopy utilisation rate in UTI diagnosis, no. (%)	238 (85.0)
Antibiotic prescribed	
Amoxicillin-clavulanate	140 (50.0)
Nitrofurantoin	63 (22.5)
Ciprofloxacin	31 (11.1)
Co-trimoxazole	22 (7.9)
Cephalexin	14 (5.0)
No antibiotic prescribed	10 (3.6)
Mean no. of gaps per patient (SD)	0.81 (0.86)
No. of gaps per patient, no. (%)	n=228
0	116 (41.4)
1	114 (40.7)
2	40 (14.3)
3	6 (2.1)
4	4 (1.4)
Distribution of gaps, no. (%)[a]	
Gaps in history and documentation	72 (31.6)
Last menstrual period not documented	68 (94.4)
Gaps in examination	1 (0.4)
Gaps in investigation	45 (19.7)
Urine culture not sent in complicated UTIs	27 (60.0)
Urine culture sent in uncomplicated UTIs	15 (33.3)
Gaps in diagnosis	22 (9.6)
Urine microscopy clear, still treated with antibiotics	6 (27.3)
Gaps in labelling	7 (3.1)
Gaps in management/follow-up	30 (13.2)
Male UTI not referred to urologist	13 (43.3)
Gaps in antibiotic prescription	51 (22.4)
Antibiotic prescribed for excessive duration	23 (45.1)
Ciprofloxacin prescribed for uncomplicated UTIs	13 (25.5)
Nitrofurantoin prescribed for elderly	11 (21.6)

SD: standard deviation
[a] Total number of gaps may not tally as each patient encounter may have multiple number of gaps.

with increased gaps in history and documentation (P<0.001). Patients with uncomplicated UTIs were more likely to have gaps in history or documentation (odds ratio [OR] 4.32, 95% CI 1.88–9.92).

For our Poisson regression, the variance for number of gaps was 0.74. The goodness-of-fit test value divided by degree of freedom was 0.91 and the omnibus test was P<0.05. After adjusting for sex and clinic characteristics, patients with complicated UTIs or non-UTIs had a significantly increased incidence of care gaps (risk ratio [RR] 2.20, 95% CI 1.57–3.09), compared to those with uncomplicated UTIs. The incidence rate of gaps in care decreased by 1.6% (RR 0.984, 95% CI 0.977–0.992) for each 1-year increase in age.

This study had 2 main findings. First, history constituted majority of the gaps, especially among young female patients with uncomplicated UTIs, pertaining to documentation of their last menstrual period. This highlighted a potential antibiotic safety issue, as ciprofloxacin and co-trimoxazole are not recommended for use in pregnant women. Secondly, patients presenting with complicated UTIs or non-UTIs had more frequent care gaps.

Our study identified significant lapse in antibiotics prescribed for UTI, accounting for more than one fifth of all lapses identified. Dosing errors were mostly mitigated locally due to electronic dosing

recommendations. However, antibiotic duration was left to the discretion of physicians. A fixed, pre-programmed medication order including recommended dose, frequency and duration will reduce prescription gaps and improve medication safety.

Ciprofloxacin prescription for uncomplicated UTIs was also an issue. In Singapore, increasing ciprofloxacin resistance has been found in urinary *Escherichia coli*, which translates to increased treatment failure rate in uncomplicated UTIs.[5] Ciprofloxacin was also found to be inappropriately used for the treatment of multiple outpatient infections, contributing to the development of multidrug resistant organisms. Guidelines can mitigate its usage, which was also listed as an antibiotic in the WATCH group (antibiotics that should be monitored by health authorities to prevent spread and further emergence of antibiotic resistance), according to the World Health Organization Access, Watch, and Reserve classification.

Our study also found that patients with complicated UTIs or non-UTIs had more frequent gaps in care. This echoed what was found in other settings internationally, where errors occurred in special groups of patients with asymptomatic bacteriuria, such as the elderly; patients with diabetes, urinary catheter in-situ, urinary tract dysfunction; and patients after transplantation. While major guidelines adequately covered diagnosis and management of uncomplicated UTIs, management of complicated UTIs and non-UTIs were less emphasised. Therefore, it would be prudent to continue education of physicians in this area to bridge these gaps.

We acknowledge that clinical practices are constantly evolving and geographically dependent, hence limiting the generalisability of this study probably to the primary care context in Singapore. Future studies with larger sample size could be replicated across all 3 public primary care institutions to reduce risk of type 1 error.

With the Singapore guideline for uncomplicated UTIs in place since November 2023,[10] our attention can turn to addressing complicated UTIs and masquerades. By doing so, we can improve physicians' confidence in managing UTIs, reduce inappropriate antibiotic use, and deliver high-quality and safe care to all patients.

Declaration

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Institutional Review Board Approval

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board of the National Healthcare Group (2023/00275) on 1 June 2023.

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LETTER TO THE EDITOR

The emergence of otter attacks in Singapore: A case series and strategies for management

Shaun Kai Kiat Chua[1], Joel Yeh Siang Chen[1] *MBBS*, Stephanie Sutjipto[2] *MMed (Int Med)*, Jingwen Ng[1], Remesh Kunnasegaran[1] *FRCSEd (Ortho)*

Dear Editor,

Singapore is experiencing an unprecedented increase in the number of smooth-coated otters (*Lutrogale perspicillata*). Since 2017, the local otter population has more than doubled to at least 170. This has led to an increase in the number of otter-human attacks since 2021.[1,2] While common animal attacks like dog bites are well documented with established management, there is a lack of literature studying the outcomes and management of the increasingly common otter attacks in Singapore. To date, there has only been 1 published case report, which documented an attack by local river otters (*Lontra canadensis*) in Quebec, Canada.[3] This letter aims to evaluate 3 relatively recent cases of otter attacks presented at Tan Tock Seng Hospital, Singapore and propose key management strategies in addressing future attacks.

The 3 cases of otter attacks are summarised in Table 1. Cases 1, 2 and 3 sustained multiple scratches and bite wounds primarily on the upper and lower limbs. No signs of systemic infections, fractures and retained foreign bodies were noted. Intraoperative tissue cultures were taken for cases 1 and 2. All were managed with same-day wound debridement, with case 1 receiving toilet and suture for facial lacerations. For pharmacological treatment, all were given intramuscular tetanus toxoid (IM TT). Case 1 was managed with intravenous (IV), per oral (PO) amoxicillin-clavulanate (Augmentin, GlaxoSmithKline) and PO doxycycline. Case 2 was managed with PO Augmentin only. Case 3 was managed with IV and PO Augmentin, PO ciprofloxacin and post-exposure rabies prophylaxis. All cases reported smooth wound healing and were clinically well within a week of discharge, with non-significantly raised infective markers and no fractures noted on X-rays. It was noted that case 3 reported continuous ankle numbness due to sural nerve injury from the attack. Consent was obtained for the use of case details and photographs in all reported cases.

Evaluation (examination, injury pattern and complications). Despite good outcomes, the variability in investigations and management needed exempli-fies the requirement for institutional guidelines to manage otter attacks in Singapore.

The initial history should focus on injuries sustained and time of presentation post-injury. Complications like neurovascular compromise must be ruled out. A comprehensive past medical history including risks of immunocompromise will also help triage patients who are at a higher risk of infection.[4]

Physical examination should differentiate between scratches (classically longer superficial linear wounds) versus bite wounds (classically elliptically shaped with 4 main puncture wounds) as seen in Table 1. Identifying wound depth, retained foreign material, injury to surrounding structures (tendon, bone, nerves and vessels) and signs of infection (purulent discharge, rapidly progressing erythema, fever and low blood pressure) are vital in determining urgency and treatment modality.

Regarding complications, the predominant smooth-coated otters have small and blunted teeth, with one of the lowest bite forces in the otter family.[5] Unlike cat bites that cause deeper penetrating bites or dog bites that cause powerful crush injuries, otter bites are at lower risk of systemic infection and deep tissue injury or fractures.[6] Nonetheless, for bites, or major wounds involving areas with limited soft tissue coverage (face, hands, joints and over the tibial region) or prosthetic devices (prosthetic joints and vascular grafts), an initial X-ray of the affected area can rule out retained foreign bodies (teeth and nail), fractures and involvement past the subcutaneous tissues.

[1] Department of Orthopaedic Surgery, Tan Tock Seng Hospital, Singapore
[2] National Centre for Infectious Diseases, Singapore
Correspondence: Dr Shaun Kai Kiat Chua, Department of Orthopaedic Surgery, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore 308433.
Email: schua041@e.ntu.edu.sg
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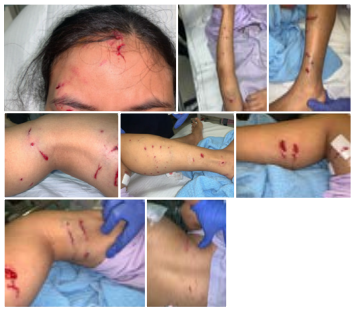
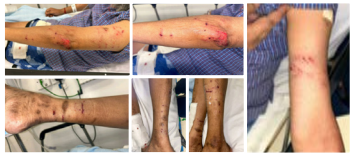
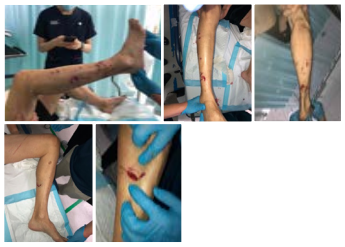
Table 1. Summary of cases of otter attacks presented to our institution.

Case	Age (years), sex	Relevant past medical history	Date of injury[a] (time), location	Mechanism of injury	Injury list (bites/scratch wounds)	Investigations	Medical treatment	Surgical treatment	Complications (infection, neurovascular injury)	Clinical photos of injuries
1	27, female	Nil	2/11/2023 (0620H), Singapore	Unprovoked attack by >5 otters	**Face**: 3 full-thickness superficial lacerations **Upper limbs**: 2 partial-thickness and 4 full-thickness superficial lacerations; 12 full-thickness bites **Lower limbs**: 4 partial-thickness bites, 14 full-thickness bites **Back**: 1 partial-thickness superficial laceration, 2 full-thickness laceration	WBC 18.7 CRP 0.5 Intraoperative tissue cultures obtained: NAD X-rays: nil fractures or foreign bodies	IM TT IV Augmentin 1 week PO Augmentin 1 week PO doxycycline 2 weeks	1. Toilet and suture of facial lacerations 2. Wound debridement of upper and lower limb wounds 3. Wound debridement and closure of upper and lower limb wounds	Nil	
2	60, male	Type 2 diabetes mellitus, hypertension	3/11/2023 (0620H), Singapore	Unprovoked attack by >15 otters	**Upper limbs**: Multiple full-thickness superficial lacerations, 9 full-thickness bites **Lower limbs**: 1 full-thickness superficial laceration, 18 full-thickness bites	WBC 16 CRP 12.2 Intra-operative tissue cultures obtained: NAD X-rays: nil fractures or foreign bodies	IM TT PO Augmentin 3 days	1. Wound debridement of bilateral lower limb and left upper limb wounds	Nil	
3	70, male	Chronic hepatitis B, hypertension	9/4/2023 (0620H), Singapore	Provoked attacked by 20–30 otters	**Lower limbs:** 4 full-thickness bites, multiple small wounds	WBC 21.3 CRP not done Intraoperative tissue cultures not obtained X-rays: nil fractures or foreign bodies	IM TT Rabies prophylaxis (day 0, 3, 7 and 15) PO ciprofloxacin 3 days IV Augmentin 3 days PO Augmentin 5 days	1. Wound debridement of bilateral lower limbs	Sural nerve injury secondary to otter attack with residue numbness on follow-up	

CRP: C-reactive protein; IM TT: intramuscular tetanus toxoid; IV: intravenous; NAD: no abnormality detected; PO: per oral; WBC: white blood cells
[a] day/month/year.

Infection (vaccinations and antibiotics) For fully vaccinated patients (i.e. received at least 3 doses of tetanus toxoid-containing vaccine), IM TT is recommended if the last dose was administered ≥5 years ago for major wounds, or ≥10 years ago for minor wounds.[7,8] For patients with <3 doses of tetanus toxoid-containing vaccine or unknown vaccination status, tetanus toxoid-containing vaccine should be administered irrespective of wound severity. Additionally, human tetanus immunoglobulin is recommended for major wounds in patients with <3 doses or unknown vaccination status.[7]

Post-exposure rabies prophylaxis (rabies immunoglobulin and vaccination) is unnecessary for otter bites sustained in Singapore, which has been declared rabies-free since 1953.[9] However, otter bites sustained outside of Singapore should be promptly considered for post-exposure rabies prophylaxis.

Empiric antibiotic therapy should be considered for all mammalian bites, including otters. The recommended choice of antibiotics would include PO or IV Augmentin.[10] As there is limited evidence reporting the oral or claw bacteria flora of the otter population in Singapore, antibiotic choice should provide broad coverage of gram-positive and gram-negative bacteria, and bacteria commonly associated with water exposure (e.g. *Aeromonas* species and *Plesiomonas* species) and anaerobic bacteria.[10] The decision between PO or IV antibiotics depends on patient clinical status and bite location to prevent complications like sepsis. IV antibiotics are preferred for patients showing signs of sepsis, rapidly progressing erythema, worsening condition despite initial oral antibiotics, immunocompromised individuals, or bites at locations that are at risk for deeper infections: near bones (e.g. anteromedial tibia with lack of soft tissue coverage), joints or prosthetic devices. In such cases, prompt surgical assessment and close in-hospital monitoring are also recommended. For uncomplicated superficial wounds in patients not meeting these criteria, consider a course of oral Augmentin with early follow-up for signs of infection progression.[10]

Prophylactic antibiotic treatment is typically advised for 3–5 days, while empiric treatment for established infection is usually given for 5–7 days.[10] In cases of deep or complicated infections, particularly near bone and joints, obtain intraoperative tissue cultures for culture-directed antibiotics. In addition, antibiotic courses may be extended, and consultation with an infectious diseases specialist is advisable.

Surgical intervention Surgical irrigation and debridement in the operating theatre should be considered in deeper wounds with depth that cannot be fully assessed on examination or for foreign material that cannot be removed by bedside.[11] Intraoperative tissue cultures should also be obtained as per indicated above.

With an increasing otter population, clinicians will continue to face dilemmas in the management of otter-human attacks without an established guideline. With the limited case studies available, this letter highlights the severity of otter attacks that can occur unprovoked and in groups leading to extensive soft tissue injuries. Nonetheless, if treated with the abovementioned management strategies, we found that patients generally have good recovery outcomes without significant complications like persistent infections, sepsis and fractures. This letter hopes to serve as a guide for future management of otter attacks in primary and tertiary healthcare institutions.

Declaration

All authors have no affiliations or financial involvement with any commercial organisation with a direct financial interest in the subject or materials discussed in the manuscript.

Keywords: *animal bites, infectious diseases, orthopaedic surgery, otter attacks, pharmacology, rabies, tetanus*

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ANNALS, ACADEMY OF MEDICINE, SINGAPORE
81 Kim Keat Road, #11-00 & #12-00 NKF Centre, Singapore 328836
Email: annals@ams.edu.sg | Website: https://www.annals.edu.sg