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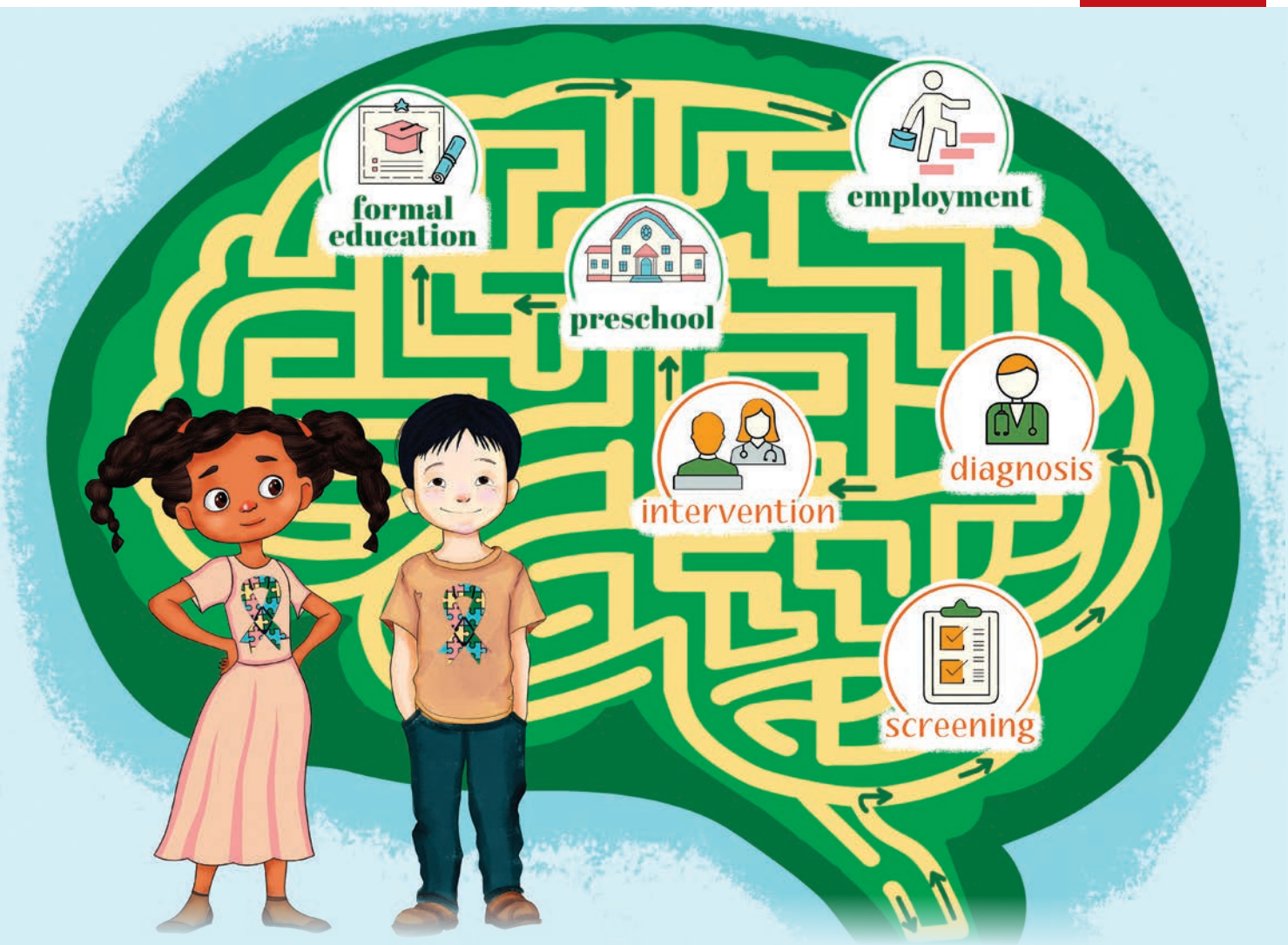

2023 clinical practice guidelines on autism spectrum disorder in children and adolescents in Singapore

Updated clinical practice guidelines now cover an expanded age-range and include new sections on "Education and Transition", "Co-occurring Conditions in Autism", and "Follow-up and Prognosis" (See full article, p.241)

Illustration by Nata Blackthorn

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EDITORIAL

Illicit drug consumption in Singapore: Where are we in the fight against drugs?

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Illicit drug consumption is associated with significant negative health, financial and social consequences. Yet, illicit drug consumption remains highly prevalent and continues to be a growing problem worldwide. In 2021, 1 in 17 people aged 15–64 in the world had used a drug in the past 12 months. Notwithstanding population growth, the estimated number of drug users grew from 240 million in 2011 to 296 million in 2021.[1]

To our knowledge, as the first nationwide study to rigorously investigate the prevalence and correlates of illicit drug consumption in Singapore, Subramaniam et al. not only fill a critical gap in the local literature but also contribute to the discourse on substance use epidemiology and its implications for clinical practice, research and policy.[2]

The study's findings reveal that the lifetime and past 12-month prevalence of illicit drug consumption in Singapore are 2.3% and 0.7%, respectively. Although these rates appear much lower than those reported in Western countries, they should not lull us into a false sense of security. It is crucial to note that the study's community sample does not include institutionalised individuals, such as prison inmates among whom substance use disorders are exceedingly prevalent—in Singapore estimated at 60–70% of inmates.[3] Furthermore, potential underreporting due to fear of legal repercussions in Singapore may underestimate prevalence. Nonetheless, these numbers alone are not negligible by any measure.

This study found that younger individuals aged 15–34 were at higher risk of lifetime consumption of drugs. The mean age of onset was 19.6 years, with 28.9% of those who endorsed lifetime drug consumption having done so before the age of 18. The identification of younger age as a risk factor for illicit drug consumption aligns with global trends.[4] Youth mental health has been a focus in Singapore amid concerns of rising mental health issues and suicide.[5] A complex interplay of individual, familial and community factors places youth at increased risk of drug abuse.[6] Neurobiologically, the prefrontal cortex, responsible for decision-making and impulse control, is not fully developed until the mid-20s. Thus, youth are more susceptible to novelty-seeking and risk-taking behaviours, which include experimenting with illicit drugs.[7] Peer influence is an important proximal risk factor in adolescent substance use, and youth are uniquely vulnerable to the effects of social media and digital communication, which tend to normalise and even glamourise substance misuse.[8] Concurrently, the rapid proliferation of transnational e-commerce has made the barrier to drug procurement worryingly low, and detection impossibly daunting.[9] Given that early substance use dramatically increases the risk of substance use disorder, targeted prevention strategies should focus on children before the sensitive adolescent period.[10]

The finding that current and ex-smokers, as well as those with hazardous alcohol use were at higher risk of drug consumption highlights the need to screen for illicit drug use and the use of multiple substances in individuals with substance use disorders. It also suggests that broader policies and efforts to discourage smoking and excessive alcohol consumption may reduce the risk of illicit drug use.

Notably, this study found that cannabis was the drug that was most first consumed (82.8%) and most frequently (68.0%) consumed across the lifetime. This finding stands in contrast to the 2023 annual statistics by Central Narcotics Bureau of Singapore showing cannabis coming in third (9% of total arrests), after methamphetamine (52%) and heroin (33%). This disparity is yet another reason this study is important—relying on arrest data alone may give us a skewed impression of actual prevalence. The legalisation and medicalisation of cannabis in many countries may contribute to lower perceived risk, which has been associated with a high risk of abusing cannabis in adolescents.[11]

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Consequently, targeted prevention and intervention strategies should focus on at-risk populations and debunking myths about the safety of recreational cannabis consumption.

The "stick" of zero tolerance approach as a nation has served as a strong deterrence. The mammoth task that lies ahead would be the "carrot" of education and treatment/rehabilitation. Repeated cannabis use during adolescence may result in long-lasting changes in brain function that can jeopardise educational, professional and social outcomes.[12] Yet, survey by the National Council Against Drug Abuse in 2020 found that the support among youths aged 18–30 for Singapore's zero-tolerance approach against drugs was 82.5%, lower than the 88.3% for those above the age of 30.[13] Perhaps more nuanced ground-up initiatives that engage youth and acknowledge their views and concerns need to be employed to gain their buy-in and formulate approaches to encourage abstinence from illicit drugs.

The observation of higher rates of anxiety disorders, chronic insomnia and depression among people who have used illicit drugs beckons a "chicken and egg" question. The Singapore Mental Health Study 2016 revealed that a significant proportion of individuals with mental health conditions do not seek help.[14] While efforts to improve mental health literacy and access to care have likely reduced these figures, there remains a significant number of individuals with untreated anxiety disorders, depression and chronic insomnia who are reluctant to step forward. It is possible that some turn to illicit drugs to self-medicate, which perpetuates the underlying mental health problems, creating a vicious cycle.[15] On the other hand, illicit drug use itself can be a contributor to mental health problems. Our national zero tolerance strategy relies on both supply interdiction and control, and demand reduction. This is often achieved by providing good assistance to substance users to completely stop their addictive urges and improve mental health such as those available at our National Addictions Management Service at the Institute of Mental Health. While Singapore has developed many support groups like 12-step Narcotics Anonymous groups, and therapy groups at the Singapore Anti-Narcotics Association, Singapore After-Care Association and WE CARE Community Services, it is important that medical professionals have the skills and knowledge to help identify, refer and treat persons who struggle with substance use disorders. This will significantly reduce demand in combination with our law enforcement policies.

Translating to on-the-ground measures, the study's findings underscore the need for increased vigilance in screening for substance abuse. Part of Singapore's National Mental Health and Well-being Strategy is to develop community mental health services, and it is imperative that measures are in place at these community-based services to perform timely screening for illicit drug use. This is especially crucial for people at risk, such as those who smoke and report hazardous alcohol use—both risk factors for lifetime illicit drug consumption.

This is a call for action to refine strategies that are already in place. The work of Subramaniam et al. highlights the need for targeted prevention and early intervention, particularly among youth, and suggests a place for screening measures in the community setting. At the population level, more can be done to address treatment gaps in mental health and addictive disorders. As we witness the devastating effects of illicit drug use in other countries, we must remain vigilant and adapt to face new challenges brought about by changing attitudes and advancements in technology.

Keywords: *epidemiology, illicit drugs, mental health, psychiatry, public health, substance use disorder*

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EDITORIAL

Promoting evidence-based care for children and adolescents on the autism spectrum

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Autism spectrum disorder (ASD) is aneurodevelopmental disorder that has been increasing in worldwide prevalence,[1] including Singapore. In this latest issue of the *Annals*, we share the latest Singapore Clinical Practice Guidelines (CPG) for Autism in Children and Adolescents, discussed by Wong et al.[2] This is the culmination of the tremendous effort of cross-sectoral professionals coming together to generate recommendations of practice for the community, aspiring in goals of using high-quality evidence to promote high-quality care for families and children on the autism spectrum. The first CPG on Autism Spectrum Disorders in Preschool Children was published in March 2010,[3] and the current updated version presents an opportunity to extend the guidelines to adolescents, as well as bring together more professionals within other non-health sectors to participate in its shaping. We highlight some of the key features of the CPG in tandem with evolving and important issues pertinent to practitioners in Singapore in the field of ASD.

The CPG emphasises the role of developmental surveillance and the need to seek immediate specialist care in the presence of any concerns of ASD without adopting a "wait-and-see approach". This area of ASD is one that is evolving rapidly with evidence being generated for ASD surveillance in young children, so that early intervention can be timely and appropriate. In primary care, various local studies have started evaluating and validating culturally-relevant ASD-specific screening tools within child developmental visits, paired with clinical assessment of children. Ten years ago, the psychometric characteristics of the Modified Checklist for Autism in Toddlers (M-CHAT) was evaluated.[4] The M-CHAT has since evolved to the Modified Checklist for Autism in Toddlers, Revised with Follow-Up (M-CHAT R/F), which holds promise as a feasible, practical, valid and acceptable screening tool in primary care, based on a recent large-scale study among well-children aged 18 months.[5] In parallel, and in line with the shifts towards an inclusive childhood ecosystem, equipping teachers in the early years in detection of young children with symptoms will be equally important. Additionally, what remains to be studied would be the acceptance of local parents towards developmental surveillance and screening and their cultural attitudes towards action—as we are still seeing delayed seeking of help due to varied responses to an ASD positive-screen or ASD diagnosis. Worldwide, evidence suggests that low-income children or children with lower-educated parents are also more likely to be missed[6] as they commonly do not attend developmental surveillance visits at primary care, or because parental awareness is low. Our developmental surveillance and screening for ASD would need to reach them, as they are at highest risks of missing time-sensitive periods of early intervention.

An ASD diagnosis in a child has enormous impact on the parent and family. Most critical to parents would be "What can I do to help my child?" Their urgency, mixed with desperation, is usually met with vast options of programmes, treatments and claims of quick fixes. Parents and professionals may be confused by the myriad of offerings of newer trials and non-evidence-based practices. A section of the CPG of interest to practitioners will be that on Complementary and Alternative Medications (CAM) in ASD. The current guidelines serve as a quick reference, containing updates on an array of CAM that elucidate current and graded evidence regarding controversial treatment modalities and investigations in ASD. Nutraceuticals, gluten-free casein-free diets (GFCF diet) and neurofeedback remain popularly explored by parents and patients locally. Evidence-grading revealed that many of these more popular treatments are still based on limited evidence without well-conducted trials. Use of such treatments were hence not supported in the CPG, which also highlighted some of these as having potential for harm. What remains the "grey zone" would be what constitutes agreed "evidence" for parents—who are happy to buy

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any hope for improvement or cure based on anecdotal evidence or observational studies. Physicians should uphold professional standards and serve to gatekeep against unsafe, ineffective and costly, or unethical business-driven practices in CAM, so that parents can draw informed decisions.

The CPG also offers evidence-based reviews and recommendations on newer pharmacological treatments in co-occurring conditions, as well as in the treatment of core symptoms. What is encouraging within the past 10 years is the proliferation of newer drugs and pharmacological trials, based on theoretically hypothesised mechanisms in the treatment of ASD. What is disappointing is that many of these studies are inconclusive or as yet of insufficient evidence and can only be explored on a research basis or on selected patients, than larger populations. However, in the spirit of science—we must bear continued hope of emerging research—where initial empirical evidence can be combined with good pathophysiological explanations for newer treatments. This is especially important in children with severe features.

Timely with the publication of this CPG is the Singapore government's announcement of an expansion of early intervention services for young children who have been found to have ASD and development needs.[7] Although the CPG has outlined various evidence-supported developmental and behavioral approaches—very often parents will still bring a query of "which therapy is better" and "is my child's therapy enough?" These questions will never be well answered because many of these therapies have not been compared, and often it is not possible for these studies to be directly comparable at all. Because ASD is a complex disorder and each child's intervention requires setting unique goals—it is rather impossible for a single metric to demonstrate a single program's superior efficacy or improvements.[8] Instead, we should balance the ramping up of services with providing professionals with training in many of the evidence-based approaches—so that the quality of care we provide to children is always of high quality. This should happen across government and privately-run early intervention centres, and it is our duty to the children and families that we do so.

Despite all our national efforts, resource-limitations remain for professionals serving the children, and and the state, requiring newer government efforts to ramp up capacity and increase subsidies.[9] Additionally, even if professionals adopt high-quality evidence programmes—no good can be done if our services continue to lag behind demand and there is inequity in service access. In addressing these treatment gaps, we could shift towards equipping parents with core skills, or parent-mediated ASD intervention for core symptoms in young children with ASD. Delivery models can also address treatment gaps, and novel models—e.g. adopting modalities including telehealth—can fill in intervention dosing gaps and can address long therapy wait-times and could also be cost-effective.[10] These solutions are also now part of further evaluative studies in Singapore. Additionally, efforts have been invested in looking at the global functional outcomes of children receiving early intervention[11]—so that we can understand better their clinical progress and measure accurately the child and the family's functional outcomes. Hopefully the future will hold promise on how different children with different clinical trajectories can allow the care and intervention goals to be more customised, with a view to better adult outcomes.

A lifespan perspective to supporting ASD individuals and their families is highlighted as important in the CPG—including transition planning for adolescents to adulthood and community living. Additionally, holistic needs of these individuals across the entire lifespan need to be addressed, including adaptive functioning and emotional wellbeing, in addition to academic achievement. This will maximise the quality of life of the individual on the autism spectrum in the long run. The latest Enabling Masterplan 2030, which is a roadmap to support persons with disabilities to enable their inclusion and contribution—mirrored the need for these recommendations to be implemented through a few strategic themes. For example, a new taskforce will study community living models for these individuals, as well as employment options for them in adulthood. The College of Family Physicians in Singapore is also equipping general practitioners through a course in caring for individuals with intellectual disabilities and ASD. Special education schools continue to expand in capacity, equipping children with the necessary skills for adulthood, while mainstream schools will be better resourced for manpower and specialised interventions for children with additional needs.[12]

Our work on an inclusive society towards individuals with ASD is not done. This latest CPG, commissioned by the College of Pediatrics and Child Health, reveals the continued passion and compassion of clinicians and professionals to drive the sector collectively and progressively. These guidelines should not simply be an evidence document, but hopefully become actively adopted and implemented in our services and care for these children and families.

Keywords: *adolescents, autism spectrum disorder, children, clinical practice guidelines, evidence, paediatrics*

Disclosure

No conflict of interests to declare.

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ORIGINAL ARTICLE

Prevalence of consumption of illicit drugs and associated factors from a nationwide epidemiological survey: The Singapore Health and Lifestyle Survey

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ABSTRACT

Introduction: The primary aims of the current nationwide study were to establish the lifetime and 12-month prevalence of consumption of illicit drugs and its correlates in the general population of Singapore.

Method: A representative sample of 6509 Singapore residents (Singapore citizens and permanent residents) aged between 15 and 65 years were randomly selected for participation. Questionnaires were administered to assess the consumption of illicit drugs and collect information on correlates. All analyses were weighted to produce prevalence estimates for the consumption of drugs and other measured outcomes. Rao-Scott chi-square test and logistic regression analyses were performed to determine the association of sociodemographic and clinical characteristics with lifetime consumption of illicit drugs.

Results: The study was completed with a response rate of 73.2%. The lifetime prevalence of consuming illegal drugs was 2.3% (95% confidence interval [CI] 1.9–2.8) (n=180). Compared to individuals aged 15–34, those aged 50–65 (odds ratio [OR] 0.3, 95% CI 0.2–0.7) had lower odds of lifetime drug consumption. Current smokers (OR 4.7, 95% CI 2.7–8.3) and ex-smokers (OR 5.9, 95% CI 3.2–11.1) had significantly higher odds of lifetime drug consumption than non-smokers. Individuals with hazardous alcohol use (OR 3.3, 95% CI 1.7–6.5) had higher odds of lifetime drug consumption than those without hazardous alcohol use.

Conclusion: This is the first nationwide study to examine the prevalence of illicit drug consumption in the general population of Singapore. The results highlight the need to increase awareness of drug consumption in Singapore, especially among parents, teachers, healthcare workers and others who work with young people.

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Keywords: epidemiology, hazardous alcohol use, illicit drug consumption, Singapore, smoking

CLINICAL IMPACT

What is New

- This nationwide study is one of the first to establish the prevalence of illicit drug consumption in Singapore.
- Our findings highlight that those belonging to the younger age group, current and ex-smokers, as well as those with hazardous alcohol use, were at higher risk of lifetime consumption of drugs.

Clinical Implications

- The results help to inform healthcare workers and others who work with young people on illicit drug consumption in Singapore.
- Our data can help policymaking and further enhance prevention and early detection in the population.

INTRODUCTION

Substance use disorders (SUDs) are characterised by the uncontrolled use of a substance by an individual despite its harmful consequences.[1,2] The prevalence of consumption of substances and SUDs varies widely across countries. This difference in prevalence can be attributed to factors such as study methodology (the substance included in the study, whether survey or administrative data were used), drug policies across countries, and the demographic and cultural profiles of the population.

According to the United Nations Office on Drugs and Crime World Drug Report, in 2020, an

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estimated 284 million people worldwide aged 15–64 (mostly men) had used an illicit drug within the last 12 months.[3] Of the people who had used drugs in the past year, about 13.6% suffered from SUDs.[3] The National Survey on Drug Use and Health (NSDUH) conducted annually in the US found that in 2021, 21.9% of people aged 12 or older (or 61.2 million people) used illicit drugs in the past year. Of these, 16.5% (46.3 million people) had an SUD as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) in the past year.[4] The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) found that around 28.9% (83 million) of adults (aged 15–64) in the European Union had used illicit drugs at least once in their lifetime. In comparison, 7.7% (22.2 million) had used it in the past year.[5]

On the other hand, data from Asian countries are limited. For example, a survey conducted in 2019 in India suggests that about 2.8% of the population had consumed any cannabis products in the past year, while 2.1% used some form of opioids.[6] In Hong Kong, data on illicit drug consumption come mainly from the Central Registry of Drug Abuse.[7] Data from 2021 reported 6019 drug abusers. Among those reported, 2388 or 41% were reported as heroin abusers, and 4099 or 70% were reported as psychotropic substance abusers.[7]

Several sociodemographic factors have been associated with the consumption of substances. Younger age and male gender are significantly associated with a higher prevalence of consumption of substances.[3,8-10] An Australian-New Zealand study examined the association between frequency of cannabis consumption before age 17 and high school noncompletion, university non-enrolment and degree non-attainment by age 25. The study found that adolescent cannabis consumption (weekly or more) was associated with 1.5 to 2-fold increases in the odds of high school noncompletion, university non-enrolment and degree non-attainment.[11] Individual, community and country-level socioeconomic characteristics can directly or indirectly influence drug consumption. NSDUH found that among persons who reported lifetime use of illicit drugs, persons with a family income less than USD 20,000 were 36% more likely to report having substance use problems compared to those with a family income ≥ USD 75,000.[8]

Singapore, a city-state located at the southern tip of the Malay Peninsula, takes a zero-tolerance stance against drugs by adopting a comprehensive drug control strategy that tackles drug supply and demand. The multipronged strategy is spearheaded through preventive drug education; strict anti-drug laws; rigorous enforcement; international engagement and rehabilitating that includes treating, counselling and reintegrating drug offenders into society.[12] However, information on the consumption of drugs in Singapore is limited to arrest data. According to statistics from the Central Narcotic Bureau, 2826 drug abusers were arrested in 2022. Of these, about 28% (802) were new abusers. Methamphetamine (1451), heroin (994) and cannabis (236) were the most commonly abused drugs.[12] However, no study has examined the prevalence of consumption of illicit drugs (i.e. the non-medical consumption of drugs prohibited by national law) in the Singapore general population. Therefore, the primary aims of the current study were to establish the lifetime (any consumption during the person's life) and 12-month (consumption in the last year) prevalence of illicit drug consumption and its sociodemographic and clinical correlates in the general population of Singapore.

METHOD

Study design

The Health and Lifestyle Survey was a nationwide population survey that was undertaken to establish the prevalence of behavioural and substance addictions among those aged 15–65 years in Singapore. Trained interviewers conducted the survey over 15 months, from April 2021 to July 2022.

Sample size

The sample size for the study was calculated by conducting statistical power calculations for binary proportions to provide a precise estimate of a margin of error (MoE) equal to 0.05 for the overall and sub-groups. We assumed a statistical power of 0.80, with the Type 1 error at α=0.05. The design effect after oversampling by age and ethnicity was 1.765. As no local data on the prevalence rate of drug consumption could be used as a reference, we generated 2 power calculations based on an approximation of prevalence rates between 1% and 2%, respectively. In each calculation, we assumed specific, realistic sample sizes (e.g. n=5500, 6000, 6500) and computed the MoE for key quantities of interest. Using this approach, we determined that a sample size of 6500 would provide sufficient precision to estimate 1–2% of drug consumption with a relative standard error of 11.5–16.4% and an MoE of 0.3–0.5% for the overall prevalence estimate.

Participants

A representative sample of Singapore residents (Singapore citizens and permanent residents) aged between 15 and 65 years were randomly selected from an administrative database. The inclusion criteria were that participants had to be Singapore residents, aged 15–65 years, belonging to any of the 4 ethnic groups in Singapore (Chinese, Malay, Indians and others), and literate in English, Chinese, Malay or Tamil. Exclusion criteria were (1) inability to complete the interview due to severe physical or mental health conditions, (2) illiteracy, (3) hospitalisation or (4) institutionalisation lasting the entire duration of fieldwork.

Survey methodology

A survey firm was employed to conduct the study, and respondents were approached by trained lay interviewers. Participants were sent an invitation letter and subsequently approached using door-knocks. A verbal consent was sought in person. If the participants were willing to participate in the study, a tablet with the survey was handed over to them to complete the questionnaires after the collection of basic sociodemographic data by the interviewer.

However, on 14 May 2021, the research team was informed of the need to suspend face-to-face recruitment due to the imposition of COVID-19-related restrictions. As a result, the team adopted a hybrid approach (face-to-face consent and online questionnaire) for all subsequent interviews. After getting the consent, the interviewers provided the participants with a QR code/hyperlink for accessing the survey as well as a unique code, which the participant had to key in to start the survey. The unique code prevented duplicate attempts or misuse of the link. Participants could not make any changes after submitting the survey.

Questionnaires

The European Model Questionnaire and the guidelines provided by EMCDDA for conducting population surveys of drug use were used to develop a questionnaire that assessed the lifetime and 12-month prevalence of drug consumption.[13] Participants were asked about their consumption of illicit drugs, that is, cannabis, heroin, cocaine, methamphetamine, ecstasy, ketamine, nimetazepam, buprenorphine, new psychoactive substances and prescription drugs (i.e. benzodiazepines/tranquilisers, sedatives/hypnotics/barbiturates and steroids) in their lifetime and in the past year. Misuse of prescription drugs was established using 2 additional questions: (1) was this prescribed by a medical practitioner and (2) did you take more than the prescribed dosage? All those who stated that they had consumed a drug (illicit or licit) ever in their lifetime were asked about their mode of drug consumption, age of initiation of drug consumption and reasons for taking drugs. They were also asked about the severity of drug consumption using a checklist based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria for substance use disorder. However, for the current study, we will focus only on the drugs prohibited by national law in Singapore, that is, cannabis, heroin, cocaine, methamphetamine, ecstasy, ketamine, nimetazepam, buprenorphine, new psychoactive substances, and not on the misuse of prescription drugs.

The Patient Health Questionnaire-9 was used to screen for the presence and severity of depression, while the Generalised Anxiety Disorder-7 (GAD-7) was used to screen for generalised anxiety disorder.[14,15] The Insomnia Severity Index was used to assess sleep problems.[16] The Alcohol Use Disorders Identification Test was used to examine drinking habits and hazardous alcohol use.[17] Yes/No questions captured the smoking history, and participants were classified as current, past and never smokers based on their replies. The Chronic Medical Conditions Checklist captured doctor-diagnosed chronic physical conditions and a list of common mental illnesses in Singapore.[18] Please see the details of the questionnaires and the cut-offs used in Supplementary File S1.

Information on the sociodemographic profile of the respondents, including age, gender, ethnicity, living circumstances, marital status and education level, were collected. Data on socioeconomic status (e.g. current occupational status, income and sources of income) were also obtained.

Ethical considerations

Interviewers obtained verbal consent instead of signed written informed consent to prevent any documentation of the participants. Furthermore, no identifiers were collected to ensure that participants could not be linked to their data. A waiver of parental consent was requested and obtained from the institutional review board so that the minors would not feel apprehensive while answering the sensitive questions. All questions had response options, such as "I prefer not to answer" and "don't know" to allow participants to skip any question they felt was sensitive. Encrypted data from the interviews (without identifiers) were stored on the tablets and downloaded weekly by the survey firm to ensure complete confidentiality. Contact details of the respondents

were not shared with the research team, and the survey firm destroyed all contact records after 3 months of completion of the survey.

The National Healthcare Group Domain Specific Review Board (ethics committee) approved the study procedures and provided ethical approval.

Analysis

In order to account for the stratified disproportionate sample design, the data were weighted to adjust for the differential probability of the selection of respondents, non-response and post-stratified by age, gender and ethnicity between the survey sample and the Singapore resident population of 2020. All analyses were based on this weighted sample to produce prevalence estimates for the consumption of drugs and other measured outcomes as well as to describe the sociodemographic profile of the study population. Categorical variables were summarised as weighted percentages and unweighted frequencies. Continuous variables were reported as weighted mean with standard deviation (SD). Rao-Scott chi-square test and logistic regression analyses were performed to determine the association of sociodemographic and clinical characteristics with lifetime consumption of illicit drugs. The results of the logistic regression analyses were provided as odds ratio (OR) and 95% confidence interval (CI). Standard errors were estimated using Taylor's linearisation to adjust for the disproportionate stratified sampling design. All analyses were performed using SPSS Statistics software version 23.0 (IBM Corp, Armonk, NY, US) and Stata/MP version 17.0 (StataCorp, College Station, TX, US) using 2-sided tests at a significance level of 0.05.

RESULTS

A total of 6509 respondents were included in the analysis, with a response rate of 73.2%. The weighted mean age was at 40.9 (SD 14.2) years. Most individuals were aged 15–34 years old (36.3%, n=2404), female (50.8%, n=3353), of Chinese ethnicity (73.6%, n=2130), had degree/professional/post-graduate and qualification (36.4%, n=2035), were married (57.7%, n=3839) and employed/self-employed (75.8%, n=4709). They had a personal income below SGD2000/No income (42.0%, n=2419) (Table 1).

Prevalence of lifetime and past 12-month illicit drug consumption

The lifetime prevalence of consuming illegal drugs was 2.3% (95% CI 1.9–2.8) (n=180). Among those who consumed illicit drugs in their lifetime, the mean age of onset was 19.6 (SD 6.7) years, with 28.9% (n=35) consuming illegal drugs before reaching 18 years of age. The prevalence of lifetime illicit drug consumption was higher among those aged 15–34 years old (2.8%), males (2.9%), those belonging to other ethnicities (5.7%), with tertiary educational qualification (2.5%), separated/widowed/divorced (4.0%), those who were unemployed or temporarily laid off (4.5%), ex-smokers (7.5%) and those with hazardous alcohol use (9.7%) (Table 2).

The past 12-month illicit drug consumption prevalence was 0.7% (n=58). Given the low prevalence, no further analysis was done on this group. The prevalence of illicit drug abuse among those with illicit drug consumption was 23.3%, while that of drug dependence was 13.0% (using DSM-IV-TR criteria).

The first drug consumed and most frequently consumed illicit drug

Cannabis was the most common drug that was first consumed (82.8%, n=70) in the lifetime, followed by methamphetamine (4.5%, n=7) and ecstasy (4.0%, n=3) (Table 3). Among the illicit drugs consumed in the lifetime, cannabis (68.0%, n=45), methamphetamine (15.5%, n=14) and heroin (6.5%, n=10) were most frequently consumed (Table 3).

Sociodemographic and clinical correlates of lifetime illicit drug consumption

Age, ethnicity, employment status, smoking status and hazardous alcohol use were significantly associated with lifetime drug consumption (Table 4). Compared to individuals aged 15–34, those aged 50–65 (OR 0.3, 95% CI 0.2–0.7) had lower odds of lifetime drug consumption. Smokers (OR 4.7, 95% CI 2.7–8.3) and ex-smokers (OR 5.9, 95% CI 3.2–11.1) were more likely to have lifetime drug consumption than non-smokers. Individuals with hazardous alcohol use (OR 3.3, 95% CI 1.7–6.5) had higher odds of lifetime drug consumption than those without hazardous alcohol use.

Those with lifetime drug consumption had higher odds of having clinical anxiety (OR 2.2, 95% CI 1.1–4.6) and clinical insomnia (OR 2.0, 95% CI 1.2–3.4). Those with lifetime illicit drug consumption were more likely to report that a doctor had diagnosed them with depression or major depressive disorder (OR 4.1, 95% CI 2.0–8.6), bipolar disorder (OR 9.6, 95% CI 1.5–60.3), anxiety disorder (OR 3.4, 95% CI 1.4–8.1) and psychosis or schizophrenia (OR 8.8, 95% CI 1.4–56.3) (Table 5).

Table 1. Sociodemographic characteristics of the sample.

		Weighted % (Unweighted n)
Age group	15–34	36.3% (2404)
	35–49	31.3% (2270)
	50–65	32.4% (1835)
Gender	Female	50.8% (3353)
	Male	49.2% (3156)
Ethnicity	Chinese	73.6% (2130)
	Malay	13.7% (2162)
	Indian	9.2% (1911)
	Others	3.5% (306)
Education	No formal education/Primary	7.4% (539)
	Secondary school	23.8% (1555)
	Vocational institute/Institute of Technical Education/Pre-university/Junior college/Diploma/International baccalaureate	32.4% (2289)
	Degree/Professional qualification and post-graduate and above	36.4% (2035)
	Others	0.02% (3)
Marital status	Married	57.7% (3839)
	Single	36.5% (2202)
	Separated/Widowed/Divorced	5.8% (404)
Employment	Employed/Self-employed	75.8% (4709)
	Economically inactive/Students	20.6% (1431)
	Unemployed/Temporarily laid off	3.6% (249)
	Others	0.06% (2)
Personal income	Below SGD2000/No income	42.0% (2419)
	SGD2000–SGD3999	25.0% (1441)
	SGD4000–SGD6999	18.4% (818)
	SGD7000 and above	14.6% (600)

Missing values: education (n=88), marital status (n=64), employment (n=118), personal income (n=1231).
Economically inactive includes housewives and retirees.

DISCUSSION

The current study is one of the first conducted in Singapore to examine the prevalence and correlates of illicit drug consumption. The study found that the prevalence of lifetime and 12-month illicit drug consumption in the population was 2.3% and 0.7%, respectively. The prevalence of illicit drug consumption in Singapore was much lower than that reported in studies conducted in the US, Europe and Australia, which reported rates of 21.4% (in the past year), 28.9% (at least once in their lifetime)[5] and 43% (at some point in their life), respectively.[4,19]

Among respondents who endorsed lifetime illicit drug consumption, cannabis was the most common drug first consumed and the most frequently consumed drug in the lifetime. According to the Alcohol, Drugs and Addictive Behaviours Unit at the World Health Organization, cannabis is the most widely cultivated, trafficked and abused illicit drug globally. About 147 million people, that is, 2.5% of the world population, consume

Table 2. Sociodemographic characteristics of the sample stratified by lifetime illicit drug consumed.

	No illicit drug use (n=6281)	Lifetime illicit drug use (n=180)	*P* value
Age group			0.031
15–34	97.2% (2312)	2.8% (75)	
35–49	97.3% (2198)	2.7% (62)	
50–65	98.6% (1771)	1.4% (43)	
Gender			0.012
Female	98.3% (3269)	1.7% (67)	
Male	97.1% (3012)	2.9% (113)	
Ethnicity			<0.001
Chinese	98.1% (2077)	1.9% (44)	
Malay	97.0% (2080)	3.0% (62)	
Indian	96.9% (1836)	3.1% (57)	
Others	94.3% (288)	5.7% (17)	
Education			0.912
No formal education/Primary	97.7% (517)	2.3% (14)	
Secondary school	98.0% (1497)	2.0% (42)	
Vocational institute/Institute of Technical Education/Pre-university/Junior college/Diploma/International baccalaureate[†]	97.6% (2213)	2.4% (61)	
Degree/Professional qualification and post-graduate and above	97.5% (1971)	2.5% (60)	
Others	100% (3)	0% (0)	
Marital status			0.222
Married	97.9% (3706)	2.1% (103)	
Single	97.7% (2129)	2.3% (61)	
Separated/Widowed/Divorced	96.0% (386)	4.0% (14)	
Employment			0.008
Employed/Self-employed	97.3% (4532)	2.7% (148)	
Economically inactive/Students	99.1% (1401)	0.9% (20)	
Unemployed/Temporarily laid off	95.5% (235)	4.5% (12)	
Others	100% (2)	0% (0)	
Personal income			0.316
Below SGD 2000/No income	98.0% (2346)	2.0% (59)	
SGD 2000–3999	97.3% (1385)	2.8% (49)	
SGD 4000–6999	97.6% (792)	2.4% (23)	
SGD7000 and above	96.5% (570)	3.5% (28)	

Table 2. Sociodemographic characteristics of the sample stratified by lifetime illicit drug consumed. (Cont'd)

	No illicit drug use (n=6281)	Lifetime illicit drug use (n=180)	*P* value
Smoking status			<0.001
Smoker	94.1% (941)	5.9% (72)	
Ex-smoker	92.5% (401)	7.5% (30)	
Non-smoker	98.7% (4812)	1.3% (75)	
Hazardous alcohol use			<0.001
No	98.0% (5553)	2.0% (138)	
Yes	90.3% (161)	9.7% (21)	

[#] Rao-Scott chi-square test was used to obtain *P* value.
[†] These are pre-tertiary educational qualifications.
Missing values: education (n for no drug use = 80, n for drug use = 3), marital status (n for no drug use = 60, n for drug use = 2), employment (n for no drug use = 111), personal income (n for no drug use = 1188, n for drug use = 21), smoking status (n for no drug use = 127, n for drug use = 3), hazardous alcohol use (n for no drug use = 567, n for drug use = 23).
Economically inactive includes housewives and retirees.

Table 3. First drug used and most frequent drug used (top 3) among those who endorsed lifetime drug consumption.

	Weighted %	Unweighted frequency
What was the first drug that you have used? *		
Cannabis	82.8%	70
Methamphetamine	4.5%	7
Ecstasy	4.0%	3
Which drug did you use most frequently? [#]		
Cannabis	68.0%	45
Methamphetamine	15.5%	14
Heroin	6.5%	10

* 88 respondents with illicit drug use refused to answer this question or stated that they did not know.
[#] 105 respondents with illicit drug use refused to answer this question or stated that they did not know.

cannabis annually, compared with 0.2% consuming cocaine and 0.2% consuming opiates.[20] The short- and long-term consumption of cannabis is associated with several health and social consequences. However, the harm caused by cannabis is often underestimated, which may have contributed to its increased consumption in the past few decades.

Our data also revealed that age, ethnicity, employment status, smoking status and hazardous alcohol use were significantly associated with lifetime illicit drug consumption. The association of drug consumption with the younger age group, smoking and hazardous alcohol use are well-established globally.[3,21] Previous research has found that birth cohort effects are associated with differences in substance consumption, and that these may partially reflect trends in drug popularity, availability and perceptions of reduced harm.[22-24]

A systematic review of epidemiological studies found that among adults, current and lifetime smoking was consistently higher among adults with lifetime, past-year and past-month SUDs compared with other adults.[25] While the systematic review could identify fewer studies examining smoking among adolescents with SUDs, the results were similar to those of adult studies. Similarly, data from the 2015–2017 National Surveys on Drug Use and Health used to examine past-year SUD comorbidity combinations among 12 substances found that the 4 most common SUD combinations included alcohol use disorder.[26]

Table 4. Sociodemographic correlates of lifetime illicit drug consumption.

	OR (95% CI)	*P* value
Age group (in years)		
15–34 (Reference)		
35–49	0.7 (0.4–1.2)	0.208
50–65	0.3 (0.2–0.7)	0.005
Gender		
Female (Reference)		
Male	0.96 (0.6–1.6)	0.880
Ethnicity		
Chinese (Reference)		
Malay	1.1 (0.7–1.9)	0.602
Indian	1.4 (0.9–2.2)	0.170
Others	2.1 (1.1–3.8)	0.023
Education		
Degree/Professional qualification and post-graduate and above (Reference)		
Secondary school	0.6 (0.3–1.3)	0.200
Institute of Technical Education/Vocational institute, pre-university/Junior college, international baccalaureate	0.7 (0.4–1.3)	0.271
No formal education/Primary	0.8 (0.3–2.5)	0.711
Marital status		
Married (Reference)		
Single	0.8 (0.5–1.4)	0.519
Separated/Widowed/Divorced	1.9 (0.7–5.4)	0.210
Employment status		
Employed/Self-employed (Reference)		
Economically inactive/Students	0.4 (0.2–0.9)	0.032
Unemployed/Temporarily laid off	0.7 (0.4–1.5)	0.353
Smoking status		
Non-smoker (Reference)		
Smoker	4.7 (2.7–8.3)	<0.001
Ex-smoker	5.9 (3.2–11.1)	<0.001
Hazardous alcohol use		
No (Reference)		
Yes	3.3 (1.7–6.5)	0.001

Economically inactive includes housewives and retirees.
CI: confidence interval; OR: odds ratio

Table 5. Associations between clinical outcomes and lifetime illicit drug use.

Clinical outcomes	OR (95% CI)	*P* value
Clinical Depression (PHQ-9)	1.5 (0.7–3.1)	0.273
Clinical Anxiety (GAD-7)	2.2 (1.1–4.6)	0.037
Clinical Insomnia (ISI)	2.0 (1.2–3.4)	0.013
Presence of chronic conditions (self-reported)	1.1 (0.7–1.6)	0.825
Depression or major depressive disorder (self-reported)	4.1 (2.0–8.6)	<0.001
Bipolar disorder (self-reported)	9.6 (1.5–60.3)	0.016
Anxiety disorder (self-reported)	3.4 (1.4–8.1)	0.006
Psychosis or Schizophrenia (self-reported)	8.8 (1.4–56.3)	0.022

Adjusted for age, ethnicity, employment status, smoking status and hazardous alcohol use.
Cut-off for various scales are as follows: PHQ-9 (≥10 for clinical depression), GAD-7 (≥10 for clinical anxiety), ISI (≥15).
CI: confidence interval; GAD-7: Generalised Anxiety Disorder -7; ISI: Insomnia Severity Scale; OR: odds ratio; PHQ-9: Patient Health Questionnaire-9

Clinically, assessment and treatment often focus on a substance-specific SUD. However, early diagnosis and intensive treatment of multiple SUDs is of utmost importance. Multiple SUDs are more persistent than individual SUDs and are associated with an elevated risk of developing comorbid psychiatric and physical health problems.[27] Furthermore, multiple SUDs may adversely affect treatment outcomes (e.g. cigarette smoking predicts worse treatment outcomes among those with illicit drug dependence).[28]

Studies conducted elsewhere have reported an association between unemployment and consumption of illicit drugs.[29,30] Our study, on the other hand, found that those who were economically inactive/students were less likely to endorse lifetime drug consumption than those who were employed. Several reasons are possible for this association. First, it is possible that given the stringent laws, access to drugs is not easy, and the cost of illicit drugs may be higher in Singapore. These factors may have limited the consumption among the economically inactive and student category who have limited financial resources. Second, it is possible that the economically inactive group, that is, retirees and homemakers, constitutes a low-risk group who are less likely to take drugs. Third, it is also possible that the use of evidence-based approaches in school to prevent substance abuse and other protective factors, such as having a structured curriculum and school connectedness, could have reduced the risk of consumption of illicit substances in students.[31,32] Last, it is possible that those who start consuming drugs at an early age may drop out of school.[33] This could also lead to the lower association between students and illicit drug consumption observed in the study.

The study also found that illicit drug consumption was associated with poor health outcomes. Those with lifetime drug consumption were more likely to have clinical anxiety (as assessed by GAD-7); clinical insomnia; self-reported, doctor-diagnosed depression; bipolar disorder; anxiety disorder and psychosis/schizophrenia. While several other studies substantiate these associations, the takeaway point is that the consumption of substances is associated with poor health and well-being of the individual.[34-36] However, given this study's cross-sectional nature, we cannot establish causality. While it is possible that substance consumption leads to anxiety, it is also possible that those with anxiety disorders use substances as a form of self-medication.[37,38]

Certain limitations must be kept in mind while interpreting the results of this study. First, this was a household sample, so it excluded residents of nursing homes, hospitals, prisons and those with unstable housing. Second, about 30% of the sample was not interviewed (due to refusal to participate in the study). This non-response could lead to an underestimation of the true prevalence. Third, participants may have under-reported or denied their symptoms. They might be reluctant to share their personal experiences due to either fear of legal repercussions or embarrassment, as alcohol and drug consumption remain stigmatised behaviours in Singapore. Thus, the true prevalence of drug consumption in Singapore may be higher. Fourth, to ensure confidentiality, we only included respondents who were literate and could complete the questionnaires independently. Fifth, the study

results are subjective to recall bias, especially the consumption of substances over a lifetime. Last, this being a cross-sectional study, we cannot determine causality. Thus, the relationship between drug consumption and psychological distress is difficult to establish.

On the other hand, the study has several strengths. First, the study used a nationally representative sample; the response rate of 73% makes our results generalisable to the Singapore population. The team also put in several safeguards to ensure the confidentiality and protection of personal data, which led to the willingness of people to participate and share information about high-risk behaviours. In addition, stringent quality control measures ensured data integrity and data quality.

In conclusion, this is the first nationwide study that has examined the prevalence of illicit drug consumption in the community-dwelling population of Singapore using robust scientific methods. It is essential to maintain a strong commitment to monitoring relevant changes in the prevalence of drug consumption and the early identification of emerging trends in the attitudes towards the consumption of illicit drugs in the future. Such data will further strengthen preventive and treatment efforts across Singapore.

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ORIGINAL ARTICLE

Healthcare burden of cognitive impairment: Evidence from a Singapore Chinese health study

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ABSTRACT

Background: Cognitive impairment (CI) raises risks for unplanned healthcare utilisation and expenditures and for premature mortality. It may also reduce risks for planned expenditures. Therefore, the net cost implications for those with CI remain unknown.

Method: We examined differences in healthcare utilisation and cost between those with and without CI. Using administrative healthcare utilisation and cost data linked to the Singapore Chinese Health Study cohort, we estimated regression-adjusted differences in annual healthcare utilisation and costs by CI status determined by modified Mini-Mental State Exam. Estimates were stratified by ex ante mortality risk constructed from out-of-sample Cox model predictions applied to the full sample, with a separate analysis restricted to decedents. These estimates were used to project differential healthcare costs by CI status over 5 years.

Results: Patients with CI had 17% higher annual cost compared to those without CI (SGD4870 versus SGD4177, $P<0.01$). Accounting for the greater mortality risk, individuals with CI cost 9% to 17% more over 5 years, or SGD2500 (95% confidence interval 1000–4200) to SGD3600 (95% confidence interval 1300–6000) more, depending on their age. Higher cost was mainly due to more emergency department visits and subsequent admissions (i.e. unplanned). Differences attenuated in the last year of life when costs increased dramatically for both groups.

Conclusion: Ageing populations and higher rates of CI will further strain healthcare resources primarily through greater use of emergency department visits and unplanned admissions. Efforts should be made to identify at risk patients with CI and take appropriate remediation strategies.

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Keywords: burden, cognitive impairment, end-of-life, healthcare, healthcare cost, Singapore, survival, utilisation

CLINICAL IMPACT

What is New

- Our study demonstrates that individuals with cognitive impairment tend to experience higher rates of unplanned healthcare utilisation, such as visits to emergency departments and subsequent hospital admissions.
- Additionally, those with cognitive impairment face significantly higher overall healthcare costs when compared to individuals without cognitive impairment.

Clinical Implications

- These findings confirm the growing concern regarding the burden of cognitive impairment on healthcare systems, especially within ageing populations, as evidenced by increased healthcare utilisation and escalating costs.

INTRODUCTION

Individuals with cognitive impairment (CI) are predisposed to injuries, infections and treatment complications,[1] have poorer treatment compliance, and face greater difficulties with post-discharge care.[2] These challenges, exacerbated by comorbidities,[3-6] lead to poorer ambulatory care management, reduced contacts with primary and outpatient care providers, and greater use of emergency department (ED) visits, more unplanned admissions, and longer length of inpatient stays.[7-9] Roughly two-thirds of those with CI will also develop dementia.[10]

The above suggests that rising rates of CI will increase health expenditures. Yet, this is not necessarily the case as those with CI have higher mortality risk.[11,12] Those with CI may also be less aggressively treated and therefore less likely

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to receive life-extending treatments, such as dialysis, cancer treatments or surgeries.[13,14] This may result both because these patients face greater difficulty adhering to treatment guidelines, such as post-surgical care and because surrogate decision-makers may be less inclined to pursue life-extending or elective treatments for someone with CI.[15,16] Hence, while unplanned healthcare utilisation is likely greater for those with CI, planned utilisation may be less due to both the mortality effect and the possible attenuation of planned care. Therefore, whether those with CI have higher or lower expenditures than those without is ultimately an empirical question.

We address this question by quantifying differences in healthcare utilisation and costs for those with and without CI using a retrospective analysis of a population-based cohort, the Singapore Chinese Health Study cohort, linked to administrative healthcare records.[18] Our primary analysis compared utilisation and costs between those with and without CI. We expect that those with CI will have higher utilisation and costs associated with ED visits and unplanned admissions (i.e. through the ED) but will have lower utilisation and costs associated with outpatient visits and planned hospital admissions (i.e. not through the ED). Moreover, we expect that the hypotheses for outpatient visits, ED visits and unplanned admissions are more likely to hold for those at greater ex ante risk of dying because CI complicates treatment for other conditions and ambulatory care management. On the other hand, the hypothesis for planned admissions is more likely to hold for those at lower ex ante risk of dying as these patients face less urgency for life-extending treatment. In the last year of life we expect cost differences between those with and without CI to attenuate, both because those with CI are less likely to receive life-extending treatments and because those without CI are likely to be much more expensive than in non-terminal years.[7,8,17]

As a secondary analysis, we combined the expenditure and survival estimates to quantify the expected 5-year per capita burden of CI for varying ages between 65 and 90. We hypothesised that the 5-year burden of CI will attenuate with increasing age due to increased mortality risk attributable to CI. These results will help policy-makers better understand drivers for end-of-life costs and budget for future health expenditures that will come with Singapore's ageing population.

METHOD

The Singapore Chinese Health Study is a longitudinal cohort study that recruited 63,257 Chinese residents aged 45–74 years and residing in public housing estates during recruitment from 1993 to 1998; at the time of recruitment, about 86% of Singapore population resided in these estates.[18] Trained interviewers used a structured questionnaire to collect information on usual diet, lifestyle factors and medical history from consenting participants. Our study focused on respondents of the third follow-up interview (n=16,947), conducted from 2014 to 2016, which examined cognitive function among the participants using the Singapore-modified version of the Mini-Mental State Exam (SM-MMSE).[19] Although an MMSE cut-off point of 23 to 24 is usually used to define CI in Western countries,[20] previous studies have showed that MMSE score is significantly affected by education level.[21,22] As education level in our population was generally low, we used education-specific cut-off points from the Shanghai Dementia Survey which had a comparable education level with our study population.[21] Individuals with CI were identified by SM-MMSE scores <18, <21 and <25 for those with no formal education, with primary school education, and with secondary school or higher education, respectively. Vital status as of 31 December 2019 and date of death were obtained from linkage with the Singapore Registry of Births and Deaths.

Healthcare utilisation and cost

Data on healthcare utilisation and costs from 2014 to 2019 were obtained by linking the Singapore Chinese Health Study (SCHS) cohort to administrative data from the Ministry of Health. The latter captures cost and utilisation data from public and private acute hospitals in Singapore for admissions, day surgeries, hospital outpatient visits and visits to government-run polyclinics.[23]

Healthcare utilisation was examined in terms of having any visits, number of visits and length of stay for hospital admissions. We consider all ED visits and all hospital admissions following an ED visit as unplanned. Healthcare costs were taken from the non-subsidised bill amount and adjusted to 2021 Singapore dollars (SGD) using the healthcare consumer price index.

Burden estimation

We used regression analysis to estimate the differences in healthcare utilisation and cost between cognitively impaired and cognitively intact individuals, controlling for potential confounders, including age, gender, education, residence type, whether they lived alone, health conditions (e.g. body mass index and self-reported chronic conditions), and year-fixed effects. Probit regression was used for the probability of having at least 1 visit or

admission. Negative binomial regression was used for number of visits and length of inpatient stay.

A 2-part model was used to quantify healthcare cost a year from the survey date to account for the fact that many individuals do not utilise ED or inpatient services.[24] The first part is a probit model which estimated the probability of having a positive cost. The second part is a generalised linear regression model (GLM) with log link function and gamma-distributed errors that estimated non-zero costs.[25] For the analysis of cost in the last year of life, we found the GLM with log link function and gamma-distributed errors to be a reasonable fit as the probability of having a positive cost was high.

Since CI was assessed only once for the SCHS cohort in the third follow-up survey, our primary analysis focused on estimating CI burden in the 12-month period immediately after survey to test our hypotheses on differences in utilisation and costs over different healthcare settings as a function of CI status. To investigate the extent to which our hypotheses hold for those with different underlying risk of dying, we conducted a stratified analysis by the 12-month ex ante mortality risk—defined here as the out-of-sample predicted probability of dying as discussed in the following paragraph—running separate regressions for those in the top 25% risk and those in the bottom 75% risk. For comparisons of healthcare utilisation and cost in the last year of life, we assumed that decedents who were cognitively intact during the interview remained so until death.

Survival estimation

A stratified Cox proportional-hazards model, controlling for the same set of predictors used in the burden estimation, was used to estimate survival differences attributed to CI, as well as generate ex ante mortality risk predictions. Stratification was performed over cancer status, which failed the proportional hazards test based on Schoenfeld residuals. To obtain ex ante mortality risk, we implemented a 10-fold out-of-sample prediction procedure that involved randomly partitioning the sample into 10 equal-sized subsamples. For each subsample, the survival model was fitted on the other 9 subsamples and out-of-sample predictions were generated for the withheld subsample.

Expected 5-year cost

We projected the expected total 5-year cost of cognitively impaired and cognitively intact individuals beginning at ages 65, 70, 75, 80, 85 and 90 years to investigate any offsetting effects of increased mortality for older individuals. The projections were based on 3 sets of age-specific predictive margins over CI status: (1) annual survival probabilities; (2) total end-of-life cost in the last 12 months of life; and (3) annual non-end-of-life cost. Predictive margins were averaged over those whose ages were within 2 years of the reference age to ensure other covariates such as health conditions are representative (e.g. predictive margin for a 70-year-old is averaged over those aged 68 to 72). The expected 5-year cost for an individual is then the probability-weighted sum of end-of-life and non-end-of-life costs in each year, with costs beyond the first year discounted at 3% per annum. Standard errors and 95% confidence intervals were calculated based on 2000 bootstrap replications. Similar to the analysis of the end-of-life costs, the projections assumed CI status remains unchanged throughout this period.

RESULTS

Table 1 presents the demographic and health characteristics of individuals participating in the third SCHS follow-up interviews. Approximately 14% of respondents had evidence of CI based on the SM-MMSE scores. These individuals were more likely to be female, older, less educated, and residing in 3-room flats or smaller. They were also more likely to be unhealthy, have a higher risk of cardiovascular disease, and more likely to have reported being diagnosed with hypertension, diabetes, stroke, arthritis and Parkinson's. However, they were also less likely to have reported having high cholesterol, gout and cancer. By the end of 2019, individuals with CI were more than twice as likely to have died than those without CI.

The first 2 columns of Table 2 report the regression-adjusted healthcare utilisation and costs incurred within a year from interview. Overall, individuals with CI were more likely than those without CI to have at least one visit to the ED (26% versus [vs] 20%, $P<0.01$) and at least 1 unplanned admission (18% vs 13%, $P<0.01$). On average, individuals with CI spent 1.22 more days in the hospital than those without ($P<0.01$), and these days were mostly attributed to unplanned admissions. In terms of total healthcare costs, individuals with CI cost about SGD700 or 17% more per year than those without CI (SGD4870 vs SGD4177, $P<0.01$), which were largely driven by higher costs for unplanned admissions. Costs for outpatient visits were significantly lower for individuals with CI ($P<0.05$). There were no differences in utilisation or costs of planned admissions. Utilisation and cost of ED without admission were significantly higher for individuals with CI ($P<0.05$).

Columns 3 to 6 of Table 2 report results stratified by ex ante mortality risk (see Supplementary

Table 1. Sample characteristics by vital and cognitive impairment status.

Cognitive status	No CI (n=14,504)	CI (n=2443)
Panel A: Demographics		
Men, %	41.4	37.0
Age, mean	72.0	76.7
Level of education, %		
None	18.0	24.0
Primary	45.3	41.6
Secondary and above	36.7	34.4
Living alone, %	7.8	7.9
Housing type, %		
HDB 1-2 room	4.2	6.8
HDB 3-room	30.6	36.4
HDB 4 room	38.1	36.1
HDB 5 room or exec	24.3	19.0
Private or others	2.7	1.7
Panel B: Health measures		
BMI group, %		
≤18.4 (underweight)	6.5	7.2
18.5–22.9 (low CVD risk)	42.2	39.9
23.0–27.4 (moderate CVD risk)	40.6	40.7
≥27.5 (high CVD risk)	10.8	12.2
High blood pressure, %	61.9	66.1
Heart attack/angina/heart failure, %	9.6	10.1
Coronary bypass/angioplasty, %	7.1	7.4
Stroke, %	4.7	8.1
Diabetes, %	22.0	26.1
High cholesterol, %	57.6	53.1
Gout, %	6.2	4.3
Cancer, %	6.8	5.6
Chronic lung disease, %	1.0	0.8
Arthritis, %	18.4	20.1
Kidney failure, %	1.3	1.6
Parkinson's disease, %	0.5	1.2
Deceased by 2019, %	7.1	17.6

BMI: body mass index; CI: cognitive impairment; CVD: cardiovascular disease

Materials Tables S1 and S2 for fitted survival model and its discriminative power). Approximately 35% of those with higher mortality risk had CI, while only 8% of those with lower mortality risk had CI. Individuals with the same CI status but with higher risk of dying over the next year had substantially higher healthcare utilisation and costs in all settings. Among those with lower mortality risk, ED and unplanned inpatient utilisation remained significantly higher for individuals with CI. However, the difference in total costs was smaller and not statistically significant. This is because despite having significantly higher costs for unplanned admissions, individuals with CI had significantly lower costs for planned admissions. Healthcare burden associated with CI was also generally larger in absolute terms for those with higher mortality risk. Incremental ED visits and unplanned admissions associated with CI were relatively greater and more statistically significant in magnitude for this group. Similar results were found for healthcare costs. Additionally, high mortality risk individuals with CI incurred significantly lower outpatient costs than those without (SGD187, $P<0.05$). Total costs associated with CI was SGD1177 ($P<0.01$) for those with higher mortality risk; but for those with lower mortality risk it was only SGD251 and not statistically significant. Alternative estimates restricted to a subsample of those with matched CI propensity scores (Supplementary Materials Table S3) yielded similar findings.

Table 3 reports the regression-adjusted healthcare utilisation and costs incurred in the last year of life. Utilisation of ED and inpatient service settings were substantially higher than Table 2 but were more similar between CI status. Although the lack of statistically significant differences may be partly due to the smaller sample size, we note that the absolute difference between those with and without CI was also smaller. Outpatient visits and planned admissions at the end of life were significantly lower for individuals with CI. Unplanned inpatient costs were also lower for individuals with CI. There was little difference in costs by place of service or overall in the last year of life.

Table 4 presents the expected 5-year total healthcare cost by age and CI status. Costs increase with starting age and were significantly higher for individuals with CI by about SGD2500 to SGD3600 (i.e. SGD500 to SGD720 per year), based on the 95% bootstrapped confidence intervals. The incremental cost associated with CI rose initially with age, peaking at around age 80 before falling. A breakdown of the survival

Table 2. Healthcare utilisation and cost, a year after the interview.

Ex ante mortality risk	All (n=16,939)		Bottom 75% mortality risk (n=12,703)		Top 25% mortality risk (n=4236)	
Cognitive status	No CI	CI	No CI	CI	No CI	CI
Panel A: Any visit/admission, %						
Outpatient	94.1	93.6	93.2	93.2	96.6	96.5
Emergency department	19.7	25.7***	16.0	18.7**	30.9	40.2***
Emergency department without admission	9.6	12.0***	8.6	10.0	12.4	16.1***
Inpatient	16.3	21.9***	12.6	15.0**	27.5	36.1***
Planned inpatient	6.1	6.3	5.2	4.5	8.9	9.7
Unplanned inpatient	12.6	18.2***	9.0	12.3***	23.5	31.8***
Panel B: Number of visits/admissions, mean						
Outpatient	10.4	10.1*	9.76	9.67	12.4	12.0
Emergency department	0.30	0.46***	0.22	0.31***	0.52	0.81***
Emergency department without admission	0.11	0.15***	0.10	0.12	0.16	0.20***
Inpatient	0.27	0.40***	0.19	0.24**	0.49	0.74***
Planned inpatient	0.08	0.08	0.07	0.06	0.13	0.14
Unplanned inpatient	0.18	0.31***	0.12	0.19***	0.36	0.60***
Panel C: Length of inpatient stay, mean days						
All admissions	1.66	2.88***	1.00	1.60**	3.38	5.73***
Planned admissions	0.43	0.50	0.31	0.23	0.78	1.08
Unplanned admissions	1.24	2.45***	0.71	1.41**	2.60	4.86***
Panel D: Costs (2021), SGD						
Total	4177	4870***	3283	3534	6072	7249***
Outpatient	1790	1673**	1623	1631	2265	2078**
Emergency department	74	110***	55	73***	132	196***
Emergency department without admission	30	36**	26	29	43	54**
Inpatient	2292	3118***	1616	1745	4348	5830***
Planned inpatient	986	895	844	458***	1388	1621
Unplanned inpatient	1299	2157***	778	1283**	2910	4327***

CI: cognitive impairment
Estimates are regression-adjusted, controlling for factors listed in Table 1 and time-fixed effects. Statistically significant differences between the cognitively intact and impaired are indicated by asterisks: *P<0.1, **P<0.05, ***P<0.01.

probability and undiscounted cost for each year reveal what is driving this u-shaped pattern (Supplementary Materials Table S4). The CI burden increased initially with age because incremental costs, both non-end-of-life and end-of-life, increased with age. However, higher mortality attributable to CI also increased with age, offsetting the additional costs with an increasingly lower probability of surviving. Hence, the projected costs subsequently fell with age.

Table 3. Total healthcare utilisation and cost in the last year of life.

Cognitive status of decedents (n=1454)	No CI	CI
Panel A: Any visit/admission, %		
Outpatient	97.7	94.8**
Emergency department	89.9	92.4
Emergency department without admission	29.0	31.9
Inpatient	89.7	91.1
Planned inpatient	35.0	26.6***
Unplanned inpatient	84.5	85.8
Panel B: Number of visits/admissions, mean		
Outpatient	16.7	13.5***
Emergency department	2.57	2.59
Emergency department without admission	0.41	0.40
Inpatient	2.76	2.65
Planned inpatient	0.63	0.47**
Unplanned inpatient	2.13	2.17
Panel C: Length of inpatient stay, mean days		
All admissions	24.8	26.4
Planned admissions	4.58	4.44
Unplanned admissions	20.3	22.0
Panel D: Costs (2021), SGD		
Total	34,469	33155
Outpatient	3515	2736***
Emergency department	699	697
Emergency department without admission	122	118
Inpatient	30,228	29745
Planned inpatient	7523	6553
Unplanned inpatient	22,847	22927

CI: cognitive impairment.
Estimates are regression-adjusted, controlling for factors listed in Table 1 and time-fixed effects. Statistically significant differences between the cognitively intact and impaired are indicated by asterisks: *P<0.1, **P<0.05, ***P<0.01.

DISCUSSION

This study quantified the annual and 5-year per capita burden of CI for an elderly Chinese population in Singapore. Using our annual estimates and assuming 44,000 individuals have CI in Singapore,[26] the aggregate burden is about SGD134 million over 5 years, or SGD27 million annually. This figure represents only 0.1% of the nation's total health expenditure today, but it is likely to rise dramatically in the future given the ageing population and rising rate of CI.[27] While several cost-of-illness studies have been published for CI,[28-33] only 2 studies, both from the US, focused on its impact on healthcare utilisation at the end-of-life.[7,8] Our findings are largely consistent with results from these studies.

The higher cost among those with CI resulted because these individuals utilised more ED and inpatient services, most of which were unplanned. As hypothesised, those most at risk of dying had the greatest difference. This may result from CI complicating treatment for other health conditions such as end-stage renal disease and cancer, which require good ambulatory care management and high patient adherence. Among the subset with lower mortality risk, those with CI had fewer planned admissions, shorter associated stays, and significantly lower costs. This could be due to efforts on the part of caregivers and providers to avoid costly and invasive discretionary treatments for those with CI. When mortality risk was higher, utilisation patterns did not appear to differ by CI status, perhaps because treatment is less discretionary in these circumstances.

During the last year of life, we found that older adults with CI had fewer outpatient visits and planned admissions but total cost appeared similar between those with and without CI. The similarity in costs is possibly because of the high and variable costs associated with dying, which makes it difficult to tease out costs specifically related to CI.

Our results show that the bulk of the CI burden is from ED visits and unplanned admissions. Common causes for ED visits among those with CI include pneumonia, heart failure, urinary tract infection and fall-related injuries.[34] Future research should investigate the extent to which such cases can be avoided or diverted to lower-cost outpatient and community care settings, and whether strategies to do so are cost-effective.

We also found evidence of lower expenditures on planned hospitalisations among those with lower risk of dying, suggesting that doctors or surrogate decision-makers may be less inclined to pursue costly elective treatment for patients with CI. A better understanding of treatment choices and their consequences for patients with CI should be an area of future research.

This study has several limitations. First, our estimates are limited to medical costs. They do not include the cost of private primary care clinics, nursing homes, other non-institutional care (e.g.

Table 4. Expected 5-year total healthcare cost (2021, SGD).

Cognitive status	No CI	CI	Incremental cost
Starting age			
65	15,200 (14,400 to 16,000)	17,800 (16,000 to 19,600)	2500 (1000 to 4200)
70	18,400 (17,600 to 19,200)	21,400 (19,600 to 23,300)	3000 (1200 to 5000)
75	21,600 (20,700 to 22,700)	25,000 (23,100 to 27,000)	3400 (1300 to 5600)
80	25,000 (23,600 to 26,700)	28,500 (26,500 to 30,900)	3600 (1300 to 6000)
85	27,400 (25,400 to 29,900)	30,800 (28,000 to 33,700)	3400 (1000 to 6000)
90	28,700 (25,800 to 32,100)	31,300 (28,400 to 34,800)	2700 (200 to 5200)

CI: cognitive impairment.
The 95% confidence intervals are based on 2000 bootstrap replications, reported in parentheses. Costs beyond the first year were discounted at the rate of 3%.

day care, home care), and large indirect costs associated with informal caregiving.[35,36] Second, estimates were based on the Chinese population in Singapore only, so results may not generalise to the roughly 25% of the population who is not Chinese.[37-39] Third, CI status was measured only once at the start of the study. Our analysis assumed those who are cognitively intact remain so until the end of the analysis period. This attenuates the burden of CI because a proportion of those who were cognitively intact during the survey may later become impaired, thus increasing costs. Restricting our ex ante mortality risk analysis to within a year of the survey reduced this bias, but this approach was not feasible for the analysis of the last year of life due to too few deaths. Nevertheless, we argue that this bias is likely small given the short follow-up period. Another potential source of bias is that costly chronic conditions (e.g. cancer) may have a higher likelihood of being under-reported or unobserved by individuals with CI, resulting in overestimating the CI burden. However, it is not clear whether the lower prevalence observed in our sample is due to misreporting or undiagnosed cases due to a lack of health screening.

CONCLUSION

The anticipated increase in burden associated with CI is a concern for many countries with an ageing population. We show that this concern is valid but partly attenuated by greater mortality risk and less use of planned healthcare services. Regardless, ageing populations and higher rates of CI will further strain healthcare resources. Efforts should be made to identify the most at-risk patients with CI, including which components of CI (e.g. behavioural/psychological issues, physical/functional decline) have the largest impact, and take appropriate remediation strategies.

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REVIEW ARTICLE

2023 clinical practice guidelines on autism spectrum disorder in children and adolescents in Singapore

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ABSTRACT

Introduction: Autism is a neurodevelopmental condition that is increasing in prevalence worldwide. There has been an exponential increase in autism-related research since 2010, when the first Singapore Clinical Practice Guidelines (CPG) on autism was published. Understanding of autism has since evolved to adopt a lifespan approach beyond that of a childhood condition. The aim of this CPG was to provide an updated set of recommendations for children and adolescents to aid clinical practice for professionals.

Method: A multidisciplinary workgroup that comprised representatives from various sectors worked on this CPG. Clinical questions were organised into 10 different sections, each with its own subgroup of members. Seventeen existing international guidelines were evaluated using the Appraisal of Guidelines for REsearch & Evaluation II (AGREE-II) framework, of which 4 met criteria to act as references. Literature review across multiple databases was conducted between January 2011 to 2023; Grading of Recommendations, Assessment, Development and Evaluation (GRADE-like) methodology was used to synthesise evidence. Recommendation statements were derived, following Delphi-style consensus surveys among the workgroup. The draft guidelines underwent external review and public consultation before being formalised.

Results: Recommendation and good practice statements pertaining to care of children and adolescents on the autism spectrum across 10 different sections were developed. Evidence matrices complement these recommendations and detail relevant evidence behind each recommendation statement.

Conclusion: It is intended for these guidelines to promote effective management and healthcare services for children and adolescents on the autism spectrum, by reinforcing good and evidence-based clinical practice within our national context.

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Keywords: autism, autistic disorder, child, clinical guidelines, GRADE, recommendations, consensus

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CLINICAL IMPACT

What is New

- These updated clinical practice guidelines now cover an expanded age-range of children and adolescents on the autism spectrum.
- As such, there are new sections on "Education and Transition", "Co-occurring Conditions in Autism" and "Follow-up and Prognosis" as compared to the previous 2010 edition.

Clinical Implications

- The guidelines use rigorous methodology to provide professionals with evidence-based recommendations on various aspects related to autism, taking into consideration local context and cost-effectiveness, leading to locally-relevant clinical applicability.

INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental condition that presents as differences in social communication and social interaction, together with restricted, repetitive behaviours.[1] These social communication and interaction differences, as well as restricted, repetitive behaviours, are also referred to as the "core symptoms" of autism. The first edition of the Academy of Medicine, Singapore-Ministry of Health (AMS-MOH) Clinical Practice Guidelines (CPG) on ASD in Pre-school Children was published in 2010.[2] Since then, research within the field of autism increased exponentially, giving rise to a need for updated guidelines that cover a wider age range of children. Apart from new and expanded sections including "Co-occurring Conditions in Autism", "Education and Transition", "Follow-up and Prognosis" and "Professional Training", the 2023 CPG also takes significant steps in framing autism within the concept of neurodiversity, and using neurodiversity-affirming language wherever possible. The guidelines do not seek to cure autism but to improve care and services for the autistic community.

The prevalence of autism in Singapore is estimated to be 1 in 150 of the population,[3] but some countries report a prevalence as high as 1 in 36.[4] The support needs and prognosis are variable between individuals, whose needs also evolve across the lifespan. There are also significant long-term demands placed on many caregivers.[5] The majority of individuals are diagnosed in childhood, hence the importance of having clear evidence-based guidelines focusing on this age group.

Objectives and scope

The primary objectives of the guidelines are to:

(1) Promote effective healthcare for children and adolescents on the autism spectrum, by reinforcing good and evidence-based clinical practice, as well as to facilitate changes in professional practice that may not be consistent with current best practice.
(2) Evaluate and promote evidence-based practices within the local Singapore context.

The guidelines are written to assist professionals who are involved in the surveillance, screening, diagnosis, intervention and long-term management of children and adolescents on the autism spectrum; as well as for caregivers. The subterms "healthcare professionals" and "educational professionals" are used where these may be distinct, while "professionals" encompass both groups. Intervention and management of any autistic child should be individualised depending on specific needs, with input from experienced professionals who have sound knowledge of guideline recommendations.

Target population

The target population covered by these guidelines includes children from infancy to adolescence who have autism of any severity. Where appropriate, special groups have been given special attention, such as girls on the autism spectrum, racial or cultural differences, or socially-disadvantaged families.

METHOD

The 22-member core workgroup and 15 subgroup members comprised developmental paediatricians, psychiatrists, a primary care physician, allied health professionals (psychologists, speech and occupational therapists, and a social worker), educators, early interventionists, and most importantly, caregivers of children on the autism spectrum. The workgroup members represented public and private healthcare sectors, the educational sector, and various social service agencies.

Existing local publications were reviewed to identify service gaps, such as the "Autism Enabling Masterplan" by the Autism Network Singapore,[6] and "Understanding the Quality of Life of Children and Youth" study by the National Council for Social Services.[7] Seventeen international guidelines on autism were independently reviewed and rated using the Appraisal of Guidelines for REsearch & Evaluation II (AGREE-II) Instrument,[8]

using a staged appraisal approach with a focus on domain 3 to achieve >70% as a priority, and >50% for domains 1, 2, 4 and 6 as secondary requirements. Only 4 existing guidelines were of sufficiently high quality for use as references.[9-12]

Key Population, Intervention, Comparator, Outcome (PICO) clinical questions were developed and search strategies using key words from these were run in the following electronic databases: CINAHL, Cochrane, Embase, Medline, PsycINFO, Proquest, PubMed, ScienceDirect, Scopus, Web of Science, as well as grey literature databases (e.g. Google Scholar, Proquest, ClinicalTrials.gov, conference abstracts). The search period was restricted to January 2011 to June 2023. Systematic reviews, meta-analyses, interventional and observational studies were evaluated using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology,[13] taking into account certainty and magnitude of effects, risk-benefit balance, cost-effectiveness, feasibility, stakeholder acceptability, and the context of prevailing legal and national policies in Singapore. Key recommendation (R) or good practice point (GPP) statements were then derived from the evidence collated into an evidence matrix (EM). Evidence that was not amenable to GRADE evaluation resulted in GPP instead of R statements, but both R and GPP statements hold similar importance in terms of implementation. All statements underwent workgroup-wide consensus rating on a scale of 1 (strongly disagree) to 9 (strongly agree), using the RAND/UCLA Appropriateness Method to calculate a median score, Interpercentile Range Adjusted for Symmetry score, and a disagreement index.[14] Statements that reflected disagreement or any consensus rating under 5 were revised and put through further rounds of consensus survey voting until group consensus was obtained.

The final draft of the guidelines was reviewed by a panel of 6 independent external local and international reviewers, which included autistic individuals and their caregivers, and was also published on the College of Paediatrics and Child Health, Singapore website for a month for a public consultation exercise. Comments from the reviewers and public consultation were taken into account in the formation of the final recommendations.

A new scoping review has been planned for 2028.

KEY RECOMMENDATIONS

The full "Main Guideline Document", together with the complete list of references, the "Executive Summary of Recommendations", "Lay Version", and "Supplement 1 (Evidence Matrices)" and "Supplement 2 (Public Consultation and External Reviews)" are available on the Academy of Medicine, Singapore website (https://www.ams.edu.sg/latest-news/2023-guidelines-on-autism-spectrum-disorder-in-children-and-adolescents).

Surveillance, screening and diagnosis

As in the 2010 CPG, early identification of autism (GPP1.1) via an ongoing national developmental surveillance programme (GPP1.2) remains key.[15] Effective developmental surveillance should take place over sequential and repeated visits as a child grows[16] (GPP1.3). Early signs of autism may not always be evident in very young children, or stereotypical behaviours may only become apparent at a later age. Apart from developmental surveillance being conducted during well-child visits with healthcare professionals (GPP1.4), preschool teachers' concerns about a child's communication, social interaction, play and behaviour should also be elicited in preschool developmental surveillance programmes (GPP1.5), and early specialist referrals initiated if concerns are noted (GPP1.6). Early signs of autism are listed in Table 1 and highlighted in GPP1.7. Additionally, professionals should remain vigilant for possible autism in any child or adolescent with ongoing difficulties relating to communication, social interaction, behaviour or mental health (GPP1.8).

Developmental screening refers to the use of brief, validated and standardised screening tools to identify children who might require a comprehensive evaluation for developmental delays/disorders.[16] Level I screening is conducted with the general population (i.e. an unselected group), while Level II screening is conducted with selected populations with a higher likelihood of autism, such as younger siblings of autistic children.[17] Commonly used screening tools include the Modified Checklist for Autism in Toddlers, Revised with Follow-up (M-CHAT-R/F). While the universal use of autism-specific screening tools in the general paediatric population is not currently recommended (R1.10), targeted screening may be considered for children with factors associated with an increased likelihood for developing autism (GPP1.9). These include the following:

- History of autism in a sibling
- Prematurity of <35 weeks' gestation or birth weight <2500 g
- History of neonatal hypoxic encephalopathy
- Having a genetic syndrome associated with autism
- Intrauterine exposure to maternal anti-epileptic medication

Table 1. Early signs of autism.

The early signs of autism include the following:

At 12 months of age:

- Little or no eye contact
- Lack of social smiling or shared excitement with a glance or smile
- Lack of babbling
- Little or no use of waving bye, reaching for hugs, pointing to needs or holding up objects to show them to someone
- Little or no response to name being called.

At 18 months of age—all the above and including:

- No single words (e.g. mama, papa, bye-bye, etc.)
- Lack of imitation of actions (e.g. nursery rhyme actions) or words (e.g. trying to say a word when taught)
- Lack of interest in other children.

At any age:

- Avoidance of or difficulty maintaining eye contact
- Poor response to name being called
- Loss of previously acquired speech, babbling or social skills (regression)
- Preference to be alone or play alone, or difficulty making friends
- Difficulty in sharing interests or enjoyment with others
- Difficulty in understanding other people's feelings or reading their facial expressions
- Delayed speech and language development
- Repetitive language, echolalia (often repeating words or phrases when not meant to), excessive talking "at" others, or unusual prosody of speech (monotonous or accented)
- Repetitive play, behaviours or body movements
- Difficulties in adapting to changes in routines or environment
- Obsessions or extreme fixations on certain objects or topics
- Unusual reactions to the 5 senses (e.g. oversensitivity to sounds, tendency to stare closely at spinning things, tendency to sniff objects, etc.).

- Advanced parental age at child's birth (>40 years of age)
- Parental history of mental health condition.

The application of an autism-specific screening tool can supplement the clinical judgement of healthcare professionals but should not be used as the sole reason to initiate specialist referral or to exclude a diagnosis of autism (R1.11). Professionals who decide to implement the use of an autism screening tool should be aware of the psychometric properties (e.g. false positives, false negatives) and limitations of the tool, and variability in accuracy across different cultures and contexts (GPP1.12). They should also use these tools within the validated age range (R1.13). Neurophysiological or other biomarkers are not yet sufficiently developed to be accurate or reliable screening tools for autism (GPP1.14).

Professionals involved in diagnosing autism in children and adolescents should use the current version of either the Diagnostic and Statistical Manual of Mental Disorders (DSM)[1] or International Classification of Diseases[18] (GPP1.15), and be aware that some children may not meet diagnostic criteria on the DSM-5-TR (5th edition, text revision; Table 2) when they would have done so on the DSM-IV-TR (4th edition, text revision). Some of these children may meet a diagnosis of social communication disorder (Table 3) instead, and may still need interventions similar to those on the autism spectrum (GPP1.16).

Children being evaluated for autism should have a medical examination to facilitate a comprehensive evaluation (GPP1.17), and a multidisciplinary approach to diagnosis is recommended whenever possible (GPP1.18). However, a single-clinician approach to diagnosing autism may be considered when the following conditions are met (GPP1.19):

- Conducted by specialist medical practitioners or psychologists with adequate training and experience in diagnosing autism in children and adolescents (Table 4).
- Include multisource feedback from various settings in order to obtain a comprehensive profile of the child/adolescent being assessed.
- Include direct observation and interaction with the child/adolescent being assessed.
- Include thorough contemporaneous documentation on the child/adolescent's symptoms of autism that meet the prevailing international diagnostic criteria for autism (e.g. DSM-5-TR)

Assessment and diagnosis of autism should not solely rely on autism-specific diagnostic instruments (e.g. Autism Diagnostic Observation Schedule), but should encompass a holistic profile of the child/adolescent including developmental, medical and social history; physical examination; consideration of differential diagnoses and co-existing conditions; cognitive, sensory, academic and adaptive behaviour profiles, as well as strengths, skills and needs to

Table 2. DSM-5-TR criteria for autism spectrum disorder (terminology as per DSM-5 publication).

To meet diagnostic criteria for autism spectrum disorder, a child must have persistent deficits in each of 3 areas of social communication and interaction (see A1 through A3 below) plus at least 2 of 4 types of restricted, repetitive behaviours (see B1 through B4 below):

A. Persistent deficits in social communication and social interaction across multiple contexts, as manifested by all of the following, currently or by history:
   1. Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions or affect; to failure to initiate or respond to social interactions.
   2. Deficits in nonverbal communicative behaviours used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication.
   3. Deficits in developing, maintaining and understanding relationships, ranging, for example, from difficulties adjusting behaviour to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.

B. Restricted, repetitive patterns of behaviour, interests or activities, as manifested by at least 2 of the following, currently or by history:
   1. Stereotyped or repetitive motor movements, use of objects, or speech (e.g. simple motor stereotypies, lining up toys or flipping objects, echolalia, idiosyncratic phrases).
   2. Insistence on sameness, inflexible adherence to routines, or ritualised patterns of verbal or nonverbal behaviour (e.g. extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat same food every day).
   3. Highly restricted, fixated interests that are abnormal in intensity or focus (e.g. strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interests).
   4. Hyper- or hyporeactivity to sensory input or unusual interest in sensory aspects of the environment (e.g. apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement).

Specify current severity:
Severity is based on social communication impairments and restricted, repetitive patterns of behaviour. For either criterion, severity is described in 3 levels: Level 3 – Requires very substantial support, Level 2 – Requires substantial support, and Level 1 – Requires support.

C. Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life).
D. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.
E. These disturbances are not better explained by intellectual disability (ID) or global developmental delay. ID and autism spectrum disorder frequently co-occur; to make comorbid diagnoses of autism spectrum disorder and ID, social communication should be below that expected for general developmental level.

Specify if:
- With or without accompanying intellectual impairment
- With or without accompanying language impairment
- Associated with a known medical or genetic condition or environmental factor
- Associated with another neurodevelopmental, mental, or behavioural disorder
- With catatonia

Note: Individuals with a well-established DSM-IV diagnosis of autistic disorder, Asperger syndrome, or PDD-NOS should be given the diagnosis of autism spectrum disorder.

PDD-NOS: pervasive developmental disorder not otherwise specified

Table 3. DSM-5-TR criteria for social communication disorder (terminology as per DSM-5 publication).

A. Persistent difficulties in the social use of verbal and nonverbal communication as manifested by all of the following:
   1. Deficits in using communication for social purposes, such as greeting and sharing information, in a manner that is appropriate for the social context.
   2. Impairment of the ability to change communication to match context or the needs of the listener, such as speaking differently in a classroom than on the playground, talking differently to a child than an adult and avoiding use of overly formal language.
   3. Difficulties following rules for conversation and storytelling, such as taking turns in conversation, rephrasing when misunderstood and knowing how to use verbal and nonverbal signals to regulate interaction.
   4. Difficulties in understanding what is not explicitly stated (e.g. making inferences). A non-literal or ambiguous means of language—for example, idioms, humour, metaphors and multiple meanings, which depend upon the context for the interpretation.

B. The deficits result in functional limitations in effective communication, social participation, social relationships, academic achievement or occupational performance, individually or in combination.

C. The onset of the symptoms is in the early developmental period, but the deficits may not become fully manifest until social communication demands exceed limited capacity.

D. The symptoms are not attributable to another medical or neurological condition, or to low abilities in the domains of word structure and grammar and are not better explained by autism spectrum disorder, intellectual disability, global developmental delay or another mental disorder.

Table 4. Criteria for specialist medical practitioners or psychologists with adequate training and experience in diagnosing autism in children and adolescents.

Criteria (both 1 and 2 need to be met)	
Professional qualification	Medical practitioners Specialist registration with the Singapore Medical Council in paediatrics, psychiatry or neurology *Or* Psychologists Registered or eligible to be registered with Singapore Register of Psychologists (SRP) *and* holding a master or doctorate degree in clinical/neurological/educational psychology that has a practicum component.
Clinical experience in autism diagnosis	The professional should have at least 3 years of experience working in a multidisciplinary team that conducts autism diagnostic assessments in order to have an understanding of the wide variation in presentation across the spectrum and of the normal variance in child development; how gender, cognitive ability and other medical/genetic factors may affect presentation; and have adequate decision-making abilities to know when to refer a child on for multidisciplinary team diagnoses instead. Having attended formal training on a validated autism-specific diagnostic tool would also be beneficial, as well as knowing when and how to use the tool appropriately.

facilitate management plans (R1.20). Information gathered to make a diagnosis should include reports on or observations of the child in various settings (GPP1.21), and professionals should consider that gender, cultural differences, and intellectual disability can affect presenting features (GPP 1.22–1.24).

Aetiology and investigations

As there is strong genetic heritability for autism, professionals should closely monitor children with first-degree relatives on the autism spectrum (GPP2.1), and be aware that some genetic conditions (e.g. Fragile X syndrome, Angelman syndrome, Tuberous sclerosis, Rett syndrome, PTEN Hamartoma tumour syndrome and Down syndrome) may be associated with autism (GPP2.2).[19] Such children should be referred to a genetic specialist for diagnostic assessment and counselling (GPP2.10), and discussion on the appropriate test/s to be ordered (GPP2.11).[20] The use of some anti-epileptic medication (especially sodium valproate) during pregnancy is associated with an increased probability of the child developing autism, and healthcare professionals should discuss the indications and side-effects of various anti-epileptic medications with pregnant women when required (GPP2.4).[21] However, the use of paracetamol and epidural analgesia during pregnancy and labour does not need to be avoided (GPP2.3, 2.5). There is insufficient evidence of an association between autism and maternal anti-depressant use in pregnancy. Parents should be reassured that childhood vaccinations are not associated with autism, and should proceed with their child's vaccination schedule as recommended on the National Childhood Immunisation Schedule.[22] Healthcare professionals should continue to provide nationally recommended childhood vaccinations to autistic children, including the MMR (measles-mumps-rubella) vaccine (GPP2.6).

Investigations such as heavy metal concentration testing, magnetic resonance imaging of the brain, electroencephalography, and inborn error of metabolism screening are not routinely recommended, except for selected children who present with specific clinical features (GPP2.7–2.8, 2.12–2.14), or pica (GPP2.9). Routine stool investigations for yeast or microbiota profile are also not recommended (GPP2.15).

Intervention

The objectives of intervention in autism are to promote child health and well-being, enhance emerging competencies, minimise developmental delay, remediate disabilities, prevent functional deterioration, and promote adaptive parenting and overall family functioning. It is crucial to formulate an individualised plan with input from a variety of specialists, in response to the changing needs of the autistic child/adolescent across the developmental phases. Monitoring of response to any intervention is also a core element and responsibility in all clinical practice.

Evidence-based interventions for autism currently include augmentative and alternative communication (e.g. Picture Exchange Communication System),[23] cognitive behavioural therapy (CBT),[24] communication-based interventions (e.g. language training),[25] developmental interventions (e.g. Developmental Individual-Difference Relationship-Based model [DIR]/Floortime),[26] early intensive behavioural intervention (i.e. comprehensive Applied Behaviour Analysis intervention),[27] emotion regulation therapy (ERT), naturalistic developmental behavioural interventions (e.g. Early Start Denver Model, pivotal response training),[28] play-based intervention,[29] sensory

integration therapy,[30] sensory environmental modifications and sensory modulation strategies, social skills intervention[31] and visual supports (R3.1–3.10, 3.12, 3.13). Weighted vests, however, are not recommended (R3.11). The evidence-based interventions largely aim to support and improve social communication skills, joint attention, social participation and play skills, and the acquisition of skills pertaining to self-care/adaptive abilities and daily routines in autistic individuals. Some intervention approaches, like CBT and ERT, more specifically target emotion-related issues, such as anxiety and anger.

Pharmacological treatment

Pharmacological treatment of any co-occurring conditions in autistic children/adolescents should only be undertaken by physicians with appropriate specialist training in the use of such medication. Physicians who prescribe more than one medication should be vigilant about the possibility of drug interactions, and monitor for clinical response and possible side effects. Response to medications may also be different for autistic children/adolescents. While pharmacological agents may be used for specific indications, psychological, behavioural and environmental strategies should continue to be used in conjunction with pharmacotherapy.

Currently, no pharmacological agent has sufficient evidence to justify use for improving the core symptoms of autism (R4.13–4.30). Ongoing research results are awaited for oxytocin and bumetanide. Some specific indications for use of pharmacological agents are presented below.

Attention-deficit hyperactivity disorder (ADHD). Methylphenidate should be the first-line medication, and be used in conjunction with non-pharmacological approaches (R4.1).[32] Atomoxetine may be considered if methylphenidate has been tried unsuccessfully or is contraindicated/not tolerated (R4.2).[33] Guanfacine may be considered as a third-line agent (R4.3).[34]

Challenging behaviours and psychiatric conditions. Risperidone and aripiprazole can be used for challenging behaviours (irritability and hyperactivity) in the short term, but can cause weight gain and somnolence (R4.4).[35] Other medications such as selective serotonin re-uptake inhibitors, tricyclic antidepressants, anticonvulsants, mood stabilisers and mirtazapine may be used for specific co-occurring mental health disorders, such as anxiety, depression or obsessive-compulsive disorder (R4.5–4.8).

Sleep. Melatonin can be considered for sleep issues if there is no benefit from a psychosocial intervention.[36] It should be used in conjunction with a psychosocial intervention and in consultation with a specialist trained in assessing and managing sleep issues in autistic children/adolescents (R4.12).

Education and transition

Healthcare and educational professionals should adopt an individualised assessment approach, which takes into account a child's cognitive abilities, achievement skills, adaptive functioning, behavioural skills and socio-emotional competencies, when determining an appropriate educational placement and planning educational supports needed by autistic children across mainstream and Special Education (SPED) school settings.[37] For some children on the autism spectrum, the national curriculum and in-class support could be appropriate, whereas others may require significant curriculum customisation and instructional adaptations, which are offered in a SPED school setting.

The recommendation statements for education and transition highlight the importance of an inter-agency collaborative approach and caregiver/child involvement in deciding on educational placement options for autistic children, as well as for anticipating and planning ahead for key transition periods, such as from preschool to formal school settings, and then on to post-school pathways (i.e. employment support) (GPP5.1–5.19). Alignment with the Ministry of Education's professional practice guidelines[37,38] and its Comprehensive Needs Assessment report for transition support are also recommended.

Complementary and alternative treatment

Complementary and alternative treatment or medicine (CAM) use is common among autistic children/adolescents although there is limited evidence for benefit for the majority of CAM. Given this and the potential for harm of some CAM treatments, professionals should be prepared to discuss the evidence for each CAM with caregivers (GPP6.1). If there is parental preference to use a specific CAM, shared decision-making between professionals and parents is strongly encouraged, such that treatment trials are time-based with clear objectives and outcome measures (GPP6.1). CAM treatments should not replace mainstream interventions, and implications on financial resources should also be considered.

The CAM therapies considered in these guidelines were evaluated in terms of evidence pertaining to benefits on the core symptoms of autism as well as the potential for harm. The recommendations are phrased such that CAM interventions that demonstrate no evidence of

Table 5. Summary of recommendations on complementary and alternative medicine.

Type of recommendation	Complementary and Alternative Medicine (CAM)
CAM that should NOT be used in the treatment of children and adolescents on the autism spectrum	Antimicrobial therapy Aromatherapy Chelation therapy Chiropractic, osteopathy and craniosacral therapy Facilitated communication Helminth therapy Hyperbaric oxygen therapy Immunoglobulin therapy Microbial transfer therapy Stem cell therapy Vagal nerve stimulation
CAM that is not recommended as treatment for core symptoms of autism in children and adolescents	Acupuncture Amino acid supplementation Animal-assisted interventions Art therapy Auditory integration therapy Camel milk Coenzyme Q10 Dance movement therapy Digestive enzymes Folinic acid Gluten-free casein-free (GFCF) diet Ketogenic diet Mesalazine Mindfulness intervention Minerals including zinc, magnesium and iron Neurofeedback Omega-3 fatty acids Probiotics Qigong massage or other types of massage Secretin Sulforaphane Transcranial direct current stimulation Vitamins including B12 and B6
CAM that may be considered in children and adolescents on the autism spectrum	Music therapy Visual motor exercises

treatment benefit and/or significant potential for harm "should not be used", while those with insufficient evidence of treatment benefit with no/low potential for harm are "not recommended". A summary of these recommendations is shown in Table 5; while detailed references for each CAM is available in the published guidelines.

CAM therapies that should not *be used* in the treatment of autism include antimicrobial therapy (including antibiotics and antifungal agents), aromatherapy, chelation therapy, chiropractic, osteopathy and craniosacral therapy, facilitated communication, helminth therapy, hyperbaric oxygen therapy, immunoglobulin therapy, microbial transfer therapy, stem cell therapy and vagal nerve stimulation (R6.18–6.20, 6.22–6.25, 6.27, 6.34, 6.37, 6.41).

CAM therapies that are not recommended as treatment for core symptoms of autism include acupuncture, amino acid supplementation, animal-assisted interventions, art therapy, auditory integration therapy, camel milk, coenzyme Q10, dance movement therapy, digestive enzymes, folinic acid, gluten-free casein-free (GFCF) diet, ketogenic diet, mesalazine, mindfulness intervention, minerals including zinc, magnesium and iron, neurofeedback, omega-3 fatty acids, probiotics, qigong massage or other types of massage, secretin, sulforaphane, transcranial direct current stimulation and vitamins including B12 and B6 (R6.2, 6.4–6.6, 6.8–6.17, 6.21, 6.26, 6.28, 6.29, 6.31, 6.32, 6.35, 6.36, 6.39, 6.40).

While vision therapy is not recommended as treatment for core symptoms of autism, visual motor exercises may be considered for selected children who have visual difficulties. There is emerging evidence that such exercises have the potential to improve social communication and reduce repetitive behaviours in these children[39] (R6.33). Similarly, music therapy may be recommended as a complementary intervention approach due to evidence for an increase in global improvement, improved quality of life and reduced total autism severity following its use[40] (R6.30).

Guiding principles in the use of CAM also include the recommendation that a healthy diet of a

variety of fresh foods is recommended in all autistic children/adolescents, similar to the general population. Healthcare professionals should be equipped with information on recommended daily allowances of nutritional supplements and be able to discuss with caregivers the possible benefits and harms of the various supplements and dosages. Intake of vitamins, minerals and probiotics in the form of natural fresh food should be encouraged (GPP6.3). Those who exhibit symptoms suggestive of a vitamin, mineral or amino acid deficiency should be evaluated and treated following appropriate clinical guidelines similar to the general population (R6.7). Finally, autistic children/adolescents are recommended to engage in a variety of physical activities, at age-appropriate intensity and frequency, as per standard guidelines pertaining to physical activity in children (R6.38).

Co-occurring conditions

Co-occurring conditions are common in autism and should be considered when symptoms and signs of conditions are present, independent from the core features of autism.[41] These conditions can be classified into neurodevelopmental conditions, medical conditions and mental health conditions (Table 6). Challenges in recognising co-occurring conditions include atypical presentations different from the general population, and diagnostic overshadowing with over-attribution of symptoms to autism alone.[41] Such conditions can have negative effects on the overall functioning of the child/adolescent, as well as on the individual and their family's quality of life. It is thus important that autistic children/adolescents be followed up serially at spaced intervals in a holistic manner to identify symptoms of co-occurring conditions, if any (GPP7.1).

Neurodevelopmental conditions that are known to be associated with autism include learning difficulties, impaired adaptive function, ADHD, developmental coordination disorder, language disorder, intellectual disability and sensory processing difficulties.[42,43] Professionals should be aware of the increased likelihood of these conditions and initiate appropriate specialist referrals and/or management in the presence of related symptoms (R7.2–7.6, 7.8). Children who have global developmental delay (GDD) should be evaluated towards the end of the child's preschool period for the presence of intellectual disability as the diagnosis of GDD should not be used when the child is past 5 years of age (R7.7).

Mental health conditions including anxiety, depression, obsessive compulsive disorder and bipolar disorders are common in individuals on the autism spectrum.[44] Hence, professionals should have a high index of suspicion for the presence of such conditions and refer those with clinical symptoms to appropriate specialist services for further evaluation (R7.9). Likewise, given the association between gender variance and autism, those who present with gender variance issues (where gender variance is an umbrella term used to describe gender identity, expression or behaviour that falls outside of culturally-defined norms associated with a specific gender) may need further referral for evaluation and support for their social-emotional needs (GPP7.10).[45]

Table 6. Summary of co-occurring conditions in autism.

Category	Condition
Neurodevelopmental conditions	Attention-deficit hyperactivity disorder Developmental coordination disorder Impaired adaptive function Intellectual disability Language disorder/impairment Learning difficulties Sensory processing difficulties
Mental health conditions	Anxiety disorder Bipolar disorder Depressive disorder Eating disorder Gender variance and dysphoria Obsessive compulsive disorder Oppositional defiant disorder Schizophrenia Tourette syndrome and tic disorder
Medical conditions	Dental disorders Epilepsy Feeding challenges Gastrointestinal disorders Genetic disorders Hearing impairment Obesity Puberty-related conditions Sleep disorders Visual challenges

Several medical conditions are known to occur more commonly in autistic children/adolescents.[46] These include feeding-related challenges, gastrointestinal disorders (e.g. constipation, reflux disease), hearing impairment, genetic conditions, epilepsy and visual impairment (R7.11, R7.13, R7.16, GPP2.10, GPP2.13, GPP7.12, GPP7.15, GPP7.20). Gastrointestinal disorders such as constipation may have atypical presentations, hence evaluation for the presence of a gastrointestinal disorder should be considered in those who present with unexplained, persistent or sudden-onset atypical behavioural symptoms (such as head banging or increased stimulatory behaviours)[47] (GPP7.14). Conditions including sleep disorders, obesity, dental conditions (e.g. oral cavities) and precocious puberty (in girls) also occur more commonly in autistic children/adolescents and should be

assessed during follow-up and acted on as clinically indicated (R7.18, GPP7.17, GPP7.19, GPP7.21).

Follow-up and prognosis

Long-term prognosis in autism has been associated with the presence of intellectual disability, childhood language development and severity of features of autism.[48] In addition to these, positive parenting practices, age-appropriate adaptive skills and greater opportunities for inclusion have all been positively associated with better prognosis. Hence, among autistic children/adolescents, interventions that promote positive parenting, mothering and fathering, including parent training on responding to behaviours of concern should be encouraged (GPP8.1).[50] The focus of intervention should address the holistic needs of these individuals across the entire lifespan—i.e. adaptive functioning and emotional well-being, in addition to academic achievement; and the goals of the child/adolescent and their family should also be considered (GPP8.2). Systematic transition planning that is proactive, holistic and person-centric should be encouraged for predictable major transitions, including graduation from formal schooling (GPP8.3).

Caregiver and family support

Professionals should recognise the potential impact of autism on the social, economic, physical and mental health of caregivers and adopt a collaborative and family-centred approach to support them (GPP9.1, GPP9.3). This will facilitate the provision of age- and needs-appropriate information and also support caregivers including siblings in accessing appropriate services for the child/adolescent as well as for themselves (GPP9.2). Professionals should assess caregivers' emotional well-being and provide further support as appropriate as mental health conditions (e.g. anxiety) are common in this group (GPP9.4).[50] Caregivers will require information and support across the individual's lifespan and transition points, including onset of adolescence/puberty, across educational settings and into post formal-schooling transitions (GPP9.5).[51] Caregiver education/training programmes should be incorporated within intervention programmes whenever possible, as these can improve parent-child interaction and may translate to positive child/adolescent outcomes (GPP9.6).[52]

Professional training

Any professional who works with autistic children/adolescents (including support staff within healthcare and educational settings) should be provided with access to information on autism, which can be varied in forms of delivery, depth and context and use neurodiversity-affirming language (GPP10.1). Lack of knowledge related to autism has been frequently cited as a barrier in providing optimal care and such tailored information with resources to facilitate further self-directed learning can help to address this.[53]

Implementation of guidelines

These guidelines have been disseminated widely to stakeholders across various sectors within Singapore, through formats including a formal launch at a major national paediatric conference, a symposium attended by professionals across healthcare, community care and educational settings, and email distribution. The guidelines and all related materials have also been made freely available online. A lay version of the guidelines designed for caregivers has been distributed to various agencies that serve caregivers of children and adolescents.

Potential facilitators and barriers to implementation

Strengths of these guidelines include the specific consideration given to the local context including the availability of interventions and resources, cost-effectiveness, cultural acceptability and local healthcare/educational systems. The multidisciplinary workgroup allowed for recommendations to be considered from multiple perspectives and applied across disciplines and sectors. The intentional incorporation of views of caregivers of individuals on the autism spectrum, expert reviews and public consultation have also strengthened these guidelines.

However, implementation of the recommendations in these guidelines would be under the purview of each relevant organisation (e.g. healthcare, educational or community intervention agency) and resource limitations (e.g. manpower or financial resources) may be a barrier to implementation. Such resource limitations may be applicable for varying sections of the guidelines, for example, manpower necessary for recommended transition support and financial resources for intervention provision. It is expected that the majority of the recommendations are in keeping with current practices, however, where differences in practice are present, the reason for these should be reviewed and addressed where possible.

CONCLUSION

As our understanding of autism continues to evolve, adoption of a lifespan approach to autism, beyond solely a childhood perspective is crucial. Care for children and adolescents on the autism spectrum

should be based on evidence-based practices and conducted in a holistic manner, placing the well-being of the individual and their family as the primary focus. These guidelines provide a comprehensive set of recommendations spanning several aspects of care to facilitate effective care for these children and adolescents based on good evidence-based principles.

Conflicts of interest

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

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REVIEW ARTICLE

Challenges in genetic screening for inherited endocrinopathy affecting the thyroid, parathyroid and adrenal glands in Singapore

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ABSTRACT

Significant progress has been made in the understanding of many human diseases, especially cancers, which has contributed to improved and increased survival. The Human Genome Project and The Cancer Genome Atlas project brought about a new era, with an understanding of inherited diseases at a molecular level, which subsequently facilitated the option of precision medicine. Precision medicine has helped tailor treatment decisions at an individual level, for instance in terms of surgical treatments or targeted therapies in advanced diseases. Despite the increasing advances in genetic-lead precision medicine, this has not translated into increasing uptake among patients. Reasons for this may be potential knowledge gaps among clinicians; on reasons for poor uptake of genetic testing such as for cultural, religious or personal beliefs; and on financial implications such as lack of support from insurance companies. In this review, we look at the current scenario of genetic screening for common inherited endocrine conditions affecting the thyroid, parathyroid and adrenal glands in Singapore, and the implications associated with it.

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Keywords: endocrine, endocrinology, endocrinopathy, general surgery, genetic, oncology, quality of life, syndromes

CLINICAL IMPACT

What is New

- Inherited endocrinopathies are usually suspected with the presentation of classic phenotypes and should be confirmed with genetic testing where feasible.
- Genetic screening has made precision medicine possible in most common endocrinopathies affecting the thyroid, parathyroid and adrenal glands.
- Outcomes of management of syndromic conditions affecting the thyroid, parathyroid and adrenal glands are not well reported in Singapore.

Clinical Implications

- Genetic screening uptake in the management of various endocrinopathies is poor in Singapore for reasons including lack of centralised care, poor patient uptake for cultural and religious reasons, and lack of insurance coverage despite subsidies in care.
- Improved effort is needed by all stakeholders including policymakers, clinicians, geneticists and patients themselves to improve outcomes in treating these rare conditions.

INTRODUCTION

In the current landscape of medicine, it is well known that most diseases incorporate a genetic component to some degree. Genetic testing of human diseases originated in the 1950s, and screening for genetic disorders followed a decade after.[1] It is worthwhile noting that the Human Genome Project (1990–2003), which sequenced the whole human genome, revolutionised the field of medicine, and thereby opened a wide array of novel avenues for screening, diagnosis and treatment of syndromic conditions.[2] Another landmark project in genetics, The Cancer Genome Atlas (TCGA, since 2005) has fuelled research across the globe, and provided valuable insight into the molecular biology of about 33 human cancers.[3]

Genetic testing and screening encompass finding a pathogenic or likely pathogenic variant in gene(s) involved in a specific disorder in an individual. This could be in the index patient or a relative (when inheritance is involved), where findings would guide clinicians on targeted care and provide a whole new outlook on many avenues of a patient's or relative's life. Genetic testing and screening have become an integral part of patient care, with an array of tests currently available,

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ranging from presymptomatic diagnosis to genetic predisposition tests, pharmacogenomics, detection of carriers, and prenatal and new-born screening for congenital metabolic disorders.[4] In an ever-expanding field where "genomic medicine" may become the primary modality of evaluating and managing a disease, integrating genomic medicine into clinical practice is important.

Inherited syndromic conditions are usually suspected with the presentation of classic phenotypes and should be confirmed with genetic testing where feasible. A significant proportion of endocrine syndromes seen in clinical practice has an associated genetic component, mainly affecting the thyroid, parathyroid, pituitary and adrenal glands. Currently, the clinical diagnosis is based on the anatomy of the gland involved, which helps us understand the pathophysiological mechanisms but which has significant limitations with errors in diagnosis and treatment.[5] A clear understanding of the genotype-phenotype correlation associated with molecular phenotyping is therefore essential for the optimal diagnosis, treatment, and prognosis.[5] Furthermore, appropriate screening may also provide an opportunity to offer prophy-lactic surgery in high-risk disease such as in multiple endocrine neoplasia (MEN) type 2.[6]

Despite improved availability of genetic screening, there appear to be lacunae on many fronts, which prevent an optimal management strategy for patients with inherited endocrinopathy affecting the thyroid, parathyroid and adrenal glands. In this review, we aim to investigate several of the potential issues that may have prevented uptake of genetic screening in Singapore thus far.

Endocrinopathies affecting the thyroid, parathyroid and adrenal glands

Most of the endocrine syndromes affecting the thyroid, parathyroid and adrenal glands inherited in an autosomal dominant fashion, which means that nearly 50% of first-degree relatives (FDRs) are at risk of carrying the familial pathogenic variant and would require further investigations and surveillance if found to harbour the familial pathogenic variant. In selected instances, this value is lower as some of the same syndromes present as de novo germline mutations (i.e. 10% of multiple endocrine neoplasia type 1 [MEN1] are de novo mutations[7]). The endocrinopathies affecting the thyroid, parathyroid and adrenal glands are shown in Table 1. The age of occurrence of the clinical syndrome has a wide distribution, with certain conditions occurring at an earlier age, some as young as in the first year of life, while others in later years of life. Moreover, in these conditions, certain organs are affected earlier than others, such as the parathyroid glands in MEN1 or the thyroid gland in multiple endocrine neoplasia type 2 (MEN2) conditions.[6,8]

It is important to note that both benign as well as malignant tumours can be seen in the thyroid, parathyroid and adrenal glands in these conditions, based on the mutational profile as highlighted in Table 1.[9] Moreover, in syndromes such as Cowden syndrome, some malignant tumours can occur in non-endocrine organs, such as the breast and the colon.[10] The importance of screening and detecting these tumours early in these inherited conditions, lies in the potential of offering prophylactic surgery, such that patients may have reduced cancer risk and enhanced quality of life.[10,11] Index patient screening and confirmation, would also help inform family members or FDRs of any potential risks and facilitate genetic screening for them as well.

How does genetic testing help in the management of endocrine tumours?

Genetic testing helps in the appropriate management of patients with inherited endocrinopathies in terms of optimising investigations, treatment and surveillance post-intervention. In this section, we will focus on MEN1, MEN2 and familial pheochromocytoma (PCC) and paraganglioma (PGL) to illustrate how genetics play a role in some conditions affecting the thyroid, parathyroid and adrenal glands.

Pheochromocytomas and paragangliomas (PPGLs)

PPGLs were initially characterised by the now abandoned, axiom of following the 10% rule, which was used to describe PCCs/PGLs as follows: 10% are extra-adrenal, and of those, 10% are extra-abdominal; 10% are malignant; 10% are found in children; 10% of patients are normotensive; and 10% are hereditary.[12] However, we currently know that the underlying genetic cause for the condition is much higher.[13] It is now evident that the genotype defines the phenotype of the disease, and that it thus helps us understand the pathophysiology of the disease and the biological behaviour of these tumours.[14] Genetics help predict the biochemical profile as to whether the tumours are likely or unlikely to be, for instance, adrenaline or noradrenaline-secreting. In tumours that secrete predominantly noradrenaline and its products, one can conclude that the tumours are of extra-adrenal location involving the cluster 1 genes and pseudohypoxia pathway associated with Von Hippel-Lindau (VHL) and succinate dehydrogenase (SDH) mutations.[15] Tumours associated with genetic alterations

Table 1. Syndromic conditions affecting the thyroid, parathyroid and adrenal glands.

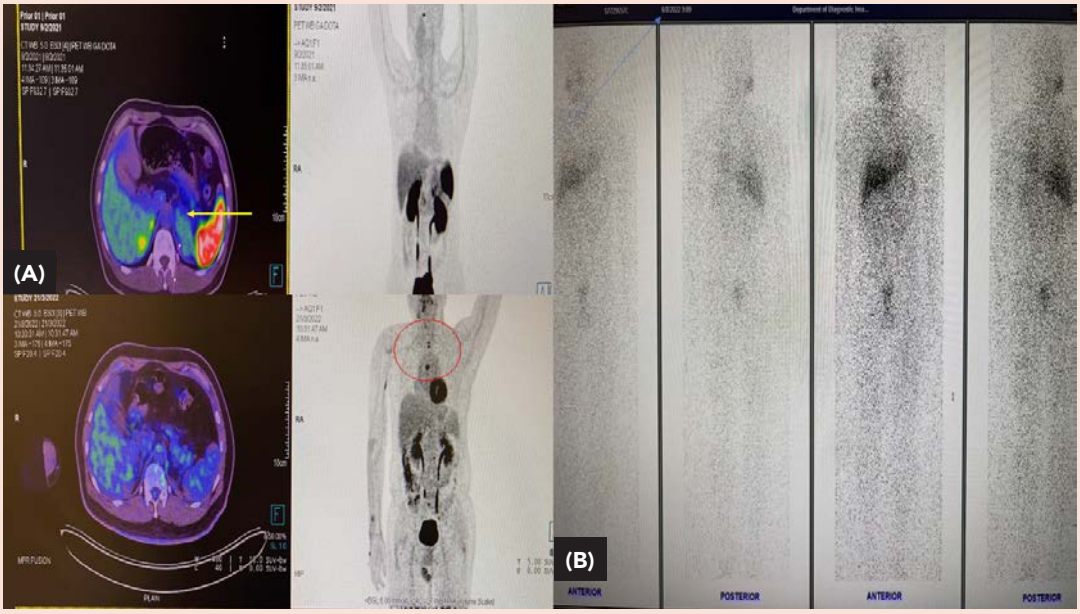
Syndrome and incidence	Affected endocrine organ/s	Presentation	Earliest age of onset/mean	Inheritance	Mutated gene/s
Neurofibromatosis type 1 (NF1) **1:3,000**	Adrenal	Pheochromocytoma	Adult onset/ 4th decade	*AD*	*NF1*
Multiple endocrine neoplasia type 1 (MEN1) **1:30,000**	Parathyroid	1^0 hyperparathyroidism	Adult onset/ 95% biochemical evidence by the 5th decade	*AD*	*MEN1*
	Pancreas	Cancer	Adult onset/ middle age		
Multiple endocrine neoplasia type 2A (MEN2A) **1:35,000**	Thyroid	Medullary thyroid carcinoma	Paediatric onset/ 2nd year onward	*AD*	*RET*
	Parathyroid	I^0 hyperparathyroidism	Adult onset/ 80% by 7th decade		
	Adrenal	Pheochromocytoma	Adult onset/ Codon 634: 70% by 6th decade		
Multiple endocrine neoplasia type 2B (MEN2B) **1:35,000**	Thyroid	Medullary thyroid carcinoma	Paediatric onset/ Codon 918: infancy	*AD*	*RET*
	Adrenal	Pheochromocytoma	Adult onset/ risk from 2nd decade		
Von Hippel-Lindau (VHL) syndrome **1:36,000**	Adrenal	Pheochromocytoma	Adult onset/ 4th decade	*AD*	*VHL*
Hereditary paraganglioma syndrome **Unknown incidence**	Chromaffin cells	Paraganglioma	Adult onset	*AD*	*SDH complex (SDHA, SDHB, SDHC, SDHD)*
Familial adenomatous polyposis **1:8,000–18,000**	Thyroid	Papillary thyroid carcinoma	Adult onset/ 3rd decade: mostly in females	*AD*	*APC*
Cowden syndrome **1:200,000**	Thyroid	Papillary/follicular thyroid carcinoma	Adult onset/ 2nd to 3rd decade	*AD*	*PTEN*
Carney complex **Unknown incidence**	Thyroid	Papillary/follicular thyroid carcinoma	Adult onset/ as early as 2nd decade	*AD*	*PRKAR1A*
Werner (WRN) syndrome **1:200,000**	Thyroid	Follicular thyroid carcinoma	Adult onset/ 3rd decade	*AR*	*WRN*

AD: autosomal dominant; AR: autosomal recessive; PRKAR1A: protein kinase cAMP-dependent type I regulatory subunit alpha; PTEN: phosphatase and tensin homologue; RET: rearranged during transfection; SDH: succinate dehydrogenase; SDHA/B/C/D: SDH complex, subunit A/B/C/D

involving the pseudohypoxia pathways tend to be more aggressive, with increased risk of malignant behaviour;[16] therefore, one could argue that these tumours may be best treated by an open approach rather than with laparoscopic surgery.[17] (Fig. 1)

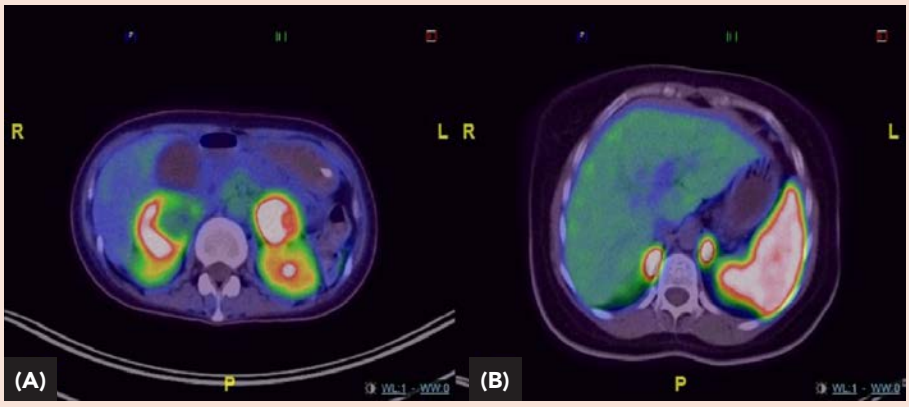
A clinical scenario commonly encountered involves the question of whether a patient should undergo total or cortical-sparing adrenalectomy for patients with bilateral adrenal tumours (Fig. 2). There is some evidence now to suggest that patients with mutations associated with low risk of malignancy, such as of neurofibromatosis type 1 (*NF1*), rearranged during transfection (*RET*) and *VHL* genes, should undergo a minimally invasive surgical approach and cortical-sparing adrenalectomy to prevent an Addisonian crisis and to avoid lifelong steroid replacement.[18] Therefore, it is recommended that all patients with PCC/PGL should undergo genetic testing irrespective of age and family history, to help manage not only this patient but also allow for screening of the affected members.[19]

Fig. 1. (A) Upper panel: A patient with SDHB mutation with a large left paraganglioma with lack of avidity on Ga-DOTA PET (indicated by yellow arrow). Lower panel: Repeat DOTA PET showing multiple bony metastasis 6-months post-surgery (highlighted in red-circle). (B) MIBG scan showing no uptake due to lack of SSTR expression.



DOTA: 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid; Ga: gallium; MIBG: meta-iodobenzylguanidine; PET: positron emission tomography; SSTR: somatostatin receptor

Fig. 2. (A) A patient with multiple endocrine neoplasia type 2B (MEN2B) codon mutation 918 with bilateral pheochromocytomas in whom cortical sparing was not possible because of the large size of the tumours. (B) Patient with multiple endocrine neoplasia type 2A (MEN2A) with codon 634 mutation with bilateral small pheochromocytomas where cortical-sparing surgery was attempted via a retroperitoneal approach.



Multiple endocrine neoplasia type 1 *(MEN1)*

MEN1 is an autosomal dominant syndromic condition caused by inactivating mutations of the *MENIN* gene, a tumour suppressor gene.[20] Though classically described to affect the 3-P's (parathyroid, pituitary and pancreas) glands, we now know that the condition predisposes to form both endocrine and non-endocrine tumours[8] (Fig. 3). The condition affects a range of age groups, but in nearly a fifth, the onset of disease is before the age of 21.[8] Primary hyperparathyroidism (PHPT) is the most common manifestation, with no gender differences and characterised by elevated receptor, parathyroid hormone levels, earlier onset of osteopaenia, and asymmetrical hyperplasia of all the parathyroid glands compared to patients with sporadic PHPT.[21] The surgical management of parathyroid disease in MEN1 is controversial in terms of what the best approach is (subtotal parathyroidectomy with bilateral thymectomy versus total parathyroidectomy and autotransplantation).[22,23] Even more controversial is the performance of a routine prophylactic thymectomy in MEN1 to prevent thymic carcinoids.[24]

One of the challenges that clinicians face in practice, is that in MEN1, there may be a delay in the diagnosis due to later appearance of symptoms, as shown in studies from Japan and France.[25,26] The delay in diagnosis can have significant consequences for the patients, as the condition is associated with high morbidity.[21] In a Dutch study including 74 patients with MEN1, patients with a genetic diagnosis had better outcome than in those where the diagnosis was based on clinical parameters only, with fewer incidences of malignancy and death.[27] The mortality risk is higher in MEN1 patients compared to normal individuals or unaffected family members.[25] Most deaths in MEN1 were due to advanced duodenopancreatic neuroendocrine tumours and thymic carcinoids.[21] Therefore, it is not only important to diagnose MEN1 as per the recommended guidelines, but once the disease manifests, screening should also be according to the recommendations to allow for appropriate and early interventions.[28]

Multiple endocrine neoplasia type 2A/2B *(MEN2A/2B)*

This condition is characterised by the presence of medullary thyroid carcinoma, PCC and PHPT. The PCC can be unilateral or bilateral, and PHPT can be a single gland or multiglandular disease, based on the specific codon mutation. For example, in patients with codon 634 mutation in MEN2A, PHPT may present with single adenomas or hyperplastic glands, unlike in a patient with codon 918 mutation wherein no adenomas are usually seen. Therein lies in the opportunity to treat both the PHPT and medullary thyroid cancer

Fig. 3. (A) Multiple endocrine neoplasia type 1 (MEN1) patient with thymic neuroendocrine carcinoma (recurrent), (B) hyperplastic parathyroid glands, (C) non-functioning adrenal carcinoma and (D) intraoperative image showing the right adrenocortical carcinoma.

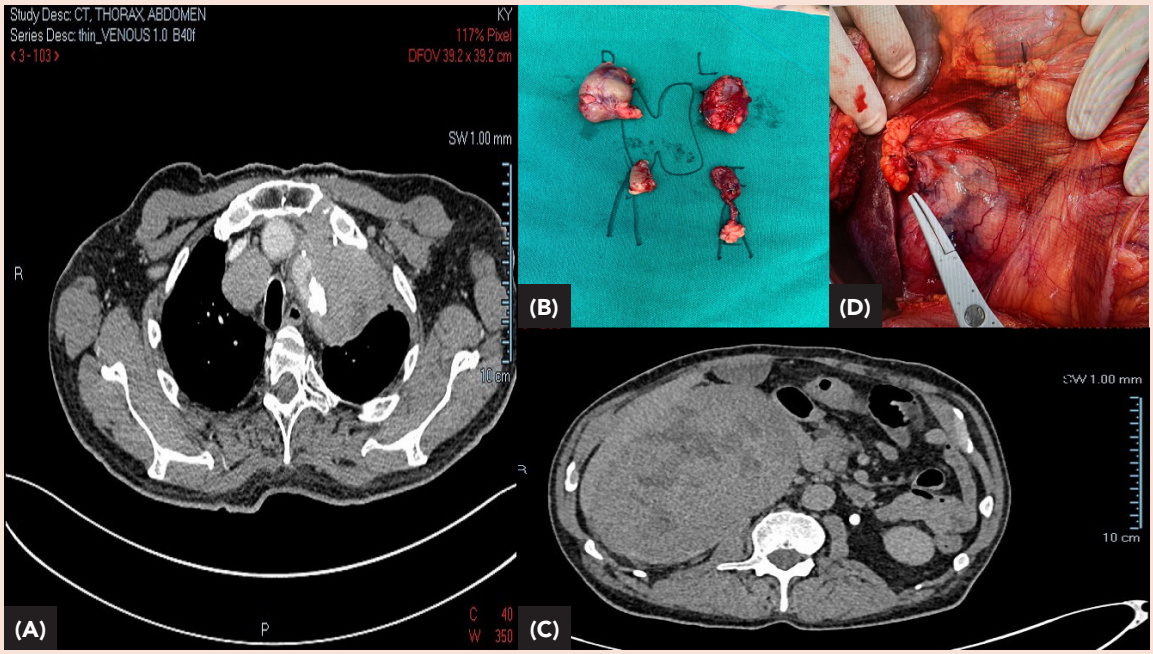


Table 2. RET gene, codon mutations and risks in inherited medullary thyroid cancer (modified from Wells et al.).[30]

RET gene	Codon mutations	Syndrome	ATA risk	ATA recommendations for thyroidectomy
10	609 611 618 620	FMTC/MEN2A	Moderate	More than 5 years of age if basal and stimulated calcitonin levels are normal
11	630 631 666	FMTC	Moderate	More than 5 years of age if basal and stimulated calcitonin levels are normal
	634	FMTC/MEN2A	High	Less than 5 years of age
13	768 790	FMTC	Low	More than 10 years of age if basal and stimulated calcitonin levels are normal
14	804 826 840	FMTC	Low	More than 10 years of age if basal and stimulated calcitonin levels are normal
15	883	MEN2B	High	Less than 5 years of age
	891	FMTC/MEN2A	Moderate	More than 5 years of age if basal and stimulated calcitonin levels are normal
16	912		Moderate	
	918	MEN2B	Highest	Less than 1 year of age

ATA: American Thyroid Association; FMTC: familial medullary thyroid cancer; MEN2A/2B: multiple endocrine neoplasia type 2A/2B; RET: rearranged during transfection

Colours denote different levels of risk. Green: highest; yellow: high; red: moderate; blue: low

(MTC) in a patient with codon 634 mutation at the same setting. By not doing genetic testing, the patients may have suboptimal surgery and may require repeat surgical interventions, which poses significant morbidity.[29] Today we can risk stratify patients based on the codon mutations, and this helps the clinician to accurately predict the nature and severity of the condition in the index patient (Table 2).

What is nowadays evident from the wealth of genomic information is that there appears to be an age-related progression from C-cell hyperplasia to cancer and that this correlates with mutation risks. In clinical terms, this means that surgical cure is possible in the form of prophylactic thyroidectomy if a child has the surgery before 1 year of age for the highest risk (i.e. M918T mutation)[29,30] and by 10 years of age in moderate high-risk mutations.[29] Basal calcitonin also has the potential to predict the stage of the disease in patients with MTC. In carriers of the mutation, it has been shown that if the basal calcitonin is within the normal range, MTC has usually not yet developed.[31] When the level of calcitonin starts rising, it generally means malignant transformation is taking place, with higher levels correlating with nodal and distant metastasis, and when metastases develop, the chances of cure become slim.[31]

Current studies and data on genetic screening in Singapore

Singapore is a developed nation with an estimated population of about 5.9 million people. It has a well-established healthcare system, which is catered by both public and private hospitals. However, comprehensive genetic services are mainly provided by 2 tertiary institutions (National University Hospital and Singapore General Hospital). Genetic services, especially in cancer-related diseases, were introduced to Singapore in 2001.[32] Even though healthcare is expensive in Singapore, the government provides subsidies to increase affordability for all its citizens,[32] but these subsidies do not extend to genetic testing. There are some data to suggest that providing subsidies may increase uptake for genetic testing and potentially reduce the overall burden of cancer care.[332]

In terms of the incidence of cancers in Singapore, the most common cancers reported in males were colorectal, prostate and lung cancers, whereas in females, breast cancer was most common, followed by colorectal and lung cancers.[34] Moreover, thyroid cancers were the seventh most common cancer in women, while cancers involving the rest of the endocrine glands were uncommon. While there are some data available on breast and colorectal cancer genetics from Singapore, there seems

to be a paucity of data when it comes to familial endocrine tumours.[35-39] The incidence of various endocrinopathies in Singapore is not well reported, apart from a few sporadic case reports of MTC in MEN2A and 2B.[40-42] Out of the limited published data, 2 series on PCC and PGLs nationally showed only a small proportion of patients underwent genetic testing.[43,44]

In a series of 124 patients diagnosed with PPGLs over a period of 11 years at a tertiary institution, Chew et al. showed that while only 27/124 (21.8%) were referred for genetic testing, only 12/27 (44.4%) actually underwent testing following counselling.[44] Moreover, this study showed that only 3.7% of sporadic tumours were referred, compared to those with a known family history of syndromic conditions. In a similar fashion, results from another tertiary institution in Singapore reported that only 13/38 (34%) patients with PPGLs were referred for genetic screening over a period of 19 years.[43] Of those referred, 10/13 (76.9%) patients underwent multigene sequencing following counselling, of whom 7 were found to have pathogenic mutations. The authors reported that in the 25 (66%) patients who did not undergo genetic testing, the reasons for this were varied, including patient choice, cost of testing and non-referral by physicians. Overall, it is evident from both studies that there was an increased likelihood of referral to genetic services for younger patients (with 50% among them being under than 20 years old). A dramatic decrease in genetic referral was seen thereafter (14.3% among those aged ≥20 to <40 years, 4.3% in those ≥40 to <60 years and 2.6% in those ≥60 years).[44]

The shortage of data on genetic screening for endocrine syndromes in Singapore could be due to several causes. An important reason is the lack of centralised care in the management of these rare conditions and therefore, not all clinicians may evaluate the patient as recommended by the various guidelines. This echoes the findings of a recent unpublished survey by the author on clinicians' attitude to genetic screening of inherited endocrinopathies across various hospitals in Europe, where a significant proportion of clinicians were not aware of any pathways or local guidelines to help them refer to a clinical geneticist. Another reason would then be insufficient genetic screening done, as highlighted in the abovementioned studies, where nearly 60% of patients were not referred for genetic screening. For most of the mentioned endocrine syndromes (Table 1), only genetic testing of index patients would confirm the diagnosis. In addition, cascade testing of FDRs is also essential. All published guidelines on the management of most endocrine conditions, such as PCC, PGL and parathyroid cancer, advocate genetic testing for all patients with these conditions.

Challenges for genetic screening in Singapore and the way forward

In Singapore, one of the reasons for poor uptake of genetic screening and testing could be the associated costs, as reported by several studies.[32,45] Courtney et al. in 2019, demonstrated that cascade testing (an efficient and cost-effective method of identifying high-risk patients) in FDRs was taken up more when this was offered as subsidised care, and the uptake tripled when it was offered for free.[33,45] An additional notable observation was that the uptake of genetic screening was higher in syndromic symptomatic patients and in the young.[45] Despite variable subsidised plans being offered for certain tests, especially for breast and colon cancers, most patients must still pay out-of-pocket for testing, thus reducing the likelihood of undergoing testing. This is despite the cost of genetic testing already being significantly lower now than in the past. There is not much data on genetics in endocrine conditions in Singapore, or on uptake among index patients and FDRs.

Another important aspect which potentially obstructs genetic screening among FDRs with syndromic endocrine conditions is the role that family plays. In the Western world, patient autonomy is paramount and it is generally the patient's own choice to share their health matters with rest of the family. In syndromic conditions, this is particularly important, as not sharing could deny FDRs the opportunity to be screened for the condition to enable targeted interventions and improve survival. Conversely, in some South Asian countries, it is still practice to withhold crucial information from the patients themselves, as this is considered being more humane.[46] The treatment decisions are made by the family as a whole, in order to provide support, strength and hope to the ailing patient.[47,48] In this light, genetic testing of index patients or FDRs could be difficult. In Singapore, there appeared to be a family-oriented approach, when cascade testing was done in clusters with inherited conditions.[45] Specifically, in our practice where patients with MEN-syndromes or PCC/PGL-syndromes were encountered, many patients declined to undergo genetic testing themselves, and in cases when they were found to be gene-positive generally, patients refused to share the information with FDRs, thus preventing appropriate treatment for them.

Furthermore, clinicians themselves probably also play a significant role in the lack of genetic

screening. Specifically, there are significant developments in genetic knowledge, and clinicians could thus find it difficult to keep up to date. This rapid pace could make clinicians feel uncomfortable, in terms of knowing which test exactly to order, or how to interpret the findings of a specific genetics test, especially for outcomes reporting on variants of unknown significance, as shown in a survey of oncologists and cardiologists.[49,50] Moreover, to understand and explain implications to patients, solid knowledge on the inheritance and penetrance pattern is of utmost importance, which could be something that some clinicians fail to understand.[51] Barriers to the uptake of genomic medicine in clinical practice by clinicians include lack of engagement and participation towards research in genomics and its implementation, and low integration of genomic data into electronic health records such as that advocated by the Implementing Genomics in Practice network.[52]

If genetics are ignored, the diagnosis of these syndromes falls solely on obtaining a 3-generation pedigree of familial conditions during consultation. However, a detailed family history is difficult to obtain in most patients, as forgetfulness and unawareness are common. Improving awareness of these syndromes and of the available services (genetic counselling, available tests and costs) through seminars and continuous medical education platforms, could be beneficial in alleviating this issue. Moreover, grant-based research could help fill the gaps in the knowledge of the population. As discussed earlier, centralised care of patients with inherited endocrinopathies, ensures uniformity of care and better outcomes for patients.

Any decision of a patient following genetic counselling, depends on a multitude of personal factors. In this regard, understanding of genetics, and a person's background and their belief system are all major players. In a recent study on genetic literacy in Singapore, it was shown that younger participants (21–40 years), with higher level of education and above-average income had more genetic literacy.[53] Importantly, genetic testing was seen as an act against "the will of God" by 38.7% in this cohort. Shaw et al. assessed factors influencing screening for breast cancer among Malay women in Singapore.[54] Participants' religious beliefs, e.g. believing a disease is caused by black magic and avoiding becoming a burden to family following a positive result, were cited as reasons not to undergo screening, by non-participants of the offered screening programmes.[54] We have encountered similar patients in our clinical practice who refused genetic screening for religious beliefs, due to worries about the impact on other siblings, or the impact on marriage.

Legal and ethical aspects of genetic testing in endocrine surgical patients

It is well-known that any results of genetic testing can impose severe changes in a person's psycho-socio-economic well-being. Because of these ramifications, the ethical and legal aspects of genetic testing have been well studied and documented. Genetic counselling and testing are thus dependent on the fundamental pillars of medical ethics, i.e. patient autonomy, non-maleficence and beneficence.[55] Genetic discrimination in one's own family, in society and in the workplace are actual issues patients could face following a positive test; thus, utmost care must be applied for confidentiality. Western medical practice has developed on from "paternalism" in the clinician-patient relationship. Despite this, dilemmas could occur when a positive diagnosis of an inherited syndrome is made. In MEN2 syndrome, where germline mutations of autosomal dominant pattern would lead to MTC in 90–100%, which is the leading cause of death, clinicians could feel a duty to inform the index patient, and the FDRs as well. As mentioned above, this feeling could potentially conflict with the index patient's autonomy and the genetic counselling of FDRs could lead to discrimination in their social circles. On the other hand, people who are found to have a MEN2 mutation are offered tailored screening with serial calcitonin measurements and prophylactic total thyroidectomy, both beneficial towards their survival. In MEN2B mutations, particular consideration of ethics should be undertaken, as affected individuals may develop MTC as early as infancy, and therefore for FDRs, prophylactic surgery is advised as early as during the first year of life.[56,57]

Two separate lawsuits in the US regarding similar inherited conditions can be applied to explain the legal issues surrounding these situations. In one of these cases, there was a failure to offer risk-reducing prophylactic surgery for a multicancer syndrome. In the other case, involving a case of familial adenomatous polyposis, it was highlighted that relaying the results to the index patient only, should be regarded as an inadequate "duty to warn". These cases fell under medical malpractice and resulted in financial settlements.[58] How straightforward the clinician should be when discussing these results should be guided by the individual patient's concerns and this should be determined at the pre-test counselling stage.[58] Informed consent should be obtained after genetic counselling prior to testing. If the suspected index patient or FDR is mentally incapacitated and/or a minor, they can be tested with the consent of a parent or a guardian (specifically important in case

of a potential MEN2 mutation). Not only is pre-genetic test counselling important, post-genetic test counselling is as essential, and this may require the disclosure of the test's implications on family members. Unfortunately, the clinician's exact duty to inform FDRs on these implications remains unclear in guidelines.[59]

An even more sensitive topic entails the reproductive considerations of adults when an inherited mutation, such as succinate dehydrogenase subunit B (SDHB) or MEN2B (codon 918), is found. Both have such high penetration, that up to 50% of offspring will be born with this mutation. Specifically, this means that MEN2B children would be exposed to surgery during infancy. Being silent yet aggressive, SDHB is in a sense even more sinister, as it is exposing individuals to lifelong surveillance at least. Raygada et al. reported a cohort of patients with an SDH-mutation, where several patients did not alter their initial intents of having children, even after a detailed discussion of the course of the disease.[60] Interestingly, one patient successfully conceived through in-vitro fertilisation with pre-natal genetic screening for SDH mutation.[60]

Genetic discrimination and insurance

In 2018, the Singapore's Ministry of Health released a code of practice in genetic testing, though this has been rescinded. These guidelines categorise genetic testing for inherited syndromes as so-called "Level 3" testing (germline mutation testing).[59] As discussed, testing positive for an inherited syndrome can result in genetic discrimination. From a financial standpoint, an individual's employability may change in light of this type of diagnosis,[61] in turn leading to unemployment, reassignments and resignations, all potentially culminating in economic constraints. Conversely, in the case of FDRs, a negative test could result in "survivor's guilt". Additionally, life, health and disability insurance companies consider not only an individual's current health risks, but also their potential future health risks, before offering coverage. Therefore, any personal genetic data predictive of such diseases (e.g. FDRs of MEN2A individuals) could diminish the chances of securing a substantial insurance policy. With the current standpoints of "genetic exceptionalism" (i.e. where genetic information is not shared), genetic data are incorporated into one's medical records, allowing them to be examined before insurance contracts.[61] Genetic discrimination in health insurance could result in an individual's policy request rejected, surcharged or restricted.[62] Some countries, such as the Netherlands, have blocked insurance companies from obtaining an individual's genetic data.[63]

CONCLUSION

Significant progress in genetics has made precision medicine possible in a wide range of inherited endocrinopathies affecting the thyroid, parathyroid and adrenal glands. Limited studies from Singapore show poor uptake of genetic screening in this country, for a wide range of reasons, which can be personal, religious or related to funding care, not only affecting the optimal management of index patient but also FDRs, who are denied the benefit of prophylactic interventions. Moreover, it seems the progress in genetics has outpaced clinicians' understanding of the complexities involved in the management of patients with inherited conditions. There needs to a concerted and coordinated effort by all the stakeholders (i.e. the Ministry of Health of Singapore, health systems, clinicians and patients) to ameliorate genetic screening, to improve outcomes for all patients with these rare conditions.

Disclosure

No conflict of interests to declare.

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COMMENTARY

Health District at Queenstown: Catalyst for translational research

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on behalf of the Health District @ Queenstown

Ageing societies dominating global demographics is not new. However, the pace of global population ageing is causing disquietude. In 2017, the global population over age 60 years exceeded those below 5 years for the first time in history, and only 3 years later, the population over age 65 surpassed those below 5.[1,2] The US took 72 years to double its proportion of population over age 65 from 7% to 14% while Sweden took 85 years, but Asia has been projected to achieve this in about 23 years, with Singapore having taken 20 years. This unprecedented ageing acceleration in populations results from longer individual lifespans due to improvements in healthcare and population health, combined with a steady decline in total fertility rate—the latter being the mean number of children per woman in her lifetime. Unfortunately, the number of years in good health has not kept pace with lengthening lifespan; consequently, time spent in poor health is increasing. This demographic change, along with a widening healthspan and lifespan gap, will have dramatic impact on economic growth, workforce composition, healthcare, housing and transportation.

For societies to remain robust despite demographic change, health for all must be a priority. Health is a state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity. All these components need to be addressed for societies to benefit from the increases in human, social and financial capital generated from longer lives. By addressing the components of well-being we will reap the healthy longevity dividends from older persons—wisdom, life experiences, emotional stability, generativity and workforce participation, with a resultant expansion of economic markets. Achieving well-being for all community members requires fundamental rethinking of how society views and engages older people. If older people are marginalised due to ageism and preconceived notions of their abilities, society will forgo enormous opportunities and possibly exacerbate inequity, loneliness and poverty. However, all of society benefits if this group is embraced as a growing resource.

Are there solutions?

Acknowledging rapidly ageing societies and the lifespan-healthspan gap, 2 recent reports reviewed the evidence and came to similar conclusions, i.e. societies must do more to ensure their populations remain robust and functional as proportion of older residents increases.[7,8] The World Health Organization (WHO) dedicated 2020–2030 as the Decade of Healthy Ageing. WHO's baseline report defines healthy ageing as "the process of developing and maintaining the functional ability that enables wellbeing in older age."[7] Although functional decline occurs with age, the trajectory is highly variable and people can maintain functional ability well into their oldest ages. The goal should be to optimise everyone's functional ability to allow all to contribute. Optimising functional ability requires a change in how we think and act towards ageing; ensuring communities foster older people's abilities; delivering person-centered rather than disease-centric integrated care; and providing access to long-term care for those who require it. This will necessitate meaningful engagement with older people, families, caregivers and others; building capacity for integrated action across sectors; linking stakeholders for shared experience and learning; and strengthening research and innovation to accelerate implementation.

In 2022, the US National Academy of Medicine dedicated their first global grand challenge to healthy longevity and commissioned an international panel to formulate a global roadmap for healthy longevity.[8] The commission defined healthy longevity as "… the state in which years in good health approach the biological life span, with physical, cognitive and social functioning, enabling well-being across populations."[8] Enabling this requires societies to have a strong social compact with social cohesion and equity at its centre,

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and with investments in key enablers. These key enablers include social infrastructure; financial security in retirement and digital literacy; housing; public spaces; safety; transportation; digital technology; health system including public health, health care delivery, long-term care; geroscience, big data innovation; and realising the longevity dividend by enabling older people who want to work, volunteer and participate in lifelong learning. Additionally, disrupters will need to be addressed: ageism, poverty, conflict, pollution and climate change. A whole-of-society multisectoral approach will be required given the complex system that health is, which will then drive a virtuous cycle in which the realisation of the longevity dividend of older populations will provide resources for subsequent investment in enablers and in addressing disrupters (Fig. 1).[8]

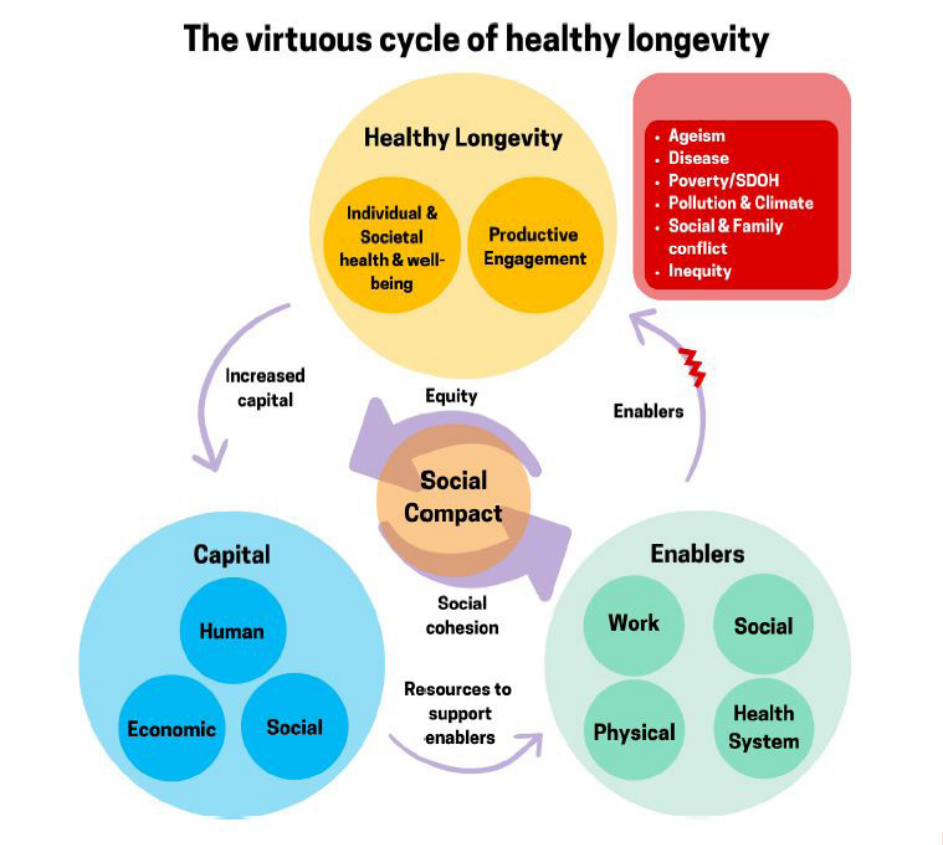
What is needed now are robust studies in a real-world environment to validate effective programmes, and where the evidence can be contextualised and translated into sustainable interventions at scale. Considering the above possible solutions, we identified Queenstown township, with its demographics and housing mix as outlined below, and located within Singapore's National University Health System's catchment area, to be an ideal study site.

The Health District @ Queenstown (HD@QT)

Queenstown is a Singapore community of approximately 95,900 residents in 2022; 22.2% are over the age of 65, qualifying Queenstown as super-aged; 80.2% of its residents live in Housing and Development Board (HDB, a statutory board under Ministry of National Development responsible for public housing in Singapore) apartments. Queenstown's demographic and socioeconomic profile is representative of what the whole of Singapore will look like in 2026 when 21% of its resident population is expected to be over the age of 65.

HD@QT was conceived with 4 goals in mind: (1) increase healthy longevity by increasing healthspan to approximate lifespan; (2) enable purposeful longevity (i.e. a long life facilitated by enjoying activities, which align with one's beliefs and values) by helping people remain engaged

Fig. 1. The virtuous cycle of healthy longevity by which societies can have a strong social compact with social cohesion and equity at its core; catalysed by investments in key enablers; and by addressing disrupters.[8]



SDOH: social determinants of health
Superscript number: refer to REFERENCES.

through work, volunteerism, lifelong learning and reskilling; (3) strengthen intergenerational cohesion such that each generation sees the value in other generations; and (4) support a community for all ages thus allowing people to live a life of meaning with dignity in the setting they choose. This is co-led by HDB, National University Health System and National University of Singapore, in partnership with public and social sectors, and with input from an international advisory panel.

Since HD@QT's October 2021 official launch, work has been organised along 6 workstreams: preventive health and care delivery, purposeful longevity, planning and design of the built environment, technology, communications and engagement, and evaluation. Co-design directs HD@QT's initiatives and rigorous research is used to assess the efficacy of interventions in achieving one or more of the abovementioned goals, along with the abilities to scale up and be sustainable. The first 2 workstreams synergise where there are opportunities (e.g. the creation of micro-jobs by the second workstream assists the first workstream by providing manpower), while the remaining 4 workstreams enable the first 2 (see Fig. 2). All workstreams operate through the principles of co-design with residents and stakeholders, and implementation and behavioural science.

Examples of programmes in each of the workstreams include:

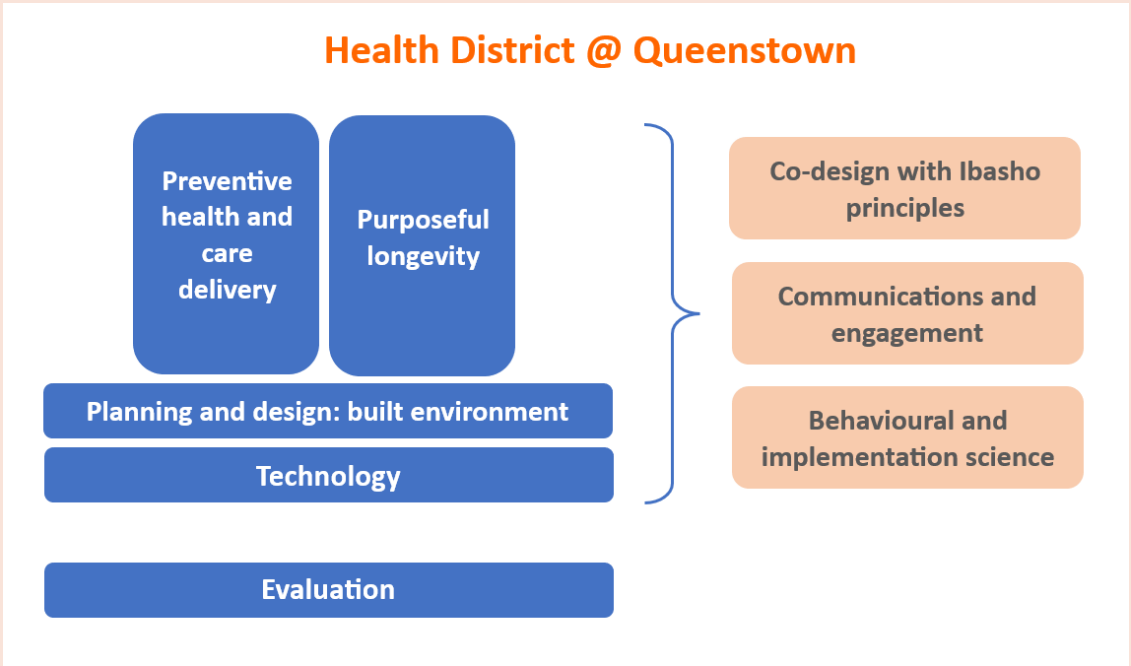
- **Preventive health and care delivery**

  Testing the optimal size, composition and ratio of an embedded, integrated healthcare and social services team to residents within public housing. This is to develop the trusted relationships required to improve health education, screening, vaccinations, medication and appointment compliance, and to address social determinants of health.
- **Purposeful longevity**

  Development of Ibasho hubs[9] that advocate for the recognition of older persons as valuable assets, empowering them to contribute meaningfully to their communities, developing micro-jobs to strengthen financial security, and trigenerational community engagement to mitigate ageism and promote social cohesion through intergenerational bonding.
- **Planning and design of the built environment**

  Working with HDB at the apartment unit, apartment block and neighborhood levels to reduce the risk of falls; encourage independent living, social interaction and physical activity while delivering services into the community and homes; and enable the use of technology. A Built Environment Well-being Index framework is being created to assist HDB in future development and refurbishment of Singapore's public housing.

Fig. 2. Health District @ Queenstown workstreams (in blue) driven by co-design, communications, and behavioural and implementation science (in orange).



- **Technology**

  Identifying and testing technology that is effective, scalable and sustainable to enable independence for older people; assist in identifying residents at increased risk of poor health; and facilitate preventive health and care delivery.

- **Evaluation**

  A detailed baseline study of 5000 Queenstown adult residents will identify, quantify and understand unmet resident needs to identify targets for future co-developed interventions.

  Assessing HD@QT's efforts involves development of a framework based on the Ageing Society Index[10] with relevant indicators identified and endorsed by an international advisory panel.[11] Mining of national administrative data sources and comparison of HD@QT's indicators with data from townships of similar demographics and housing mix will determine whether our efforts are making a difference.

- **Communications and engagement**

  Creating an effective narrative, identification of communication channels, and the use of campaigns to articulate the goals of the HD@QT, improving digital literacy and addressing misinformation are being undertaken.

Singapore will become superaged by 2026.[12] To respond to the complex challenges and allow us to seize the opportunities created, multisectoral interventions based on science and rigorous evaluation are needed to identify effective scalable and sustainable programmes to reduce morbidity and allow us to benefit from extended lifespan. To be effective, these programmes will also need to strengthen social cohesion across generations and allow people to age in the setting they choose. The HD@QT is a platform to efficiently co-create, test and validate existing programmes in a scientifically rigorous fashion. The project has been called ambitious and pathfinding by those eager to engage with and learn from it.[13] To our knowledge, no similar coordinated multisectoral effort to address the 4 goals of the HD@QT simultaneously at township level exists regionally and possibly elsewhere. We welcome our readers' interest in joining us in this initiative.

Keywords: *ageing, determinants of health, healthspan, infrastructure, population health*

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LETTER TO THE EDITOR

Screening of nasopharyngeal cancer in high-risk familial cohort: A practical approach using a screening algorithm

Dear Editor,

In Singapore, nasopharyngeal cancer (NPC) is among the top 3 cancers afflicting middle-aged males (30–49 years old).[1] Unfortunately, patients with early-stage NPC are often asymptomatic, and most patients (approx. 70%) are diagnosed with advanced disease with adversely reduced survival. First-degree relatives of NPC patients have about 4 to 10 times increased risk of developing NPC,[2] and strategies for reducing NPC-specific mortality among this high-risk group are feasible. Herein, a working group from the Chapter Board of Otorhinolaryngologists Singapore proposed a screening algorithm for these high-risk individuals of NPC based on existing available evidence.

Our algorithm expands on the existing Ministry of Health (MOH) guidelines, which recommend family history-positive individuals to be screened with Epstein-Barr virus (EBV) serology against viral capsid antigen (VCA-IgA), early antigen (EA-IgA) and Epstein-Barr nuclear antigen (EBNA1-IgA), supplemented with clinical examination including a flexible nasoendoscopy.[3]

We recommend screening of individuals with ≥1 first-degree relative with NPC, especially among middle-aged adults from 30–70 years old. We propose EBV IgA serology (anti-IgA VCA and anti-IgA EA) as a screening tool because of numerous evidence supporting its role in the risk stratification of NPC risk among familial cohorts.[4] When available, anti-EBNA1-IgA can also be incorporated. We recommend a detection threshold of EBV EA-IgA titre of ≥1:10 and VCA-IgA titre of ≥1:160 (measured via immunofluorescence assay [IFA]) as sufficiently raised for further review and follow up.[5] Screening should be combined with nasoendoscopy, which is conveniently available in Singapore and can identify subtle masses arising from clefts of the fossa of Rosenmuller. Whenever possible, photo-documentation may be performed to pick up subtle changes on interval endoscopies. In some cases, a trans-palatal endoscopic visualisation can offer a panoramic view of the Rosenmuller clefts when viewed from an inferior perspective (Fig. 2).

Cohort 1: Negative EBV serology with normal nasopharyngeal examination. For family history-positive individuals with negative EBV serologies, studies have demonstrated a much lower risk of developing NPC.[6] Presently, there is insufficient data to guide the duration of follow-up. If there are no lesions detected on nasopharyngeal endoscopic examination, a follow-up in the primary care setting with a 12–18 monthly repeat EBV serology can be feasible. If the titres become positive, or the patient develops symptoms, a referral to the ENT specialist should be made. We recommend follow-up till 70 years of age as the prevalence of NPC wanes after this age.

Cohort 2: Positive EBV serology with normal nasopharyngeal examination. If positive EBV serology is encountered with no obvious endoscopic masses, the next steps to detect NPC are not well established. The available options are: (1) continue surveillance with repeat endoscopy and EBV serology in 6–12 months; (2) perform an upfront Magnetic Resonance Imaging (MRI) post-nasal space (PNS) to detect subclinical NPC (up to 10%); and (3) perform a plasma EBV-DNA to select patients for MRI PNS. Options (2) and (3) may be recommended for patients concerned of an occult primary nasopharyngeal carcinoma that cannot be confidently excluded on endoscopic examination.

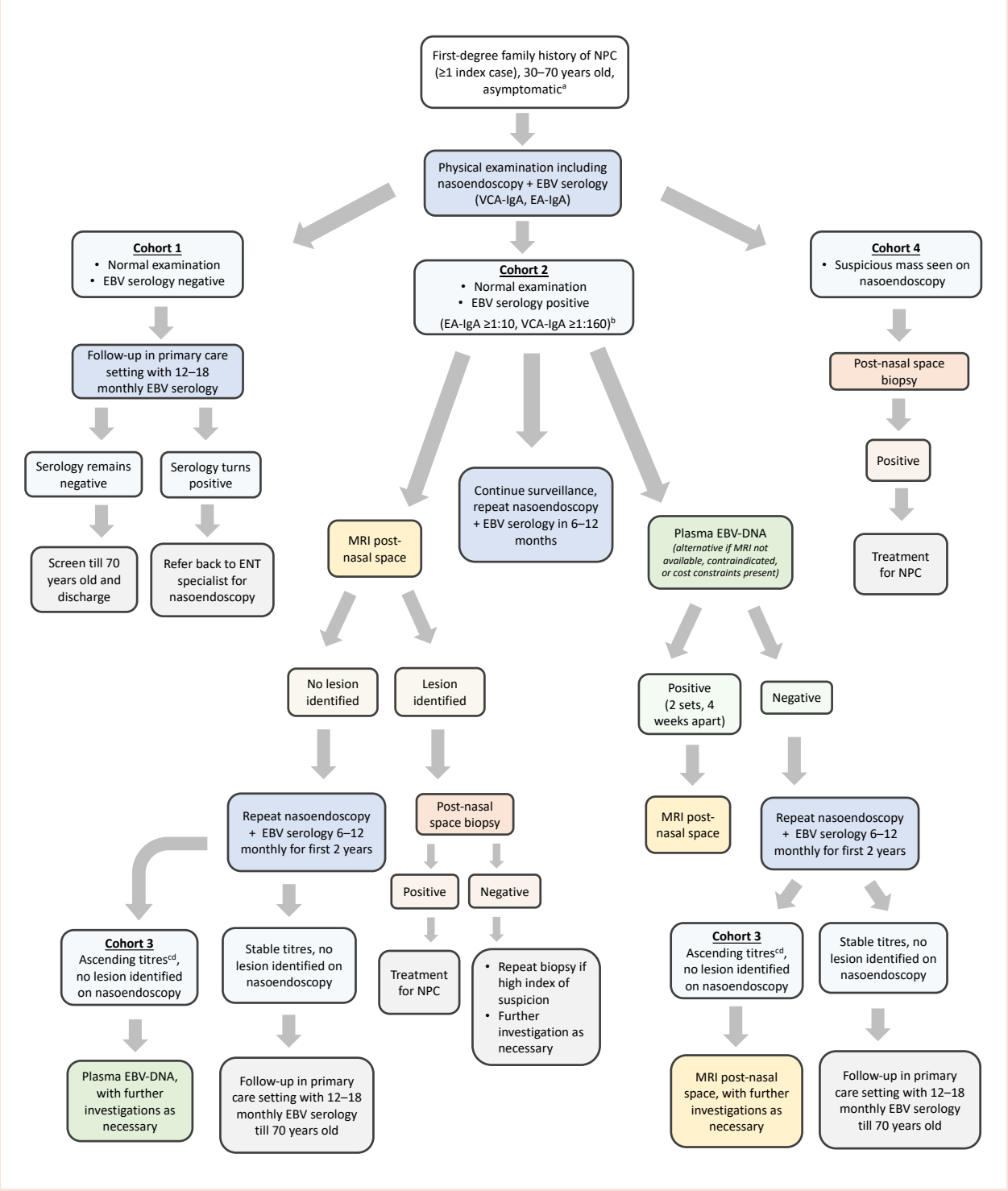
There are existing cost-effective and short MRI protocols for screening that could be performed with high sensitivity and specificity.[7] When a suspicious lesion is detected on MRI, a targeted PNS biopsy should be performed. However, these short screening protocols are not available and a standard contrast enhanced MRI is usually performed.

There is increasing evidence that plasma EBV-DNA (targeting the BamHI-W fragment) can exclude the presence of NPC with a high negative predictive value (approx. 99%).[8] Individuals with persistently positive EBV-DNA are more likely to develop NPC (relative risks of 16.8), compared to individuals initially negative for EBV-DNA.[8] A 2-time point-testing approach set 4 weeks apart is recommended to reduce the rate of false positives (up to 8%).[9] If the EBV-DNA is negative, close monitoring of 6–12 monthly with repeat nasoendoscopy for the first 2 years can be performed, especially if a baseline MRI scan was not obtained.

Nasoendoscopy and EBV serology should be performed 6–12 monthly for the first 2 years, as studies have shown that new NPC cases are commonly identified within this period.[10]

Cohort 3: Persistent raised or rising EBV serology titres with normal nasopharyngeal examination. Individuals with persistently raised EBV serology, especially up-trending titres should

Fig. 1. Proposed screening algorithm for high-risk familial cohort in Singapore.



EA: early antigen; EBV: Epstein-Barr virus; ENT: otorhinolaryngologist; MRI: magnetic resonance imaging; NPC: nasopharyngeal carcinoma; VCA-IgA: viral capsid antigen

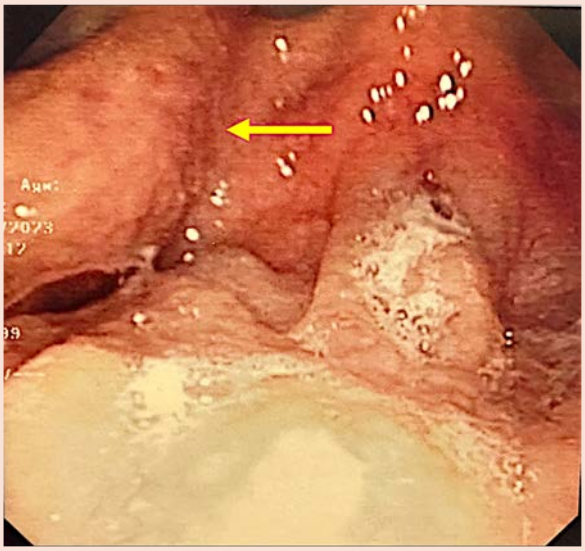
[a] Risk of NPC further increased in ≥2 affected first-degree relatives; Positive family history in sibling (especially in sister); Male; Middle age. To further encourage screening in these groups.

[b] Studies demonstrate the best test profile with highest sensitivity, specificity, PPV and NPV with EA-IgA ≥1:10 and VCA-IgA ≥1:160.

[c] Ascending titres of VCA-IgA more significant than EA-IgA.

[d] If continually ascending titres with negative MRI PNS, consider non-NPC-related malignancy.

Fig. 2. Trans-palatal endoscopic visualisation demonstrating a panoramic view of the Rosenmuller cleft (yellow arrow).



undergo regular repeat nasoendoscopy in 6–12 months. Studies demonstrate that ascending VCA-IgA titres, compared to other serology markers, may signify a relative higher risk of developing NPC (hazard ratio of 21.3 for ascending titres, compared to 6.2 for stable titres).[11] However, the mechanistic explanation of fluctuations of EBV serology in NPC development is unknown. Should no tumour be identified on follow-up, further evaluation can be performed using MRI PNS or plasma EBV-DNA to exclude occult NPC as previously discussed.

As EBV is also associated with other non-nasopharyngeal malignancies (e.g. NK-T cell lymphoma and gastric cancer), a positron emission tomography computed tomography scan can also be considered in cases of persistently positive plasma EBV-DNA and with normal nasal endoscopic findings.

Cohort 4: Positive EBV serology with a mass on nasopharyngeal examination. When a post-nasal mass is encountered, a biopsy should be performed to confirm diagnosis and appropriate treatment instituted.

A cost-effectiveness analysis study compiled by the World Health Organization (WHO) showed that screening was associated with a median 10-year reduction in NPC mortality of 52.9%.[12] Nevertheless, a prospective cost effectiveness analysis of this workflow should be performed in our local setting. Currently, our algorithm proposes IFA for the evaluation of EBV serology, but future studies should be done to validate use of EBV serology measured using ELISA technique as this method is more commonly available. Additionally, the current follow-up recommendations are based on extrapolated data, and more long-term longitudinal real-world follow-up data needs to be obtained to determine an optimal duration of follow-up. Future studies should also be done to evaluate the impact of this proposed NPC screening programme on the incidence, stage distribution and overall morbidity and mortality reduction of NPC.

In conclusion, NPC screening of individuals with family history is recommended, especially among middle-aged males. Screening should consist of a full head and neck examination, and detailed endoscopy with complete visualisation of the nasopharynx. EBV serology should also be performed, preferably using IFA with same laboratory standards for harmonisation and serial interpretation. A raised EBV serology increases the risk of developing NPC in the future, and close follow-up should be performed, especially within the first 2 years. MRI PNS is a useful tool to look for occult NPC, and may be performed for further evaluation, especially in those with increasing IgA serology assays or persistently raised plasma EBV-DNA. Plasma EBV-DNA is useful as an auxiliary test because of its high negative predictive value.

Declaration

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Keywords: *Epstein-Barr virus, family history, high risk, nasopharyngeal cancer, screening*

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LETTER TO THE EDITOR

VOWELS: A communication framework for disclosing medical errors in medical oncology and palliative care

Dear Editor,

Recognising the impact of medical errors on patients and the doctor-patient relationship has underscored the need for better communication.[1,2] For the most part, these efforts are informed by Chafe et al.'s 6 steps that entail: (1) the identification of the error in a timely fashion; (2) determination of the extent of the error; (3) constitution of a workgroup to establish the scope of the review; (4) identification of affected patients; (5) scrutiny of clinical records; and (6) the act of informing patients and other stakeholders.[3-6] The apology and open disclosure are then said to be built upon this platform.

Building on our experiences training healthcare teams on the disclosure of false positive HER2 tests for patients with breast and gastric cancers at the National Cancer Centre Singapore (NCCS), these processes need to be timely, empathetic and patient-focused. Our experience suggests that for patients, disclosure extends beyond support of autonomous choice and empowering informed decision making to include a chance to rebuild trust and to be heard and understood.

For the local healthcare team, fear of litigation needs to be overcome, and training with a purpose-built tool is required. Poor experience with a misapplied approach built around the Setting, Perception, Invitation, Knowledge, Emotions and Summary (SPIKES) protocol and failure to effectively attend to cultural sensitivity merely underline calls for a more effective approach.

Here, we forward the VOWELS approach. The acronym VOWELS conveys a commitment or "VOW to be culturally sensitive, to Empathise, Listen and Support".[7] This process draws on strategies represented by the mnemonics "AEIOU", paying special attention to the demeanour and attitude of doctors involved in the disclosure of medical errors (Table 1).[7]

While our own experiences and feedback using the tool in training residents at NCCS have been positive, further evaluations are proposed.

Disclosure

The authors declare no conflict of interest.

Keywords: *communication, disclosure, medical education, quality of life, training*

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Table 1. AEIOU communication strategy.

Strategies	Sample sentences	Notes
Apologise for the situation	"I'm sorry you are affected by this situation."	Importance of a sincere apology. An apology that they are in such a situation is not an admission of legal liability.
Empathetic response upfront	"This must be shocking/distressing/upsetting for you and your family."	Acknowledge, validate and normalise their emotions.
Information giving with pacing	"May I go through with you what we know about the situation?" "Before I start, is there anything in particular you want to find out?"	Everyone has different informational needs. Pace the information in intervals. Check in regularly if they are following.
Openness and transparency	"I will share what I know about the situation." "This is an important question. As I do not have information on this, may I direct you to someone who can answer this query?"	It is important that the patient/family perceives openness and transparency. If we do not know the answer, direct them or offer a follow-up call/appointment.
Understanding concerns	"Is there anything in particular you are worried/concerned about?"	Active listening and allowing them to share their concerns is in itself therapeutic.

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LETTER TO THE EDITOR

Prevalence of tramadol misuse: A pilot multicentre cross-sectional survey in Singapore

Dear Editor,

In Singapore, especially in our healthcare institution, the use of strong opioids for the treatment of chronic non-cancer pain is relatively rare.[1] Contrastingly, weak opioids such as tramadol are frequently prescribed for this condition, partly stemming from the widespread belief that tramadol has a better safety profile with a lower addiction risk than strong opioids.[2] However, there appears to be a change in this opinion recently.[3] In this study, we aimed to determine the prevalence of tramadol misuse in our healthcare institution, and to identify the associated risk factors.

This cross-sectional study was approved by our Institutional Review Board (IRB-D-2020/3013) and registered on the ClinicalTrials.gov registry (Identifier: NCT04813458). A waiver of written consent was approved. The Consensus-Based Checklist for Reporting of Survey Studies (CROSS) guidelines were adhered to.[4]

Patients who were seen during a follow-up visit at the participating pain clinics from September 2021 to May 2022 were screened for inclusion if they were prescribed tramadol for chronic pain for a minimum duration of 3 months. Patients who were unable to fill up the survey due to severe psychiatric comorbidities or who were illiterate were excluded.

The electronic prescriptions of the included patients were screened. Patients who fit the inclusion criteria were approached by a member of the research team. If the patient agreed to take part in the research, they would be shown a Quick Response (QR) code that was linked to the survey form on a secure platform run by the government of Singapore (http://forms.gov.sg). The patients would then complete the survey on their mobile devices.

Patients were asked about their demographic data, pain history and tramadol use (e.g. duration of use, concurrent use of other opioids, tramadol consumption, effectiveness, etc.) They were asked to fill in a number of questionnaires including the Opioid Risk Tool (ORT), Current Opioid Misuse Measure (COMM), Patient Health Questionnaire-9 (PHQ-9) and General Anxiety Disorder-7 (GAD-7).

Counts (%), mean (standard deviation [SD]) and medians (interquartile range [IQR]) were used to describe categorical, parametric and non-parametric data, respectively. To determine the factors that predict opioid misuse, a logistic regression analysis was performed. A *P* value of <0.05 was considered significant. All statistics were performed using RStudio 2022.07.01 (RStudio, Boston, MA, US).

A total of 206 patients ranging from 23 to 91 years old with a mean age of 63.0 (15.3) years were recruited. The mean duration of pain experienced by the patients was 140 months.

Tramadol was used for a mean duration of 56.2 months by the survey participants. Only 4.9% were also taking other opioid medications. Most patients reported consuming 150 mg or less of tramadol per day. In terms of its perceived effectiveness, 51 patients (24.8%, 95% confidence interval 18.9–30.7) reported tramadol having an efficacy of 76%–100%, 48 patients (23.3%) reported an efficacy of 51%–75%, 68 patients (33%) reported an efficacy of 26%–50%, 17 patients reported an efficacy of 10%–25% and 22 patients (10.7%) felt that tramadol was not effective at all in relieving their pain. Despite perceiving that tramadol was ineffective, the 22 patients (10.7%) continued with their prescription.

This study found that 96.1% of patients were assessed to be at low risk of having opioid-related complications based on the ORT. Despite this, 51 out of the 206 patients (24.8%) were found to have misused opioids based on the COMM questionnaire (Table 1). The spectrum of misuse was comprehensive and involved multiple subscales of the questionnaire, including signs and symptoms of intoxication, emotional volatility, evidence of poor response to medications, addiction, healthcare use patterns and problematic medication behaviour.

A logistic regression model was constructed using sociodemographic factors, tramadol usage patterns and the results of their anxiety and depression questionnaires. Based on this model, independent predictors for opioid misuse included singlehood (*P*=0.03), higher PHQ-9 scores (*P*<0.01) and higher GAD-7 scores (*P*<0.01). ORT scores did not strongly predict misuse behaviour.

From this study, the prevalence of tramadol misuse appears significant (24.8%). Under the World Health Organization's 1986 3-step analgesic ladder, tramadol was listed as a weak opioid, and unlikely to cause dependence and misuse compared to stronger opioids.[5,6] However, our study shows that tramadol is frequently misused.

Table 1. Rates and pattern of misuse in 206 patients.

Positive COMM (%)		**51 (24.8)**	
COMM subscale (median, [IQR])	**Positive COMM**	**Negative COMM**	***P* value**
Signs and symptoms of drug intoxication	3.00 (2.00, 3.00)	1.00 (1.00, 2.00)	<0.001
Emotional volatility	2.40 (2.00, 2.60)	1.20 (1.00, 1.40)	<0.001
Healthcare use patterns	1.67 (1.00, 2.00)	1.00 (1.00, 1.00)	<0.001
Addiction	2.00 (1.60, 2.20)	1.00 (1.00, 1.10)	<0.001
Medication misuse and non-compliance	1.67 (1.33, 2.00)	1.00 (1.00, 1.00)	<0.001

COMM: Current Opioid Misuse Measure; IQR: Interquartile range

There are a variety of tools currently used to identify those who may misuse opioids, such as the ORT, Screener and Opioid Assessment for Patients with Pain, and Brief Risk Interview. However, these tools have limitations and inconsistent accuracy in determining patients' risk levels for opioid misuse.[7] For example, the sensitivity and specificity of ORT have been found to range from 0.20–0.99 and 0.16–0.88.[7] The Centres for Disease Control and Prevention guidelines state that the usage of such tools should be complemented by discussions with patients and caregivers, and reviewing clinical records and prescription data.[8]

Our study found that high ORT scores did not appear to predict aberrant opioid use. This could be due to the low overall ORT scores observed among the study population which hindered the detection of an association. However, our study showed that high PHQ-9 and GAD-7 scores were associated with an increased risk of aberrant opioid use.

While the association between singlehood and tramadol misuse is not unique, the connection between relationship status and opioid misuse is not well understood.[9] This association could be confounded by other factors, such as economic stress or mental health issues.

This pilot study has a few limitations. First, we observed a 6% margin of error associated with our estimate of tramadol misuse. Although this margin is acceptable in survey studies, clinical decision-making may benefit from more precise estimates.[10] Second, we chose to use an epidemiological survey for our research. Therefore, all data were self-reported and could be potentially influenced by reporting or memory biases.

In conclusion, tramadol misuse is significant in our pain clinics at 24.8%, despite most patients scoring low on the ORT. Risk factors include high GAD-7 scores, high PHQ-9 scores and singlehood. Based on these results, we recommend the use of PHQ-9 and GAD-7 questionnaires in addition to an opioid risk screening tool before initiating opioids.

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