

A Comprehensive Review of Adolescents' Substance Use in Burundi: Prevalence, Risk Factors, and Associated Effects

Abstract

The prevalence of substance use among adolescents in Burundi has emerged as a significant public health concern, necessitating urgent attention and intervention. This study reviews existing literature and data on adolescent substance use, focusing on the types of substances commonly used and the associated effects. The findings indicate a troubling trend of increasing tobacco and alcohol use among young people despite regional and international efforts to combat substance abuse. The East African Community (EAC) has recognised the rising rates of substance use and has implemented policies aimed at prevention and management; however, enforcement remains inconsistent in Burundi. The review highlights the need for comprehensive national campaigns to educate adolescents and their families about the dangers of substance use, employing culturally relevant information and engaging community leaders. Additionally, the study advocates for introducing substance use education into school curricula, emphasising life skills and resilience training. Establishing adolescent-specific rehabilitation and counselling facilities is also recommended to address substance use issues effectively. Moreover, the research underscores the importance of creating job opportunities and recreational facilities to reduce idle time among adolescents, thereby mitigating the conditions that lead to substance use. The study concludes that a multi-faceted approach involving collaboration between government, non-governmental organisations, and local communities is essential to combat adolescent substance use in Burundi. By addressing the root causes and providing adequate support systems, it is possible to foster healthier environments for the youth, ultimately contributing to the community's overall well-being.

1. Introduction

Adolescence is a developmental phase associated with a higher risk of exploring and using substances such as alcohol, marijuana, and tobacco (West et al., 2020; Kyei-gyamfi et al., 2024). Substance use, whether ongoing or sporadic, is harmful and should not be trivialised, disregarded, or permitted by adolescents (Levy, 2022). Substance use is linked to a higher incidence of road traffic accidents, violence, sexual risk-taking (such as unprotected sex), mental health disorders (including learning disorders), and suicide (Kyei-gyamfi et al., 2024).

Substance use among adolescents remains a growing important public health concern in Africa (Jumbe et al., 2021). The most current Global Youth Tobacco Surveys data from 53 African countries, covering 2003-2020, found that the prevalence of tobacco use among African adolescents aged 11 to 17 years was high but similar among tobacco products (Pokothoane et al., 2024). Also, pooled estimates from sub-Saharan Africa imply that the largest proportion of alcohol usage among adolescents is in Southern Africa (40.82%), followed by East Africa (34.25%) (Ntho et al., 2024; Olawole-Isaac et al., 2018).

Burundi is an East African country characterised mostly by a young population, with 65% of its inhabitants under the age of 25. Of this young population, 23% are adolescents (Nyoni & Nyoni, 2022). The Burundi government has renewed its commitment to improve its population's health through the National Health Development Plan (PNDS III), with the goal of achieving SDG 3: "To enable all people to live in good health and to promote well-being for all at all ages." Although significant progress has been made, Burundi still needs to make more progress to achieve this goal, as adolescents and youth are vulnerable to problems such as tobacco, alcohol, and other psychoactive substances, according to the Demographic and Health Survey (DHS 2016-2017) (UNICEF Burundi, 2023). These are national public concerns that should not be dismissed by a low-income country like Burundi, which is recovering from many years of war, because, in the most serious cases, harmful drug use can lead to a cycle in which damaged socio-economic standing and ability to develop relationships feed substance use (United Nations Office on Drugs and Crime (UNODC), 2018). Hence, the systematic reviews in this paper seek to identify previous studies that focused on adolescent substance use in Burundi. This paper exposes the prevalence and associated effects of substance use among adolescents in Burundi. Thus, this paper seeks to answer the following specific questions:

What is the prevalence of substance use among adolescents in Burundi?

What is the associated effect of substance use among adolescents in Burundi?

1. Methodology

1.1. Search Strategies

The search was conducted through the Google.com search engine. The search themes included phrases related to the research issue, such as "Adolescents Substance Use/Drug Abuse/Drug Use in Burundi" and "Associated Effects of Substance Use among Adolescents in Burundi." The search yielded a large number of online databases, including Research Gate, Sage, Routledge, ERIC, IISTE, and Springer, from which 54 papers on the topics mentioned above were accessible.

1.2. Selection Criteria

Thirteen publications were chosen to examine Adolescent Substance Use in Burundi. These publications are dated from 2008 to 2024. All studies were published in English, including Burundi official documents, research papers from national and international agencies, e-books, and peer-reviewed journal articles. The papers were chosen based on their relevance to the current study and consistency in answering the research questions.

Table 1. Overview of the search results

Themes	Total search results	Selected Publications
Prevalence of substance use among adolescents in Burundi	29	7
Associated effects of substance use among adolescents in Burundi	25	6
Total	54	13

1.3. Data Analysis

The qualitative data on adolescents' substance use in Burundi was analysed using a configurational synthesis approach to Systematic Reviews of secondary data. This was done by reading and re-reading different published studies on the topics of interest to find some quality data and then exploring the relationship of similarities and disparities and some configurations emerging from the data that can be integrated, associated, and translated to understand better and explain the phenomena under investigation, answer the current research

questions, and produce new synthetic accounts of the phenomena of interest in this latest study. As a result, relevant inferences were drawn regarding the research questions.

2. Results and Discussion

2.1. What is the prevalence of substance use among adolescents in Burundi?

Substance use has long been a public health concern worldwide, including in Africa (Mupara et al., 2022). The East African Community (EAC) countries have ratified the 1961 World Single Convention on Narcotic Drugs, as well as the 2001 EAC Protocol on Combating Drug Trafficking in the African Region (Rugira, 2012); however, the EAC has noted an increase in tobacco and alcohol use among adolescents over time (EAC Secretariat, 2019).

2.1.1. Tobacco Use

In the United States, the prevalence of tobacco use among adolescents has been a concern for many years. The National Youth Tobacco Survey (NYTS) revealed that 23.6% of high school students in the U.S. had used a tobacco product in the past 30 days, including cigarettes, e-cigarettes, cigars, and smokeless tobacco. While there has been a decline in cigarette smoking among U.S. adolescents, the use of e-cigarettes has risen dramatically in recent years (Centers for Disease Control and Prevention, 2020). Also, the European School Survey Project on Alcohol and Other Drugs (ESPAD) has consistently found that tobacco use among adolescents is widespread in Europe. The 2019 ESPAD revealed that around 30% of 15-16-year-olds in European countries had smoked at least once in their lifetime, with a higher prevalence in Eastern European countries. In the Burundian context, the Burundi Global Youth Tobacco Survey (GYTS) data on the prevalence of cigarette and other tobacco use among 1,110 13-15 year adolescents indicates that 19.1% of adolescents had ever smoked cigarettes (Boy=23.9%, Girl=14.1%), 19.3% currently use any tobacco product (Boy=20.7%, Girl=16.8%), 4.6% currently smoke cigarettes (Boy=5.8%, Girl=3.2%), 16.1% currently use other tobacco products (Boy=17.1%, Girl=14.3%), and 17.8% of never smokers are likely to initiate smoking in the coming years (World Health Organization, 2008).

2.1.2. Alcohol Use

Globally, adolescent alcohol consumption is a significant public health issue. In developed countries, studies have consistently shown high rates of underage drinking. For example,

research in Europe and North America has revealed that alcohol is the most commonly used substance among adolescents, and the age of initiation has been decreasing (Danielsson et al., 2012). In the United States, the National Institute on Alcohol Abuse and Alcoholism (2020) revealed that by age 18, about 60% of adolescents have tried alcohol, and 30% have engaged in binge drinking.

According to (Egide Haragirimana and Gemma Mitchell, 2024), the total alcohol consumption among 15-19-year-olds in Burundi in 2010 was 10.7 litres for males and 4.0 for females. Nigeria, Uganda, Swaziland, Mali and Burundi - are among the top 30 countries in terms of per capita alcohol consumption. Burundi and Nigeria were also among the twenty-two countries with the most significant increase in per capita alcohol consumption among adolescents (13-19 years) between 1970 and 1996 (Wolvelaer, 2015). Moreover, Burundi is one of four sub-Saharan countries with the highest recorded consumption per capita (13-19 years) (Acuda et al., 2011). Research has shown that alcohol use disorders affect 6.8% of Burundi's population aged 15 and above, compared to 3.7% in the rest of the World Health Organisation African region. The prevalence of excessive episodic drinking (consuming at least 60 g or more of pure alcohol on at least one occasion in the previous 30 days) is 16.6% of the population aged 15 or above (WHO, 2016).

2.2. What is the associated effect of substance use among adolescents in Burundi?

The risks related to tobacco and alcohol use among adolescents are not limited to Burundi. These problems are prevalent worldwide, with adolescent populations across different countries facing similar risks. In low-income countries like Burundi, limited access to healthcare and education about the dangers of smoking and alcohol use exacerbates the situation (Alkhatib et al., 2021).

2.2.1. Health Impacts

According to (Xi et al., 2016), tobacco use is a leading cause of preventable diseases worldwide, particularly among adolescents. Exposure to second-hand smoke, especially in enclosed spaces, increases the likelihood of developing heart disease, lung cancer, and respiratory conditions (Dunbar et al., 2013). (Wang et al., 2015) revealed that second-hand smoke exposure in adolescents was associated with increased risks of asthma and respiratory infections in the United States. All types of tobacco use, such as smokeless tobacco,

cigarettes, and waterpipes, have been linked to negative health outcomes for Burundi adolescents. Tobacco consumption contributes to diseases such as lung cancer, coronary heart disease, and respiratory disorders among adolescents in the country (Niyukuri et al., 2022). Also, non-smokers who are exposed to second-hand smoke suffer the same negative health consequences as smokers. The authors later said that, long-term exposure to second-hand smoke raises the risk of coronary heart disease, lung cancer, and respiratory issues among adolescents in Burundi.

Alcohol use among adolescents often leads to an increased incidence of accidental injuries, violence, and risky sexual behaviour, all of which can have long-term health effects. Heavy alcohol consumption during adolescence can disrupt brain development, increase the likelihood of developing liver disease, and lead to higher risks of cancers, including those of the liver and pancreas (Tapert et al., 2005). According to (Pilowsky et al., 2009), early alcohol consumption can also increase the chances of developing alcohol dependence later in life. Similarly, many of the adolescents in Burundi who engaged themselves in excessive alcohol consumption had developed a variety of health conditions and disorders, such as certain types of liver disease, cancer, and heart disease (Tapert et al., 2005).

2.2.2. Socio-Economic Impact

In East Africa, the socio-economic effects of substance use are similarly profound. In countries like Kenya and Uganda, tobacco and alcohol consumption contributes to poverty by increasing household spending on tobacco and alcoholic products and medical bills related to tobacco and alcohol-related illnesses (NJERU, 2015). Lawn et al. (2019) stated that many East African adolescents who struggle with substance abuse are less likely to complete their education or gain meaningful employment as they become trapped in a cycle of addiction, crime, and poverty. This not only affects the individuals but also contributes to broader societal instability.

Substance use harms Burundi's public and fiscal health, undermining efforts to promote equity, alleviate poverty, and maintain the environment (Ranson et al., 2007). Research shows that adolescents in Burundi who turn to substance use face Socio-economic problems such as hunger and poverty, the inability to stay in school or secure a reasonable job, being "tricked" into sex in exchange for food or the promise of marriage, and accepting the risk of dangerous careers like stealing, prostitution, and selling drugs. These activities increase the

risk of HIV/AIDS, sexual violence, and criminal involvement, further perpetuating the socio-economic challenges faced by these adolescents (WHO, 2002). In Burundi, substance abuse compounds the challenge of integrating young people into the formal economy (Sommers, 2013).

2.2.3. Development Impact

According to Singer (2008), in many African countries, substance use spending leads to significant financial stress, with families in poverty often prioritising tobacco and alcohol purchases over basic life necessities. In Malawi, Mozambique, and Tanzania, tobacco and alcohol consumption alone takes up a substantial portion of household income, which could otherwise be used to improve living conditions and educational opportunities. (Kadzamira et al., 2021) The high cost of tobacco and alcohol products not only places a strain on household budgets but also exacerbates the challenges faced by adolescents in terms of education and health. According to (Cox et al., 2007), tobacco and alcohol use is associated with lower academic performance and higher school dropout rates, as adolescents who smoke are more likely to face health issues that can interfere with their studies. In addition, tobacco and alcohol consumption exacerbates health problems among adolescents (Dowdell et al., 2011). For example, smoking increases the risk of respiratory diseases, cancers, and cardiovascular conditions, which can result in long-term health complications, decreased life expectancy, and increased healthcare costs. These health burdens can further restrict economic mobility for adolescents, reducing their future employment prospects and ability to contribute to economic development. Walls et al. (2020) emphasise that the financial costs of tobacco and alcohol-related diseases are exceptionally high in low-income countries, where healthcare systems are often under-resourced and unable to provide adequate care for those affected by smoking-related illnesses. In countries like Kenya and Uganda, tobacco and alcohol spending undermines efforts to achieve poverty reduction and sustainable development. Tobacco and alcohol are often consumed by individuals in the lowest income brackets, exacerbating the cycle of poverty and reducing the ability of families to invest in long-term development opportunities (David et al. (2010)). The funds spent on tobacco and alcohol could instead be invested in infrastructure, healthcare, or education, all of which are critical for improving the well-being of adolescents and families (Onwasigwe, 2010).

Tobacco spending diverts funds away from the resources needed to lift families out of poverty. In Burundi, a smoker must spend 39.62% of GDP per capita to purchase 100 packs

of the most popular cigarettes yearly (The Tobacco Atlas, 2019). In Burundi, where the GDP per capita is low, the proportion of household income spent on tobacco products leaves families with fewer resources for essential needs such as food, healthcare, and education. This economic burden disproportionately affects adolescents, who are vulnerable to the long-term consequences of poverty, including malnutrition, lack of education, and limited access to healthcare (Sreeramareddy et al., 2014). The costs associated with treating diseases linked to smoking and alcohol abuse place a strain on the government, diverting funds from other critical areas of development, such as infrastructure and education (David et al. (2010)).

3. Conclusion

The prevalence of substance use among adolescents in Burundi, particularly in the form of alcohol and tobacco consumption, is a significant public health and socio-economic challenge. The data from various surveys and reports highlight troubling trends in adolescent behaviour, with both alcohol and tobacco use rising steadily in recent years. The health impacts associated with these substances are profound, contributing to long-term diseases such as cancer, liver disease, heart disease, and respiratory disorders, which hinder the physical and cognitive development of young individuals. Moreover, the socio-economic implications of substance use are far-reaching. Adolescents engaging in alcohol and tobacco consumption face a range of challenges, including poverty, school dropout, and an increased risk of exploitation through activities like sex for survival or criminal involvement. These issues contribute to the broader cycle of poverty, undermining efforts to promote equity and sustainable development in Burundi. The financial burden on families due to substance use further diverts essential resources away from critical needs such as education, healthcare, and overall economic development. The developmental impact of substance use is also evident, as funds that could otherwise be invested in long-term opportunities are spent on tobacco products, exacerbating household financial strain and limiting growth opportunities.

4. Recommendations

- ✓ Launch national campaigns to educate adolescents and their families about the dangers of tobacco, alcohol, and other substances. These initiatives should employ culturally relevant information and include community leaders to increase their success. Topics should include health dangers, socio-economic implications, and long-term consequences of substance use;

- ✓ Formulate and strictly enforce regulations prohibiting the sale and advertising of tobacco and alcohol to minors. Collaborate with local law enforcement to ensure compliance, particularly in rural and urban areas where enforcement varies;
- ✓ Introduce substance use education into the school curriculum, focusing on life skills, resilience, and peer pressure management. Collaborate with non-governmental organisations to equip teachers with the necessary training and resources to administer these programs effectively;
- ✓ Establish and fund adolescent-specific rehabilitation and counselling facilities to address substance use issues. To ensure long-term healing, train healthcare providers to deliver age-appropriate therapies and involve families in the therapy process;
- ✓ Create job opportunities and recreational facilities for adolescents to reduce idle time and mitigate the conditions that lead to substance use. Community-based programs, such as youth sports leagues and skill-building seminars, can provide beneficial alternatives to substance abuse.

References

- Acuda, W., Othieno, C. J., Obondo, A., & Crome, I. B. (2011). The epidemiology of addiction in Sub-Saharan Africa: A synthesis of reports, reviews, and original articles. *American Journal on Addictions*, 20(2), 87–99. <https://doi.org/10.1111/j.1521-0391.2010.00111.x>
- Alkhatib, A., Nnyanzi, L. A., Mujuni, B., Amana, G., & Ibingira, C. (2021). Preventing multimorbidity with lifestyle interventions in sub-saharan africa: A new challenge for public health in low and middle-income countries. *International Journal of Environmental Research and Public Health*, 18(23). <https://doi.org/10.3390/ijerph182312449>
- Cox, R. G., Zhang, L., Johnson, W. D., & Bender, D. R. (2007). Academic performance and substance use: Findings from a state survey of public high school students. *Journal of School Health*, 77(3), 109–115. <https://doi.org/10.1111/j.1746-1561.2007.00179.x>
- Danielsson, A. K., Wennberg, P., Hibell, B., & Romelsjö, A. (2012). Alcohol use, heavy episodic drinking and subsequent problems among adolescents in 23 European countries: Does the prevention paradox apply? *Addiction*, 107(1), 71–80. <https://doi.org/10.1111/j.1360-0443.2011.03537.x>
- Dowdell, E. B., Posner, M. A., & Hutchinson, M. K. (2011). Cigarette Smoking and Alcohol Use among Adolescents and Young Adults with Asthma. *Nursing Research and Practice*, 2011, 1–7. <https://doi.org/10.1155/2011/503201>
- Dunbar Andrew, Gotsis William, F. W. (2013). *Second-Hand Tobacco Smoke and Cardiovascular Disease Risk: An Epidemiological Review*. 21(2). <https://doi.org/10.1097/CRD.0b013e31827362e4>
- EAC Secretariat. (2019). *East African Community (EAC) Regional Policy on Prevention , Management and Control of Alcohol , Drugs and Other Substance Use*.
- Egide, Haragirimana, Gemma Mitchell, I. U. (2024). *Evaluating the progress of alcohol policies in Burundi against the WHO ‘Best Buys’ interventions: Implications for public health*. 12, 57–70.
- Jumbe, S., Kamninga, T. M., Mwalwimba, I., & Kalu, U. G. (2021). Determinants of adolescent substance use in Africa: a systematic review and meta-analysis protocol. *Systematic Reviews*, 10(1), 1–11. <https://doi.org/10.1186/s13643-021-01680-y>

- Kadzamira, M. A. T. J., Gausi, H. J., & Phiri, T. (2021). *The socio-economic impact of disease burden due to smoking in Malawi*.
- Kyei-gyamfi, S., Kyei-arthur, F., Alhassan, N., Agyekum, M. W., & Abrah, P. B. (2024). Prevalence , correlates , and reasons for substance use among adolescents aged 10 – 17 in Ghana : a cross-sectional convergent parallel mixed-method study. *Substance Abuse Treatment, Prevention, and Policy*, 19(17), 1–9.
- Lawn, W., Aldridge, A., Xia, R., & Winstock, A. R. (2019). Substance-Linked Sex in Heterosexual, Homosexual, and Bisexual Men and Women: An Online, Cross-Sectional “Global Drug Survey” Report. *Journal of Sexual Medicine*, 16(5), 721–732. <https://doi.org/10.1016/j.jsxm.2019.02.018>
- Levy, S. (2022). *Substance Use in Adolescents*. MSD Manual.
- Mupara, L. M., Tapera, R., Selemogwe-Matsetse, M., Kehumile, J. T., Gaogane, L., Tsholofelo, E., & Murambiwa, P. (2022). Alcohol and substance use prevention in Africa: systematic scoping review. *Journal of Substance Use*, 27(4), 335–351. <https://doi.org/10.1080/14659891.2021.1941356>
- Niyukuri, D., Nyandwi, J., Kamatari, O., Uwizeyimana, C., & Mikaza, C. (2022). *A leap to non-communicable diseases epidemic in Burundi : overall trends of the disproportionate burden*.
- NJERU, L. W. (2015). *THE IMPACT OF ALCOHOL ABUSE ON THE WELFARE OF RURAL HOUSEHOLDS: A CASE STUDY OF MBETI-NORTH WARD, EMBU COUNTY*. November.
- Ntho, T. A., Themane, M. J., Sepadi, M. D., Phochana, T. S., Sodi, T., & Quarshie, E. N. B. (2024). Prevalence of alcohol use and associated factors since COVID-19 among school-going adolescents within the Southern African Development Community: a systematic review protocol. *BMJ Open*, 14(2), 1–7. <https://doi.org/10.1136/bmjopen-2023-080675>
- Nyoni, S. P., & Nyoni, T. (2022). Detecting Future Trends of Adolescent Fertility for Burundi Using the Double Exponential Smoothing Technique. *International Research Journal of Innovations in Engineering and Technology*, 6(12), 148–152.
- Olawole-Isaac, A., Ogundipe, O., Amoo, E. O., & Adeloye, D. (2018). Substance use among adolescents in sub-Saharan Africa: A systematic review and meta-analysis. *South*

- African Journal of Child Health*, 12(Special Issue), S79–S84.
<https://doi.org/10.7196/SAJCH.2018.v12i2.1524>
- Onwasigwe, C. (2010). *Disease Transition in Sub-Saharan Africa: The Case of Non-Communicable Diseases in Nigeria*. 1–127.
- Organisation, W. H. (2002). Preventing HIV/AIDS and Promoting Sexual Health Preventing HIV/AIDS and Promoting Sexual Health Among Especially Vulnerable Young People. *UNICEF/UNAIDS/WHO (2002) Young People and HIV/AIDS: Opportunity in Crisis*. New York, UNICEF, July.
- Pilowsky, D. J., Keyes, K. M., & Hasin, D. S. (2009). *Adverse Childhood Events and Lifetime Alcohol Dependence*. 99(2), 258–263.
<https://doi.org/10.2105/AJPH.2008.139006>
- Pokochoane, R., Terefe, A. G., Christus, M. C., & Dadirai Mdege, N. (2024). *Prevalence and determinants of tobacco use among school-going adolescents in 53 African countries: evidence from Global Youth Tobacco Surveys*.
- Ranson, K., Poletti, T., Bornemisza, O., & Sondorp, E. (2007). *CONFLICT-AFFECTED FRAGILE STATES*.
- Rugira, J. (2012). Social factors influencing adolescents’ drug use and policy implementation in East-Africa By. *The Seventh Tanzanian – Dutch Health Workers Annual Conference “Focus on Mental Health”, November 11-12, 2012*, 1–13.
- Singer, M. (2008). Drugs and development: The global impact of drug use and trafficking on social and economic development. *International Journal of Drug Policy*, 19(6), 467–478. <https://doi.org/10.1016/j.drugpo.2006.12.007>
- Sommers, M. (2013). Adolescents and Violence Lessons from Burundi. *Institute of Development Policy and Management, University of Antwerp*.
- Sreeramareddy, C. T., Pradhan, M. M., & Sin, S. (2014). Prevalence, distribution, and social determinants of tobacco use in 30 sub-Saharan African countries. *BMC Medicine*, 12(1), 1–13. <https://doi.org/10.1186/s12916-014-0243-x>
- Tapert, S. F., Ph, D., Caldwell, L., & Burke, C. (2005). *Adolescent Brain*. 28(4).
- UNICEF Burundi. (2023). *Burundi Health Budget Analysis 2022-2023*. 1–6.
- United Nations Office on Drugs and Crime (UNODC). (2018). *Drugs and associated issues among young people and older people*.

- Walls, H., Cook, S., Matzopoulos, R., & London, L. (2020). Advancing alcohol research in low-income and middle-income countries: A global alcohol environment framework. *BMJ Global Health*, 5(4), 1–8. <https://doi.org/10.1136/bmjgh-2019-001958>
- Wang, Z., May, S. M., Charoenlap, S., Pyle, R., Ott, N. L., Mohammed, K., & Joshi, A. Y. (2015). Effects of secondhand smoke exposure on asthma morbidity and health care utilisation in children: a systematic review and. *Annals of Allergy, Asthma & Immunology*, 115(5), 396-401.e2. <https://doi.org/10.1016/j.anai.2015.08.005>
- Wolvelaer, F. Van. (2015). *Alcohol addiction treatment programmes in Bujumbura, Burundi*. 0–37.
- World Health Organization. (2008). *Global Youth Tobacco Survey (GYTS) Fact Sheet (Ages 13-15)*.
- World Health Organization. (2016). *Burundi: Alcohol consumption: Levels and patterns*.
- Xi, B., Liang, Y., Liu, Y., Yan, Y., Zhao, M., Ma, C., & Bovet, P. (2016). Tobacco use and second-hand smoke exposure in young adolescents aged 12-15 years: data from 68 low-income and middle-income countries. *The Lancet Global Health*, 4(11), e795–e805. [https://doi.org/10.1016/S2214-109X\(16\)30187-5](https://doi.org/10.1016/S2214-109X(16)30187-5)