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Clinical Research

Prevalence and Effects of Cigarette Smoking, Cannabis Consumption, and Co-use in Adults From 15 Countries With Congenital Heart Disease

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ABSTRACT

Background: The prevalence and effects of cigarette smoking and cannabis use in persons with congenital heart disease (CHD) are poorly understood. We (1) described the prevalence of cigarette smoking, cannabis consumption, and co-use in adults with CHD; (2) investigated intercountry differences; (3) tested the relative effects on physical functioning, mental health, and quality of life (QOL); and (4) quantified the differential effect of cigarette smoking, cannabis use, or co-use on those outcomes.

Methods: APPROACH-IS was a cross-sectional study, including 4028 adults with CHD from 15 countries. Patients completed questionnaires to measure physical functioning, mental health, and QOL. Smoking status and cannabis use were assessed by means of the Health Behaviour Scale—Congenital Heart Disease. Linear models with doubly robust estimations were computed after groups were balanced with the use of propensity weighting.

Results: Overall, 14% of men and 11% of women smoked cigarettes only; 8% of men and 4% of women consumed cannabis only; and 4% of men and 1% of women used both substances. Large intercountry variations were observed, with Switzerland having the highest prevalence for smoking cigarettes (24% of men, 19% of women) and Canada the highest for cannabis use (19% of men, 4% of women). Cigarette smoking had a small negative effect on patient-reported outcomes, and the effect of cannabis was negligible. The effect of co-use was more prominent, with a moderate negative effect on mental health.

Conclusions: We found significant intercountry variability in cigarette and cannabis use in adults with CHD. Co-use has the most detrimental effects on patient-reported outcomes.

RÉSUMÉ

Contexte : La prévalence et les effets de la consommation de tabac et de cannabis chez les personnes présentant une cardiopathie congénitale sont mal compris. Nous avons : 1) décrit la prévalence du tabagisme, de la consommation de cannabis et de l'utilisation concomitante de tabac et de cannabis chez des adultes présentant une cardiopathie congénitale; 2) étudié les différences entre pays; 3) examiné les effets relatifs sur le fonctionnement physique, la santé mentale et la qualité de vie (QdV); et 4) quantifié l'effet différentiel du tabagisme, de la consommation de cannabis et de l'emploi concomitant de tabac et de cannabis sur ces paramètres.

Méthodologie : APPROACH-IS est une étude transversale menée auprès de 4 028 adultes présentant une cardiopathie congénitale dans 15 pays. Les patients ont répondu à des questionnaires visant à évaluer leur fonctionnement physique, leur santé mentale et leur QdV. Le tabagisme et la consommation de cannabis ont été évalués au moyen de l'échelle HBS-CHD (*Health Behaviour Scale – Congenital Heart Disease*, pour l'évaluation des comportements liés à la santé chez les personnes atteintes d'une cardiopathie congénitale). Des modèles linéaires et des estimations doublement robustes ont été appliqués après équilibrage des groupes au moyen de scores de propension.

Résultats : Dans l'ensemble, 14 % des hommes et 11 % des femmes fumaient la cigarette seulement; 8 % des hommes et 4 % des femmes consommaient du cannabis seulement; et 4 % des hommes et 1 % des femmes fumaient la cigarette et consommaient du cannabis. De grandes variations entre pays ont été observées; le tabagisme était plus prévalent en Suisse (24 % des hommes et 19 % des femmes), tandis que la consommation de cannabis était plus élevée au Canada (19 % des hommes et 4 % des femmes). Le tabagisme avait un léger effet négatif sur les résultats rapportés par les patients, tandis que l'effet du cannabis était négligeable. L'utilisation concomitante du tabac et du cannabis avait un effet plus marqué, et influait de façon modérément négative sur la santé mentale.

Conclusions : Nous avons observé une grande variabilité entre les pays à l'égard de la consommation de tabac et de cannabis chez les adultes présentant une cardiopathie congénitale. L'utilisation concomitante du tabac et du cannabis avait les effets les plus préjudiciables sur les résultats rapportés par les patients.

Cigarette smoking is a well known cardiovascular risk factor. In individuals with congenital heart disease (CHD), smoking can be even more detrimental because of a compounded effect on already impaired cardiovascular structure and physiology. Studies conducted in different countries have found that 5%-28% of adolescents and adults with CHD smoke cigarettes.[1-13] There is evidence of geographic variability in cigarette smoking, although a direct comparison of study findings is not possible owing to the different research methods used. Furthermore, all previous studies were conducted in Europe or North America, limiting the generalizability of findings for the global population of patients with CHD.

Data on the effects of cigarette smoking in persons with CHD are scarce. One study in 26 European countries revealed that current smoking was associated with increased cardiovascular mortality in adults with transposition of the great arteries.[2] A study in the Netherlands showed that smoking predicted the development of coronary artery disease,[14] and a study in the USA demonstrated that smoking was an independent predictor for emergency department visits.[9] Overall, the relative contribution of cigarette smoking to adverse outcomes in patients with CHD is largely unknown.

Cannabis (ie, marijuana) is another substance that is frequently used in some countries. Like cigarettes, cardiovascular effects of cannabis have been described, including tachyarrhythmias, angina and acute myocardial infarction, stroke, and coronary vasospasm.[15] To the best of our knowledge, only 4 studies have reported on the prevalence of cannabis use in CHD, yielding a range of 6%-18%.[3,4,6,13] Variability in usage rates across countries has also been observed, with studies once again limited to Europe and North America. The effects of cannabis on physical and psychosocial outcomes in persons with CHD remain unexplored.

To tackle gaps in knowledge on cigarette smoking and cannabis use in CHD, the aims of the present study were to: (1) describe the prevalence of cigarette smoking, cannabis use, and their co-use in a large international sample of adults with CHD; (2) investigate intercountry differences in use among CHD patients; (3) test the relative effect of use on

self-reported physical functioning, mental health, and quality of life (QOL); and (4) quantify the differential effects of cigarette smoking, cannabis use, and co-use on those patient-reported outcomes.

Methods

Study population and procedure

The "**A**ssessment of **P**atterns of **P**atient-**R**eported **O**utcomes in **A**dults With **C**ongenital **H**eart Disease—**I**nternational **S**tudy" (APPROACH-IS) was a cross-sectional study in 15 countries from 5 continents: Argentina, Australia, Belgium, Canada, France, India, Italy, Japan, Malta, Norway, Sweden, Switzerland, Taiwan, the Netherlands, and the United States of America.[16] Inclusion criteria were: (1) diagnosis of CHD, (2) age $\geq$ 18 years, (3) diagnosis established before adolescence, (4) continued follow-up at a CHD center or included in a national or regional registry, and (5) physical, cognitive, and language capabilities to complete self-report questionnaires. Patients were excluded if they had a heart transplantation or primary pulmonary hypertension.[16] Eligible patients received a questionnaire package by mail or were approached in clinic during an outpatient visit. Overall, 4028 adults with CHD were enrolled in APPROACH-IS.[17] A detailed description of patient characteristics is provided in Table 1. A description of patient characteristics per country has been previously published.[17]

The study complies with the Declaration of Helsinki and was approved by the Institutional Review Board of University Hospitals Leuven/KU Leuven, Belgium (coordinating center), and by the local Institutional Review Boards of participating centers (when required). Written informed consents were obtained from all participants. Rationale, design, and methods of APPROACH-IS have been detailed previously in a separate methods paper.[16]

Measures

Cigarette smoking status and cannabis use were assessed with the use of the Health Behaviour Scale—Congenital Heart Disease.[18] Patients were asked: "Do you smoke cigarettes occasionally or regularly?" (yes/no), and "How often, in the last 12 months, did you take the following drugs: Cannabis (marihuana, hash)" (never; once a month or less; 2-4 times a month; 2 or more times a week). Patients who smoked cigarettes subsequently indicated how many days per month they smoked and how many cigarettes per day, which allowed us to calculate the average number of cigarettes per month.

Self-reported physical functioning was measured with the use of the physical component summary of the 12-item Short-Form Health Survey.[19] Mental health was assessed with the use of the mental component summary of the 12-item Short-Form Health Survey[19] and the anxiety and depression subscales of the Hospital Anxiety and Depression Scale.[20] QOL was evaluated with the use of a linear analog scale (LAS)[21] and the Satisfaction With Life Scale.[22] Supplemental Table S1 provides an expanded definition of the domains as applied in APPROACH-IS as well as the interpretation of scores for the individual questionnaires.

Table 1. Demographic and medical background variables in 4028 adults with congenital heart disease

Variable	n (%)
Sex: women (n = 4012)	2115 (52.7)
Median age, y (n = 4021)	32.0 (IQR 25-42)
Background (n = 3944)	
White or Caucasian	2908 (73.7)
Asian	781 (19.8)
Hispanic or Latino	131 (3.3)
Middle-Eastern or Arabic	52 (1.3)
Black or African-American	41 (1.0)
Other	31 (0.8)
Educational level (n = 3989)	
Less than high school	223 (5.6)
High school	1715 (43.0)
College degree	846 (21.2)
University degree	1205 (30.2)
Employment status (n = 4005)	
Part-time or full-time work	2554 (63.7)
Job seeking, unemployed, or disability	515 (12.9)
Homemaker or retired	331 (8.3)
Full-time student	327 (8.2)
Other	278 (6.9)
Marital status (n = 4008)	
Married or living with partner	2045 (51.0)
Never married	1753 (43.7)
Divorced or widowed	204 (5.1)
Other	6 (0.2)
Children: yes (n = 4004)	1584 (39.6)
Patient-reported New York Heart Association assessment (n = 3927)	
Class I	2109 (53.7)
Class II	1375 (35.0)
Class III	287 (7.3)
Class IV	156 (4.0)
Complexity of heart defect (n = 4028)	
Simple	1040 (25.8)
Moderate	1957 (48.6)
Complex	1031 (25.6)

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Cigarette smoking and cannabis use in the general population

Data on the prevalence of current cigarette smoking in men and women in the general population in 2013 were obtained from the World Health Organisation's Global Health Observatory data repository (http://apps.who.int/gho/data/node.main.1250).[23] Because data from Taiwan were not included in this repository, we used the Taiwan Tobacco Control Annual Report from the Health Promotion Administration, Ministry of Health and Welfare (https://www.hpa.gov.tw/EngPages/Detail.aspx?nodeid=1069&pid=6139). Data on cannabis use was obtained from the World Drug Report 2017 from the United Nations Office on Drugs and Crime (https://dataunodc.un.org/drugs/prevalence_table).[24] Most of these data was for the years 2013-2014.

Statistical analyses

Continuous data are presented as mean $\pm$ SD if normally distributed and as median (interquartile range [IQR]) if not normally distributed. Categoric variables are presented by percentage. Univariable group comparisons were performed with the use of the Mann-Whitney *U* test for nonnormally distributed data. To evaluate the effects of cigarette smoking and cannabis use on outcomes, we categorized patients into 4 groups: (1) patients who reported cigarette smoking only; (2)

patients who reported cannabis use only; (3) patients with co-use of cigarettes and cannabis; and (4) patients who did not use either cigarettes or cannabis. We used a linear model to compare the mean scores of the outcomes among the 4 groups, where the group of nonusers served as reference group.

Given that the 4 groups of users differed in baseline characteristics, the groups could not be directly compared without introducing bias. Therefore, we used propensity weighting analyses to balance the groups on relevant covariates that could potentially confound the results of an unweighted analysis. This approach mimics a randomized design, and thus it is used for causal inferences. With propensity weighting, the full study population is used, improving efficiency compared with traditional propensity-matching procedures. We used multinomial propensity weighting[25] with the use of the 4 "treatment" groups. This group assignment was modelled as the dependent variable and the demographic, and medical variables listed in Supplemental Table S2 were included as covariates. Supplemental Figure S1 depicts the effect sizes (ESs) among the groups before and after weighting. Before propensity weighting, 92 out of 354 comparisons had standardized ESs greater than 0.2, which were reduced to 34 comparisons after weighting (Supplemental Fig. S1). Weighting rendered the groups more comparable, although small residual imbalances were observed.

After propensity weighting, the groups were compared to investigate the effects of smoking and cannabis use on physical functioning, mental health, and QOL by applying a linear model with doubly robust estimations (ie, both the baseline covariates and the propensity weights were included in the regression model).[26] This approach controlled for remaining imbalances between groups.

To express the magnitude of the effect, we calculated the ES for each group of users compared with the nonusers. By taking the *t*-statistics obtained from the doubly robust estimations, the ES for the standardized mean difference was computed with the use of the following formula: $t\sqrt{([n_1+n_2]/[n_1 \cdot n_2])}$.[27] The following cutoff values for Cohen *d* were used: 0.2-0.5 indicative of a small effect, 0.5-0.8 a moderate effect, and > 0.8 a large effect.[28]

Data analysis was performed with the use of IBM SPSS Statistics for Windows, version 25 (IBM, Armonk, NY) and the Twang package[26] in RStudio, version 1.1.463.[29] A *P* level of < 0.05 was used as the cutoff for statistical significance.

Results

Prevalence of cigarette smoking and cannabis use

In our overall sample, 14% of men and 11% of women indicated smoking cigarettes occasionally or regularly. Among both men and women, the highest prevalence of cigarette smoking was in patients with mild heart defects (Fig. 1A). Cannabis use was reported by 8% of men and 4% of women. Notably, cannabis use was more frequent in men with complex and moderate heart defects than in men with mild defects (Fig. 1B). Co-use of cigarettes and cannabis was reported by 4% of men and 1% of women, with only slight differences across the levels of anatomic complexity (Fig. 1C). Patients who smoked cigarette only consumed a median of 105 (IQR 5-240) cigarettes per month, which was in line with the median of 105 (IQR 14-240) cigarettes per month in co-users ($P = 0.943$). In patients who reported cannabis use only, the pattern of usage was 59.7% once a month or less, 17.2% 2-4 times a month, and 23.1% 2 or more times a week. In co-users, the frequency of cannabis use was somewhat higher: 44.6% once a month or less, 21.7% 2-4 times a month, and 33.7% 2 or more times a week ($P = 0.076$).

Intercountry variation in cigarette smoking and cannabis use

A large intercountry variation in smoking behaviours and cannabis use was observed. The highest prevalence of cigarette smoking was found in Switzerland and the lowest in India (Fig. 2A). In most countries, men were more likely than women to report cigarette smoking; the exceptions were Argentina, Italy, and the USA. In Argentina, Australia, Malta, and Sweden, male and female patients had a similar prevalence of smoking. Compared with published national data, patients with CHD smoked cigarettes less often than people in the general population of their respective countries. In Italy and in Taiwan only, female CHD patients demonstrated a higher prevalence of smoking than women in their general populations (Fig. 2A).

Cannabis use was most prevalent in Canada, with 19% of male patients using it, followed by the USA, where 11% of male and 10% of female patients used cannabis (Fig. 2B). Patients from Asian countries, such as India, Taiwan, and Japan, seldom reported cannabis use. Similarly to cigarette smoking prevalence rates, more men than women used cannabis in most countries; the exceptions were Italy and Japan. Notably, in the USA, cannabis use in women (10%) exceeded by far the proportion of female cannabis users in the overall APPROACH-IS sample (4%). The prevalence of cannabis use in patients with CHD was lower than in the general population, except for male patients in Canada, Switzerland, Norway, and Sweden.

The relative frequency of co-use was highest in Switzerland, France, and Canada (Fig. 2C). None of the patients in Taiwan and Japan reported co-use. Italy was the only country where female patients displayed a higher prevalence of co-use than male patients. Co-use among female patients was 5 times higher in Italian APPROACH-IS patients than the overall female APPROACH-IS cohort.

Effect of cigarette smoking and cannabis use on outcomes

Propensity weighting and doubly robust estimations were performed only on patients who responded to questions about both smoking status and cannabis use (n = 3836; 95% of the total sample). Cigarette smoking had a significant negative effect on the physical component summary ($P = 0.002$), mental component summary ($P < 0.001$), anxiety symptoms ($P = 0.033$), depression symptoms ($P = 0.018$), LAS for QOL ($P = 0.012$), and satisfaction with life ($P < 0.001$; Fig. 3). For cannabis use, the only significant effect was on the physical component summary ($P = 0.027$). Co-use had a significant negative effect on the mental component summary ($P < 0.001$), anxiety symptoms ($P < 0.001$), depression symptoms ($P < 0.001$), LAS for QOL ($P = 0.009$), and

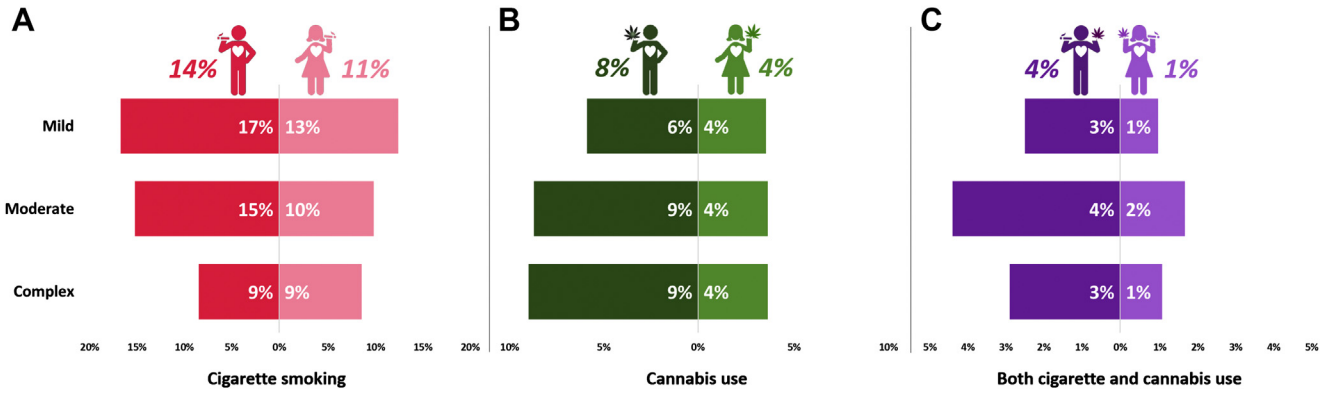

Figure 1. Prevalence of (**A**) cigarette smoking, (**B**) cannabis use, and (**C**) co-use in adults with congenital heart disease, stratified by complexity of the heart defect.

satisfaction with life ($P < 0.001$; Fig. 3). Mediator analyses showed that the effects of cannabis on the physical component summary ($P < 0.001$), mental component summary ($P = 0.025$), anxiety symptoms ($P = 0.01$), and depression symptoms ($P = 0.006$) were mediated by the dose of cannabis. The number of cigarettes per month did not mediate the relationship between cigarette smoking and outcomes.

Differential effect of cigarette smoking and cannabis use on outcomes

For cigarette smoking, the only outcome for which the ES exceeded the threshold of 0.20 (small effect) was satisfaction with life (Fig. 3). The effect of cannabis use was negligible on all outcomes. In co-users, a small effect was observed for anxiety (ES 0.42), depression (ES 0.38), LAS for QOL (ES = −0.27), and satisfaction with life (ES −0.41), whereas a moderate effect was found on the mental component summary (ES = −0.55).

Discussion

Substance use was not uncommon in persons with CHD. Men with CHD reported smoking cigarettes or consuming cannabis more often than women. Large geographic variations were observed. Smoking cigarettes occurred less frequently in patients from Asian countries. Cannabis use was most prevalent in North America and almost nonexistent in Asia. Co-use was reported in up to 7% of male patients in some countries. Cigarette smoking had a negative effect on all patient-reported outcomes, although the effects were small; cannabis use had even smaller negative effects than those observed for cigarette smoking. In contrast, the effects of co-use on outcomes was prominent, with a moderate effect on mental health.

In general, the prevalence of smoking cigarettes in patients with CHD was lower than in the general population. This finding is consistent with previous single-center studies.[1,3,6,8] The proportions of patients who reported smoking cigarettes in the present study were generally lower than those in previous studies in the respective countries. This may correspond with the declining trend in smoking behaviours as observed in the general population worldwide.[30] The magnitude of difference between the prevalence of smoking in patients with CHD and the general population may reflect, in part, the fruit of efforts to counsel patients on adopting a heart-healthy lifestyle.

An estimated 2.5% of the world population consumes cannabis.[24] In countries that participated in APPROACH-IS, about 7% of the general population uses cannabis, which is only 1 percentage-point higher than the 6% cannabis use reported by individuals with CHD. A large geographic variability was found. The use of cannabis was particularly prevalent in North America. Notably, one fifth of the male patients from Canada consumed cannabis. This suggests that cannabis use may be more widespread and more socially acceptable in North America. Indeed, cannabis use has increased over the past decades in the USA.[31] Furthermore, in Canada, an increase of cannabis consumption may be expected in the upcoming years because its use was recently legalized.[32] The large intercountry variations clearly show that cannabis use is culturally dependent and likely to be subject to local legislation. Therefore, single-center or single-country cannabis-use data cannot be generalized to the global CHD population.

A surprising finding was that cannabis use was greater in male patients with complex or moderate heart defects compared with mild defects. Underlying reasons remain speculative. It can be hypothesized that cannabis is used as a means of coping with more complex heart disease. Alternatively, it could reflect greater use of medicinal cannabis in patients with complex disease, although there are no data or clear indications for medicinal use of cannabis in CHD. Overall, in the APPROACH-IS population, complexity of CHD was not associated with the larger category of illicit drug use.[33]

Co-use of tobacco and cannabis is problematic because it is associated with greater nicotine and cannabis dependence, poor cessation outcomes, increased cancer risk, and mental health problems.[34] In the USA population, there is an increasing secular trend of co-use, which may be the result of destigmatization and legalization of cannabis.[34] Therefore, co-use in patients with CHD has the potential to become increasingly problematic in other countries that adopt similar legislation. It remains to be demonstrated whether the detrimental impact of co-use has long-term repercussions on

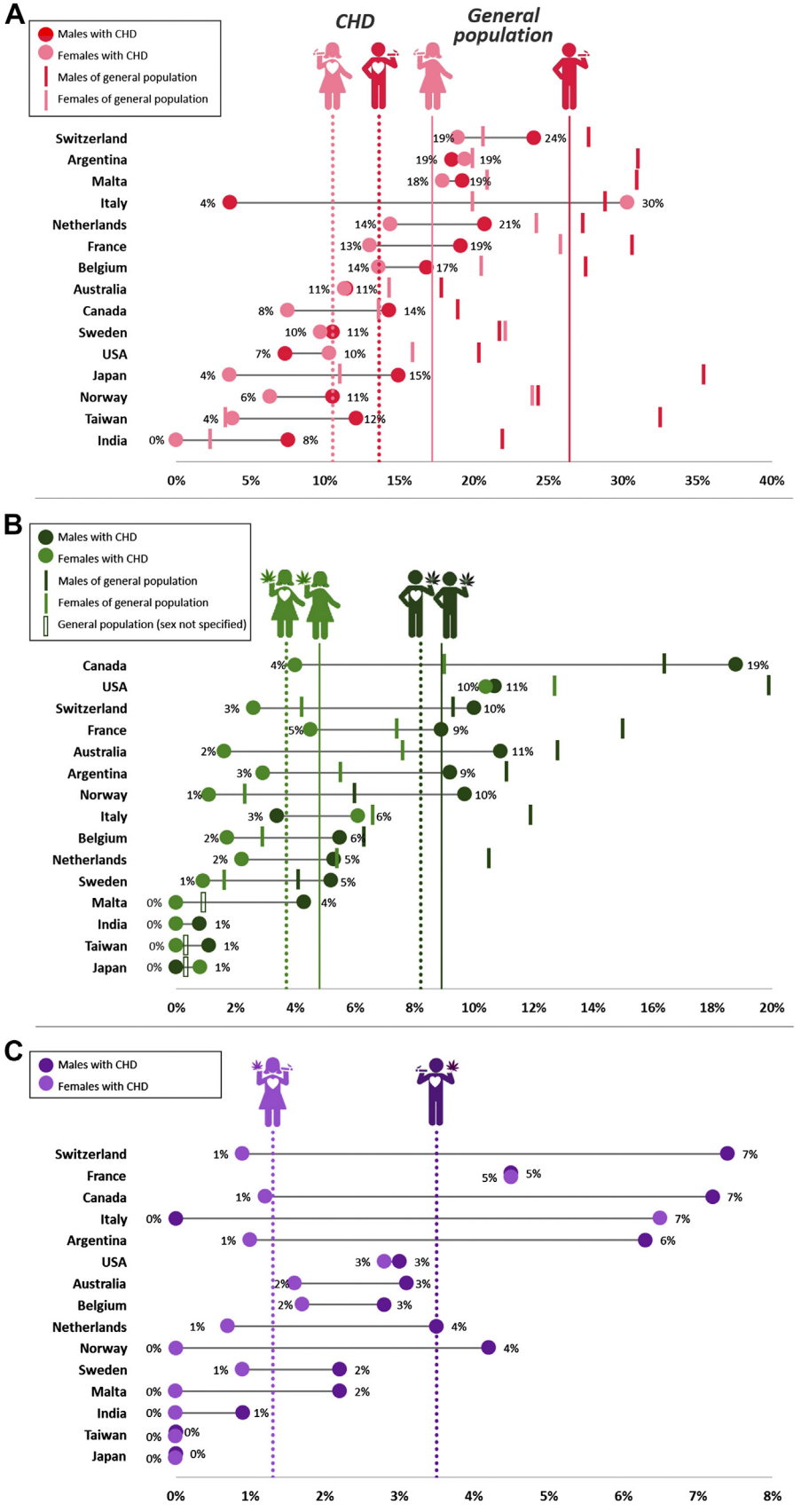

Figure 2. Prevalence of (**A**) cigarette smoking, (**B**) cannabis use, and (**C**) co-use in adults with congenital heart disease, stratified by country.

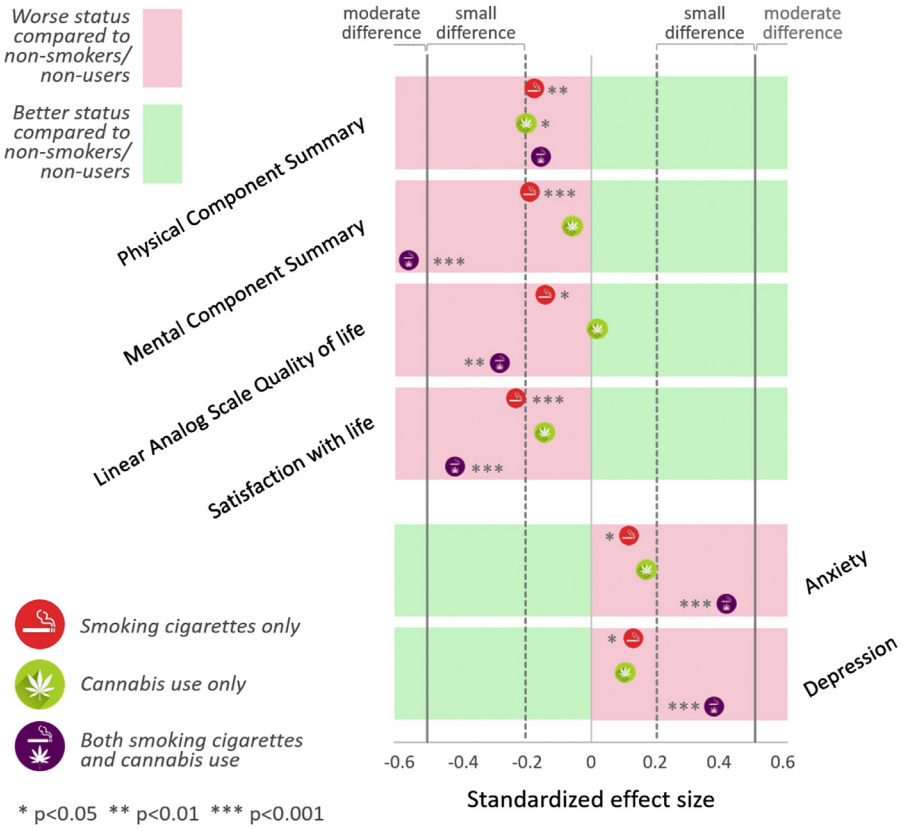

Figure 3. Effect of cigarette smoking, cannabis use, and co-use on patient-reported outcomes.

mortality and morbidity in CHD. The compounded effect of tobacco and cannabis on patient-reported outcomes observed in the present study is compatible with known pathophysiologic synergistic effects.[35] One reinforces or enhances the effect of the other. We also found that co-users smoked as much as single smokers but tended to consume a higher dose of cannabis than single users, which therefore may have a greater effect on outcomes. Indeed, the dose of cannabis fully mediated the effect of cannabis on patient-reported outcomes.

Methodologic considerations

APPROACH-IS has several strengths: We included more than 4000 patients from 15 countries, we had a high degree of complete data, and we used valid and reliable instruments to comprehensively assess the self-reported outcomes in an international sample. Furthermore, we used propensity weighting, a causal inference technique that mimics a randomized trial design.

However, some limitations inherent to APPROACH-IS and the current analyses are present.[17,36] First, although causal inference techniques were used, we cannot draw firm conclusions in terms of causality. There may be unmeasured confounding variables that produce imbalance across groups. Second, cigarette smoking and cannabis use were measured by self-report. Individuals tend to underreport health risk behaviours,[37] thus the real prevalence of cigarette and cannabis use may be underestimated in the present study. Another source of underestimation is that we assessed cigarette smoking as the only source of tobacco consumption, neglecting the fact that there are other tobacco administration routes. Third, a possible selection bias cannot be excluded, because patients who were physically or mentally incapable of completing the study questionnaires are not represented in this study.[16] Fourth, the Health Behaviour Scale—Congenital Heart Disease assesses current behaviours, and does not measure the overall duration of smoking or cannabis use. Therefore, it was not possible to evaluate the effect of pack-years or lifetime exposure to substances. Fifth, we did not adjust for other substance use or alcohol use. Because co-users might also use other substances, the effect on outcomes could be explained or moderated by those other substances. Given that the use of other recreational drugs was limited in our sample,[33] it would be unlikely to yield robust models. Sixth, the study was not designed to measure the impact of smoking or cannabis consumption on clinical outcomes such as myocardial infarction or stroke.

Conclusion

Consistent with the general world population, men with CHD smoke cigarettes and use cannabis more often than women with CHD. However, large geographic variations were observed. Cigarette smoking had a negative effect on all outcomes, although the effects were small. Effects of cannabis on patient-reported outcomes were not detectible. In contrast, the effect of co-use on patient-reported outcomes was more prominent, with a moderate effect on mental health. These findings demonstrate differential effects of tobacco only, cannabis only, and their co-use in persons with CHD. The

results can inform clinicians in their counseling and implementation of health-promoting interventions, and may serve as a benchmark for future studies aimed at determining whether these behaviours are more detrimental for persons with CHD than for their healthy peers.

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Disclosures

The authors have no conflicts of interest to disclose.

References

1. Moons P, van Deyk K, Dedroog D, Troost E, Budts W. Prevalence of cardiovascular risk factors in adults with congenital heart disease. Eur J Cardiovasc Prev Rehabil 2006;13:612-6.
2. Engelfriet PM, Drenthen W, Pieper PG, et al. Smoking and its effects on mortality in adults with congenital heart disease. Int J Cardiol 2008;127:93-7.
3. Reid GJ, Webb GD, McCrindle BW, Irvine MJ, Siu SC. Health behaviors among adolescents and young adults with congenital heart disease. Congenit Heart Dis 2008;3:16-25.
4. Zomer AC, Vaartjes I, Uiterwaal CS, et al. Social burden and lifestyle in adults with congenital heart disease. Am J Cardiol 2012;109:1657-63.
5. Eslami B, Sundin O, Macassa G, Reza Khankeh H, Soares JJ. Gender differences in health conditions and socio-economic status of adults with congenital heart disease in a developing country. Cardiol Young 2013;23:209-18.
6. Overgaard D, Schrader AM, Lisby KH, et al. Substance use, dental hygiene, and physical activity in adult patients with single ventricle physiology. Congenit Heart Dis 2014;9:75-82.
7. Khan M, Monaghan M, Klein N, Ruiz G, John AS. Associations among depression symptoms with alcohol and smoking tobacco use in adult patients with congenital heart disease. Congenit Heart Dis 2015;10:E243-9.
8. Caruana M, Grech V. Lifestyle habits among adult congenital heart disease patients in Malta. Congenit Heart Dis 2016;11:332-40.
9. Agarwal S, Sud K, Khera S, et al. Trends in the burden of adult congenital heart disease in US emergency departments. Clin Cardiol 2016;39:391-8.
10. Agarwal S, Sud K, Menon V. Nationwide hospitalization trends in adult congenital heart disease across 2003-2012. J Am Heart Assoc 2016;5:e002330.
11. Harris KC, Voss C, Rankin K, Aminzadah B, Gardner R, Mackie AS. Modifiable cardiovascular risk factors in adolescents and adults with congenital heart disease. Congenit Heart Dis 2018;13:563-70.
12. Tarp JB, Sorgaard MH, Christoffersen C, et al. Subclinical atherosclerosis in patients with cyanotic congenital heart disease. Int J Cardiol 2019;277:97-103.
13. Janssens A, Goossens E, Luyckx K, et al. Exploring the relationship between disease-related knowledge and health risk behaviours in young people with congenital heart disease. Eur J Cardiovasc Nurs 2016;15:231-40.
14. Bokma JP, Zegstroo I, Kuijpers JM, et al. Factors associated with coronary artery disease and stroke in adults with congenital heart disease. Heart 2018;104:574-80.
15. Rezkalla S, Kloner RA. Cardiovascular effects of marijuana. Trends Cardiovasc Med 2019;29:403-7.
16. Apers S, Kovacs AH, Luyckx K, et al. Assessment of patterns of patient-reported outcomes in adults with congenital heart disease—international study (APPROACH-IS): rationale, design, and methods. Int J Cardiol 2015;179:334-42.
17. Apers S, Kovacs AH, Luyckx K, et al. Quality of life of adults with congenital heart disease in 15 countries: evaluating country-specific characteristics. J Am Coll Cardiol 2016;67:2237-45.
18. Goossens E, Luyckx K, Mommen N, et al. Health risk behaviors in adolescents and emerging adults with congenital heart disease: psychometric properties of the Health Behavior Scale—Congenital Heart Disease. Eur J Cardiovasc Nurs 2013;12:544-57.
19. Ware JE, Kosinski M, Turner-Bowker DM, et al. User's manual for the SF-12v2 Health Survey second edition. Lincoln, RI: QualityMetric, 2009.
20. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361-70.
21. Moons P, van Deyk K, de Bleser L, et al. Quality of life and health status in adults with congenital heart disease: a direct comparison with healthy counterparts. Eur J Cardiovasc Prev Rehabil 2006;13:407-13.
22. Diener E, Emmons RA, Larsen RJ, Griffin S. The Satisfaction With Life Scale. J Pers Assess 1985;49:71-5.
23. World Health Organisation: World health statistics 2018: monitoring health for the SDGs, sustainable development goals. Geneva; 2018.
24. United Nations Office on Drugs and Crime: World drug report 2017. Vienna; 2017.
25. Burgette L, Griffin BA, McCaffrey D. Propensity scores for multiple treatments: a tutorial for the mnps function in the twang package. Santa Monica, CA: Rand, 2017.
26. Ridgeway G, McCaffrey D, Morral A, Burgette L, Griffin BA. Toolkit for weighting and analysis of nonequivalent groups: a tutorial for the twang package. Santa Monica, CA: Rand, 2017.
27. Lipsey MW, Wilson DB. Practical meta-analysis. Thousand Oaks, CA: Sage Publications, 2001.
28. Cohen J. Statistical power analysis for the behavioral sciences. Hillsdale, NJ: Lawrence Erlbaum, 1988.
29. RStudio Team: RStudio: integrated development for R. Boston: RStudio, 2015.

30. Ng M, Freeman MK, Fleming TD, et al. Smoking prevalence and cigarette consumption in 187 countries, 1980-2012. JAMA 2014;311:183-92.

31. Azofeifa A, Mattson ME, Schauer G, et al. National estimates of marijuana use and related indicators—National Survey on Drug Use and Health, United States, 2002-2014. MMWR Surveill Summ 2016;65:1-28.

32. Benowitz NL. Managing cannabis use in patients with cardiovascular disease. Can J Cardiol 2019;35:138-41.

33. Holbein CE, Peugh J, Veldtman GR, et al. Health behaviours reported by adults with congenital heart disease across 15 countries [epub ahead of print]. Eur J Prev Cardiol. https://doi.org/10.1177/2047487319876231.

34. Cohn AM, Abudayyeh H, Perreras L, Peters EN. Patterns and correlates of the co-use of marijuana with any tobacco and individual tobacco products in young adults from wave 2 of the PATH study. Addict Behav 2018;92:122-7.

35. Subramaniam P, McGlade E, Yurgelun-Todd D. Comorbid cannabis and tobacco use in adolescents and adults. Curr Addict Rep 2016;3:182-8.

36. Moons P, Kovacs AH, Luyckx K, et al. Patient-reported outcomes in adults with congenital heart disease: inter-country variation, standard of living and healthcare system factors. Int J Cardiol 2018;251:34-41.

37. Gerritsen M, Berndt N, Lechner L, et al. Self-reporting of smoking cessation in cardiac patients: how reliable is it and is reliability associated with patient characteristics? J Addict Med 2015;9:308-16.

Supplementary Material

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