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PHRP publishes original articles, review articles, brief reports, short communications, editorials, correspondence, and book reviews, with a focus on the following areas of expertise: emerging infectious diseases, vaccinology, zoonotic diseases, non-communicable diseases, intractable and rare diseases, and human genomics.

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Vol. 12, No. 6, December 2021

Editorial

Review Article

Original Articles

Brief Report

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Editorial

Now is the time to consider measures against next wave of COVID-19

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The Korean government has reported an average of 6,000 coronavirus disease 2019 (COVID-19) cases daily, and the case fatality rate has increased to 0.83% this week [1]. Since the complete vaccination rate exceeded 75% one and a half months ago, the government showed confidence in switching to the "with corona" policy, but according to the latest government data, this week's average incidence rate per day is 11.7 cases per 100,000 people, despite the high vaccination completion rate (81.1%) [2].

This assumption that herd immunity could allow society to return to normal in November was unfortunately erroneous. Initially, it was estimated that the number of patients would increase slightly after implementing the "with corona" policy, but it is considered somewhat surprising that the number of patients with severe disease and mortality increased. Therefore, we are faced with the following questions: what is the current situation, and what are the urgent short-term and mid-to-long-term measures to reduce the number of deaths? Since it appears that COVID-19, which has transformed to delta, Omicron variants and has spread worldwide, cannot be managed by vaccination alone, it is now time to refine countermeasures against COVID-19 as an endemic disease.

First, in the short term, it is necessary to quickly increase the booster vaccination rate for the elderly and at-risk groups. Starting at the end of February 2021, the following groups were prioritized for vaccinations: health workers responsible for infection control at health centers, doctors and nurses at hospitals, residents of nursing facilities, the elderly, and chronically ill individuals with underlying diseases. However, the antibody titers of these elderly and vulnerable groups fell faster than expected, resulting in more immune escape in this group and increasing the number of breakthrough infections. In order to strengthen the effects of boosters, the interval until booster doses has been reduced to 3 months. According to a report published on December 13, the infection prevention rate of vaccines is 57.6%, and the booster vaccination rate for those eligible aged 60 and over is 31.4%. These data mean that we cannot prevent this rapid outbreak without special measures. In addition, although the effects of vaccination on preventing serious illness and death remain 92.1% and 90.7%, respectively, as the number of patients increases, the number of serious patients is also increasing. Therefore, the goal of a complete COVID-19 vaccination schedule should be revised to include all 3 doses. At the same time, in order to reduce the exposure of the elderly population to COVID-19, gatherings should be restricted for at least 1 month at the end of 2021 and the beginning of 2022, activities associated with trace-test-isolation-

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quarantine (TTIQ) must be reinforced by recruit of infection control team.

Second, strengthened efforts should be made to increase the vaccine uptake rate among vaccine-hesitant individuals and children aged 12 to 17 years. Ultimately, COVID-19 will have to be treated as a universally vaccinated disease, as it is endemic. In other words, vaccinations for endemic diseases, such as measles and seasonal influenza, are regularly administered for eradication. Therefore, people must be convinced of the necessity of vaccination by explaining the benefits and disadvantages of the currently used mRNA vaccines. For example, adverse events have been reported in about 4 out of 1,000 people, but 96% of adverse events are mild, and diseases associated with severe side effects are very rare.

Anaphylaxis has been reported in 572 cases, myocarditis in 300 cases (Pfizer 206 cases, Moderna 94 cases). Only 10 cases of myocarditis have been reported after the AstraZeneca vaccine [3]. In the United Kingdom, COVID-19 myocarditis has been reported to occur in 40 patients per 1 million without vaccination, but in about 10 cases when 2 doses of an mRNA vaccine are administered [4]. In other words, medical personnel need to provide more accurate explanations of the benefits of vaccines in order to increase the vaccination rate. Regarding mandatory vaccinations through the National Immunization Program, it is necessary to check individuals' vaccination history when they use public facilities, just like how vaccination is a requirement for admission at the time of school entrance. In other words, the current quarantine pass should be converted into a daily measure instead of being considered a temporary measure.

Third, the health care system should be strengthened. Instead of taking measures against COVID-19 as a pandemic, it should now be recognized that COVID-19 is an endemic disease that causes more than 500,000 cases and about 5,000 deaths every year. Therefore, COVID-19 should be managed as an endemic disease that leads to a similar death toll to the estimated 2,300 to 5,300 deaths due to influenza every year [5]. Our society has accepted the reality that about 10,000 people can die from respiratory infections, including influenza and COVID-19, each year. There is a potential demand for hospitalization of 500,000 to 1 million people every year, and it is necessary to prepare a medical care system that can treat 100,000 to 200,000 intensive care unit patients with 2% of aggravated cases among all ill patients. Of course, infection control for legally defined infectious diseases must be thoroughly implemented to prevent hospital-acquired infections, and treatment will be provided free of charge as it is today, but if appropriate preventive measures are not taken and mandatory vaccinations are not received, the government will not support the fees for care. Since most patients have mild cases, the diagnosis, treatment, prevention, and isolation system should be reorganized and centered on public health centers and district medical institutions so that primary care is provided for around 80% of patients. Infection control teams, home visiting health teams, telemedicine, designated evacuation medical institutions, night call centers, and patient transport systems must be created to reduce the demand for expensive hospitalization. Oral antiviral drugs will enable primary care physicians to care for patients, and will play a role in preventing infections and reducing the quarantine period.

Fourth, a preventive system must be established. Daily efforts to avoid infection are very important for a step-by-step recovery. In addition to washing hands, mask-wearing, and ventilating, it is necessary to use Information and Communications Technology (ICT) tools and apps that help check for fever when entering various facilities (regardless of vaccination status), prompt voluntary testing in case of doubt, and determine possible contacts with confirmed cases. Through these measures, trace-test-isolation-quarantine (TTIQ) can improve performance and perfection restrictions on access can be minimized. In addition to efforts to improve vaccination at the local level, public health centers should activate a 'prevention committee system in the community' for infectious disease prevention and control by the law in order to report patients to local medical institutions, help conduct related epidemiological investigations, and provide patient education. They should be in charge of facility inspection and education to prevent cluster outbreaks. In addition, booster vaccination strategies such as *ad hoc* vaccination and TTIQ for epidemic management in case of a cluster outbreak will block transmission and reduce the side effects caused by social distancing.

Notes

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Not applicable.

Conflicts of Interest
The author has no conflicts of interest to declare.

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References

1. Our World in Data. Case fatality of South Korea [Internet]. Our World in Data; 2021 [cited 2021 Dec 13]. Available from: https://

https://doi.org/10.24171/j.phrp.2021.0338

ourworldindata.org/covid-cases.
2. Korea Disease Control and Prevention Agency (KDCA). Weekly epidemiologic report, December 13, 2021 [Internet]. Cheongju: KDCA; 2021 [cited 2021 Dec 13]. Available from: https://www.kdca.go.kr/board/board.es?mid = a20501010000&bid = 0015&list_no = 717925&cg_code = &act = view&nPage = 2. Korean.
3. Korea Disease Control and Prevention Agency (KDCA). Weekly vaccine adverse event report, December 16, 2021 [Internet]. Cheongju: KDCA; 2021 [cited 2021 Dec 17]. Available from: https://ncv.kdca.go.kr/board.es?mid = a11707010000&bid = 0032. Korean.
4. Patone M, Mei XW, Handunnetthi L, et al. Risks of myocarditis, pericarditis, and cardiac arrhythmias associated with COVID-19 vaccination or SARS-CoV-2 infection. Nat Med 2021 Dec 14 [Epub]. https://doi.org/10.1038/s41591-021-01630-0.
5. Park C, Park S, Lee G, et al. Estimation of excess mortality associated with influenzas in Korea. Public Health Wkly Rep 2021;14:1150–61. Korean.

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Review Article

Social determinants of adherence to COVID-19 preventive guidelines: a comprehensive review

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ABSTRACT

Adherence to coronavirus disease 2019 (COVID-19) preventive guidelines (ACPG) is an important strategy to control the COVID-19 pandemic effectively. The present study aimed to identify and summarize the social determinants of ACPG among the general population. A comprehensive review was performed from December 2019 to February 2021 through searching electronic databases. Two independent reviewers assessed and selected relevant studies. Next, the characteristics and main findings of the included studies were summarized. Finally, the World Health Organization's conceptual framework of social determinants of health was used to synthesize the identified social determinants of ACPG. Forty-one of 453 retrieved articles met the inclusion criteria. The study results showed different patterns of ACPG among various communities. Furthermore, 84 social determinants were identified and categorized into structural and intermediary determinants. ACPG is a set of complex behaviors associated with different individual sociodemographic and behavioral characteristics; living and working conditions; COVID-19 knowledge, attitudes, and risk perceptions; exposure to sources and information level; leisure activities; social support; trust; social norms; psychosocial well-being; socio-economic position; and the socio-economic and political context. Interventions to promote ACPG among the general population should consider the identified social determinants of ACPG.

Keywords: COVID-19; Guideline adherence; Preventive behavior; Preventive guidelines; Social determinants of health

Introduction

The coronavirus disease 2019 (COVID-19) pandemic is the third deadly coronavirus outbreak that has occurred in less than 2 decades, after severe acute respiratory syndrome and Middle East respiratory syndrome. COVID-19 is one of the most important global public health concerns and priorities [1]. Despite the implementation of medical care approaches and technical solutions in the health sector, these solutions are not enough. In this respect, adherence to COVID-19 preventive guidelines (ACPG) such as wearing a face mask, washing one's hands regularly, following stay-at-home orders, and maintaining physical distance are among the necessary important, simple, and cost-effective strategies for controlling the pandemic [2–4]. This strategy is particularly critical in low- and middle-income countries with limited medical and hospital resources. However, various factors at different levels—including the structural and psychosocial environment, as well as individual factors—may contribute to complete and efficient adherence to preventive guidelines; the consequent uneven distribution of adherence exacerbates social inequalities in health, especially in vulnerable groups [5]. Evidence has shown that perceptions of the risk of COVID-19 and the importance of ACPG vary based on political inclinations. In this respect, people with different political inclinations (e.g., Democrat rather than Republican in the USA) may have different attitudes and beliefs regarding risk levels and preferences for risk mitigation [6,7]. Some studies also reported that in societies where conspiracy theories are predominant, people are less likely to follow health-protective behaviors. Furthermore, previous research has linked crowded and unsanitary living conditions in shelters and marginalized suburbs, unsafe housing, a perception of insecurity in one's neighborhood, not having green space around one's house, less feeling comfortable at home, and low quality of life to lockdown adherence during the COVID-19 epidemic [8–11]. Marginalized people who live in crowded and unsanitary suburbs cannot wash their hands regularly due to insufficient access to tap water and sanitation at home. Moreover, they cannot adhere to physical distancing due to high population density. Precarious employment (such as having temporary and informal jobs, and limited access to social protection programs) is also associated with inequality in the risk of COVID-19 disease [12]. In this regard, evidence from the USA has shown a higher proportion of infection and mortality among African-Americans and Latinos than among other racial and ethnic groups [13,14].

The social determinants of health (SDH) refer to the social and environmental circumstances people live and work in, which shape exposure and vulnerabilities [15]. The SDH framework also provides a broad and comprehensive way to systematically assess the general population's ACPG. Applying the World Health Organization (WHO)'s conceptual framework of SDH helps recognize entry points for health planning and policy actions for current and future pandemics [16]. According to this conceptual framework, the socio-economic and political contexts of society (including governmental, economic, social, and public policies, as well as culture, and social values) place people in various socio-economic positions based on their education, occupation, income, gender, and race or ethnicity in a society [15]. These structural determinants, socio-economic and political contexts, and socio-economic status shape exposure to intermediary social determinants such as living and working conditions, behaviors, and psychosocial factors [15,17].

Although previous research has investigated the role of social factors in ACPG [4,18], no studies in the literature have yet systematically reviewed the structural and immediate circumstances that may affect adherence to preventive guidelines among the general population, especially with the SDH approach [19–21]. Therefore, the present review study aimed to identify and summarize the social determinants of ACPG among the general population.

Materials and Methods

The present study comprehensively reviewed original articles related to social determinants of ACPG among the general population based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [22]. International databases such as PubMed, Medline via PubMed, Web of Science, Scopus, and the Google Scholar search engine were searched for articles published from December 2019 to February 2021.

A sensitive search strategy was applied to retrieve relevant studies. The Medical Subject Headings controlled vocabulary system was used to define the keywords. The following search strategy was used for PubMed, and equivalent formulations were used for the other databases: (COVID-19 OR "Covid outbreak" OR "Corona Virus") AND ("social factors" OR "social determinants" OR inequality OR "socio-economic status") AND (compliance OR adherence OR adoption) AND ("COVID-19 protocol" OR "COVID-19 guideline" OR "COVID-19 recommendations" OR "social distancing" OR "wearing a mask" OR "preventive behaviors" OR "self-isolation"). Based on the population/problem, exposure/independent variable(s)/intervention, comparison, outcome, time (PECOT) framework, the included studies

were observational, interventional, and qualitative works conducted among the general population that assessed the association between at least 1 social factor and ACPG; the search was also limited to studies that were peer-reviewed and published in English (Table 1). Studies that did not provide information on the pre-specified PECOT criteria were excluded. For data management, all the retrieved studies were imported into EndNote ver. X.

Studies were screened and reviewed in 3 steps: title, abstract, and full-text review. After excluding duplicates, the titles of the retrieved studies were appraised. Next, 2 reviewers independently reviewed abstracts of the selected articles based on the inclusion criteria. Any disagreements between the 2 reviewers were resolved by consultation with a third reviewer. Finally, the full-texts of the related articles were reviewed, and relevant data were extracted. We summarized the study location, sample size, study type, and main findings. Furthermore, based on the WHO conceptual framework of SDH, we categorized the findings of the included studies into structural and intermediary social determinants of ACPG.

Results

Characteristics of Included Studies

This review study was conducted in accordance with the PRISMA guidelines [22]. Figure 1 shows details of the process from the initial search and screening to the final study inclusion. In the initial search, 453 studies were retrieved and, after excluding duplicates, 152 articles were evaluated. Finally, 41 relevant articles were included based on the inclusion criteria. Two of the included studies were

Table 1. The PECOT criteria for the research question to identify the social determinants of ACPG

PECOT	Population	Exposure/ independent variable	Comparison	Outcome	Time
The element of the question	General population	Social factors	Any comparator	ACPG	December 2019 to February 2021

ACPG, adherence to COVID-19 preventive guidelines.

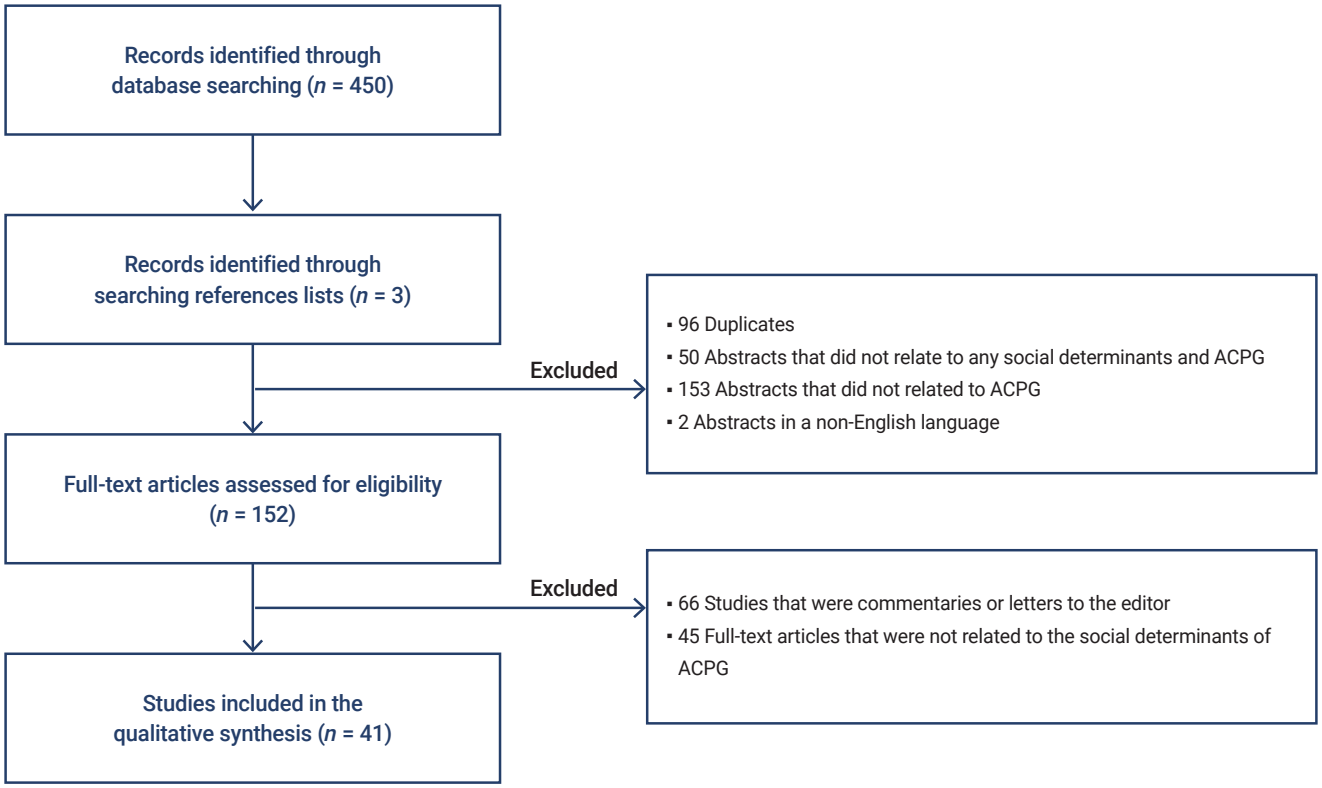

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart of the search strategy.
ACPG, adherence to coronavirus disease 2019 preventive guidelines.

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not peer-reviewed [23,24]. Among the retrieved studies, 66 were commentaries or letters to the editor, which were excluded although they addressed the role of social factors in general and SDH in particular (Figure 1).

Most of the included studies were cross-sectional, and 2 were longitudinal and prospective [25,26]. The included studies were conducted in various countries: 14 studies in the USA [6,24–37], 3 in Brazil [38–40], 8 in Asia [23,32,41–46], 5 in Africa [47–51], and the others in other countries. One study used international data [52], and 7 studies were conducted in more than 1 country [26,28,29,32,35,52,53]. Some studies mostly measured structural determinants of ACPG, while others focused only on intermediary determinants. Table 2 shows the summary characteristics of the all included studies [6,23–26,28–44,46–63]. Table S1 provides details of the selected studies [6,23–44,46–63].

After reviewing and analyzing the data, the social determinants of ACPG were extracted. Eventually, based on the WHO's SDH conceptual framework, they were categorized into structural and intermediary social determinants (Figure 2).

Result of ACPG Status

The status of ACPG varied in different communities. Various studies used different instruments to measure the status of ACPG, with most of them being self-developed measures. Many studies considered washing hands, wearing a face mask, not traveling to crowded places, adhering to quarantine, using disinfectants, not shaking hands, and social distancing as COVID-19 preventive guidelines [24,51,52,54,55]. A study in the USA also assessed social distancing by quantifying population movements within and across counties of origin by day [34].

A study in the USA showed that the average numbers of instances of hand-washing in the last 24 hours and leaving the house in the last 3 days were 13.2 times (standard deviation [SD], 13.5) and 2.5 times (SD, 4), respectively [24]. Another study in the USA found that most participants (84%) reported wearing a mask in response to the COVID-19 pandemic [33]. In addition, a study in Indonesia reported relatively high adherence to some measures of COVID-19 preventive guidelines such as social distancing (87%), using face masks (76%), and hand-washing habits (87%) [64]. In a study in Italy, Carlucci et al. [56] showed that respondents had medium to high adherence to preventive guidelines (mean, 32.59; SD, 5.22; range, 0 to 44), with an average quarantine duration of 15 days (SD, 6.64). The mean scores of adherence to preventive Polish governmental and WHO guidelines were 28.15 (SD, 7.11) and 23.99 (SD, 4.23), respectively, using 5-item and 4-item measures (7-point Likert scale) [57]. Azene et al. [51], in their study in Ethiopia, found that about half of the participants (48.96%; 95% confidence interval [CI], 45.05 to 52.89) had poor ACPG. The mean scores of adherence to preventive guidelines using a 10-item 7-point Likert scale among Nigerians women and men were 25.52 (SD, 8.22) and 28.85 (SD, 10.53), respectively [49]. Moreover, a study in Uganda reported that the studied participants had high adherence to frequent hand-washing (96%), physical distancing (90%), and cough hygiene (86%), whereas low adherence was reported for using masks (33%) and disinfecting one's phone (42%), laptop (26%), bag (20%), and TV remote control (18%) [48].

Social Determinants of Health and ACPG

Structural social determinants and ACPG

Contextual factors

The context of society, as the first element of structural social determinants, encompasses all economic, social, political, and cultural mechanisms that generate and maintain social hierarchies that influence health outcomes in a population [15]. According to our findings, political conservatism, political inclinations (e.g., Democrat, Republican, independent), political polarization, compact development (4 distinct dimensions of urban sprawl: development density, land use mix, population and employment centering, and street accessibility), geographical area (region/country and county), local economic endowments, communication of government/authorities (being clear and understandable, credible and honest, guided by the interests of the people regarding the COVID-19 crisis), governmental recommendations for home quarantine, religious beliefs, confidence in science, conspiracy beliefs, and fatalism were contextual factors associated with ACPG.

Socio-economic position

Socio-economic status is the second element of the structural social determinants defined by education, occupation, and income indicators. According to the WHO's conceptual framework, gender, race, or ethnicity are other social stratifiers that have intrinsic roles in determining people's position on a society's socio-economic ladder [15]. Some of the included studies showed that socio-economic profiles, including gender, education, household size, employment status, income, race, and ethnicity, were significantly associated with ACPG [40,41]. However, these associations were not reported in other studies [48,54]. In a study of social distance and inequality during the COVID-19 pandemic in the USA, Zhai et al. [27] found that although both rich and poor generally reduced their travel, poor people reduced their travel less than rich people, except for going to parks.

Some studies also reported that women exhibited more adherence to preventive guidelines than men [24,42]. Two

Table 2. Summary of the studies included in the present review ($n = 41$)

Social determinants	Measured variables	Direction of association (positive/negative/null)
Structural determinants		
Socio-economic and political context	Political conservatism	Negative [36]
	Political inclinations	Positive [6]
	Political polarization	Positive [6]
	Compact development	Positive [25]
	Geographical area	Positive [46]
	Local economic endowments	Positive [34]
	Communication of government/authorities	Positive [35]
	Governmental recommending for home quarantine	Positive [6,46]
	Religiousbeliefs	Negative [46,48,52]
	Fatalism	Negative [36]
	Conspiracy beliefs	Negative [52,53,57,63]
	Confidence in science	Positive [52]
Socio-economic position	Education (higher education)	Positive [6,25,38–41,46,47,53,55,56,60]
	Occupation	Positive [39,41,46,47,56,60]
	Income	Positive [23–25,34,36,38,40,41,46,48,53]
	Gender (women)	Positive [6,23,24,28,33,35,36,38–42,46–48,50,51,53–56,60,62]
	Race	Positive [6,24,33,36]
	Ethnicity	Positive [25,33,47]
Intermediary determinants		
Living conditions	Place of living	Positive [24,31,35, 39,46,48,56]
	Housing quality	Positive [40]
Working conditions	Type of work	Positive [38]
	Work in non-governmental sectors	Negative [39]
	Perceived ability to take sick leave	Positive [36]
Individual demographic characteristics and health behaviors	Age (older people)	Positive [6,23,24,30,35,36,38,39,41,46–48,50,53–56,60]
	Marital status (being single/married)	(being single) Positive [38,42] (being married) Positive [35,43,46,48,56]
	Smoking	Positive [23,39]
	Drug or alcohol abuse	Negative [29]
COVID-19 knowledge, attitudes, and risk perceptions	Health literacy	Positive [53]
	Knowledge	Positive [30,32,36,42,49–51,59]
	Attitudes	Positive [30,32,36,42,49–51,59]
	Risk perceptions	Positive [30,42,50,51,59]
Exposure to source and level of COVID-19 information	Exposure to social media	Positive [6,23,32]
	Exposure to COVID-19 preventive information	Positive [23]
	Source of COVID-19 information	Positive [48]
Attitude towards COVID-19 preventive guidelines	Attitude towards COVID-19 preventive guidelines	Positive [23]
Capacity and coping appraisal	Capacity	Positive [30]
	Coping appraisal	Positive [32]
Leisure activities	Type of leisure activities (more active people)	Positive [43]
Social norms	Social norms	Positive [26,30,31,35,54,60]
Trust	Trust in government	Positive [54]
	Trust in social institutions	Positive [38]
Psychosocial well-being	Psychosocial well-being	Positive [23,53,61]
Social support	Social support	Positive [44,46,54,61,62]

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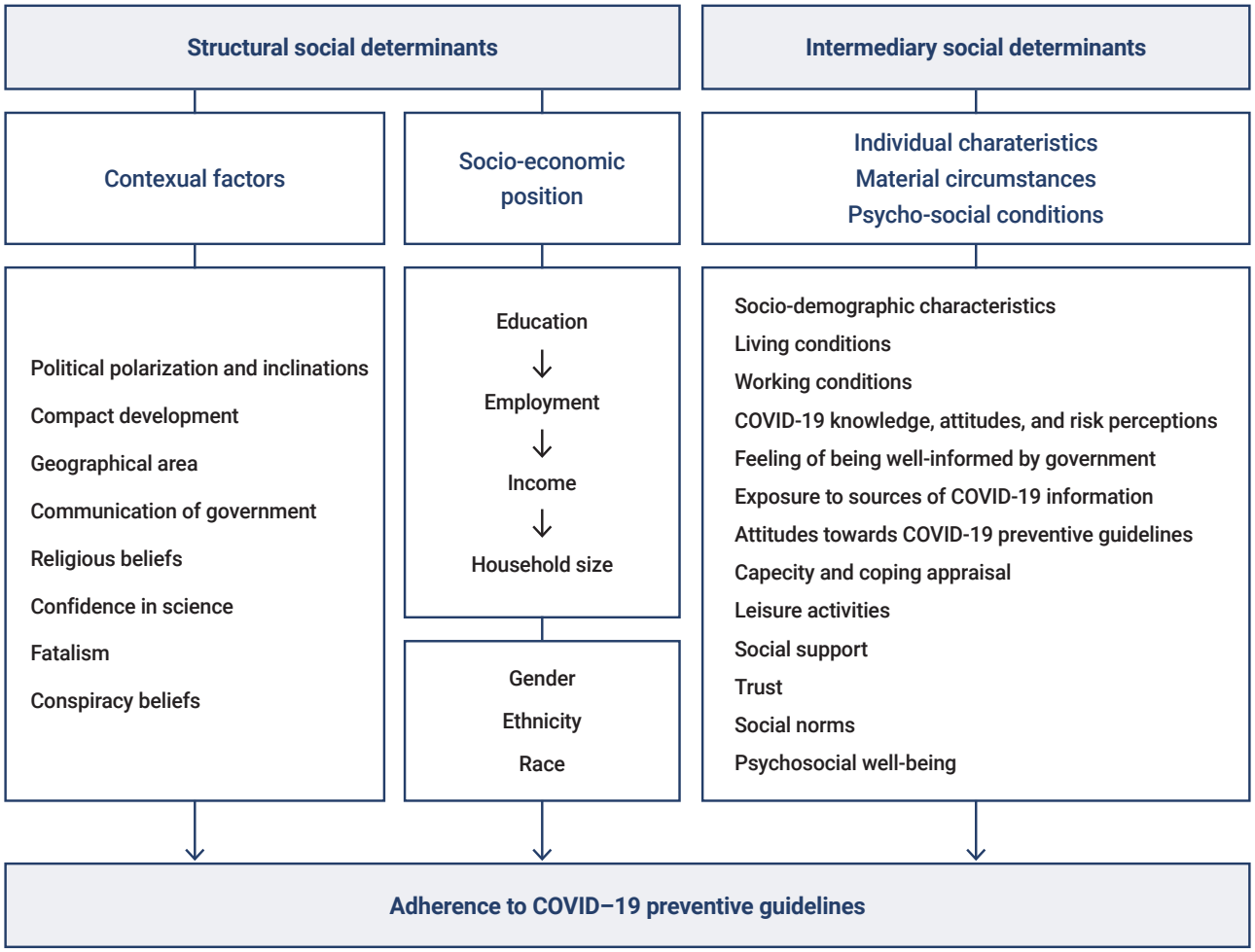

Figure 2. The social determinants of adherence to coronavirus disease 2019 (COVID-19) preventive guidelines in the present review.
The model was designed based on the World Health Organization's conceptual model of social determinants of health.

studies in Hong Kong showed that men were significantly less likely than women to engage in preventive behaviors, including washing their hands with soap and avoiding gatherings, not shaking hands, and avoiding contact with the elderly [41,55].

Furthermore, some studies showed that ethnicity and race were associated with ACPG [6,24,33]. However, 2 studies reported no association between ethnicity or race and ACPG [31,36]. A study in the USA found that race was one of the most important predictors of people's preventive behaviors, including hand-washing and traveling [24]. Accordingly, African-Americans and Hispanics were significantly more likely to wash their hands regularly than White people. However, compared to White people, African-Americans were significantly more likely to stay at home [24].

Intermediary Social Determinants and ACPG

Individual characteristics

Demographic characteristics and health behaviors

In our review study, demographic characteristics, including age and marital status, were associated with ACPG [24,41–43,54,55]. There is conflicting evidence regarding the relationship between age and ACPG [41,43,55]. According to Kim and Cho [43], older people showed more preventive behaviors than young ones. On the contrary, a study in Hong Kong showed that young people had more preventive behaviors than older people, and the most preventive behavior was reported in the age group of 25 to 44 years [41]. Furthermore, the findings of the study by Cvetkovic et al. [55] in Serbia indicated that study participants in the age group of 28 to 39 years were more likely to limit their travel, store food for a month or more, and avoid contact with the

elderly.

In contrast, people in the age group of 39 to 48 years were more likely to avoid hugging and kissing family members, friends, and acquaintances, use more disinfectants, and generally avoid contact with others. Study participants in the age group of 49 to 58 years also avoided handshaking, adhered to the recommended social distance, followed a proper diet, and avoided contact with pets [55]. A study in South Korea found that married people exhibited more ACPG than single people [43]. However, a study in Iran conversely reported that single people engaged in significantly more ACPG than married people [42].

Moreover, 3 studies showed that smoking and drug or alcohol abuse were associated with ACPG because smokers and users of alcohol or drugs were less likely to adhere to preventive guidelines. However, 1 study reported a non-significant association between smoking behavior and ACPG [46]. A study in Israel showed that people with a high level of past risk-taking behaviors were more likely to report nonadherence to the COVID-19 preventive guidelines (odds ratio [OR], 1.41; 95% CI, 1.10 to 1.81) [23].

COVID-19 knowledge, attitudes, and risk perceptions

Individuals' knowledge, attitudes, and risk perceptions were associated with ACPG [6,23,32,37,38,51,56,58]. Some studies showed that health literacy [53] and knowledge about social distancing were associated with ACPG [32,42,50,59]. A study in Iran found that attitude toward COVID-19 risk was the strongest predictor of ACPG (B = 0.362, $p = 0.009$) [42]. The results of an international study showed that COVID-19 risk perception had a significant direct association with ACPG (B = 0.35, $p < 0.001$) [52]. However, a study in the USA reported no association between COVID-19 risk perception and ACPG [31]. Furthermore, a study in Ethiopia found a significant negative association in this regard (OR, 0.61; 95% CI, 0.41 to 0.92) [51].

Exposure to the source and level of COVID-19 information

Three studies assessed the role of social media in ACPG. Two of them reported a significant association between exposure to social media and ACPG [6,32], but the third study did not find a significant association [23]. A study in Ethiopia found that people who had more exposure to COVID-19 preventive information were more likely to adhere to COVID-19 preventive behaviors (OR, 1.85; 95% CI, 1.03 to 2.43) [51]. A study also showed that the source of COVID-19 information was associated with ACPG [48]. More specifically, people who obtained COVID-19 information from healthcare workers (OR, 1.2; 95% CI, 1.01 to 1.5) and village leaders (OR, 1.4; 95% CI, 1.02 to 1.9) were more likely to adhere to COVID-19 preventive behaviors [48].

Attitudes towards COVID-19 preventive guidelines

Three studies found a significant association between attitudes towards COVID-19 preventive guidelines and adherence [23,51,60]. People who considered the preventive instructions effective and had positive attitudes about them reported more ACPG.

Material circumstances

Living conditions

The present review study indicated that place of living and housing quality were related to ACPG. A study in Brazil found that housing quality was related to keeping physical distance and adhering to stay-at-home orders during the COVID-19 quarantine period [40]. Some of the included studies that assessed variables related to respondents' place of living showed that people who lived in a large city and central states reported more ACPG [35,48,50,56].

Working conditions

Our study also revealed that working conditions were associated with ACPG [12,36,39,65]. Health workers were more likely to adhere to preventive guidelines [56], whereas those working in non-governmental sectors were less likely to adhere to preventive guidelines [39]. In a study in the USA, workers who had a greater perceived ability to take sick leave reported more adherence to hand-washing and physical distancing [36].

Psychosocial conditions

Capacity and coping appraisal

Regarding the capacity variable, only 1 study assessed the role of capacity on ACPG [30]. This study defined capacity as "I have the ability to do this" and found that capacity was the main predictor of maintaining social distancing (B = 0.09; 95% CI, 0.0 to 0.27) and intention to stay at home (B = 0.63; 95% CI, 0.46 to 0.80) [30]. One study also showed that coping appraisal was associated with social distancing [32].

Leisure activities

Only 1 of the included studies assessed the role of the type of leisure activities in ACPG [43]. That study showed that people who generally participated in cultural and art activities in their leisure time (mean, 4.275; SD, 0.499) and those involved in social (mean, 4.249; SD, 0.525) and tourism-related activities (mean, 4.223; SD, 0.482) exhibited

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more adherence to preventive guidelines [43]. Furthermore, those who participated in leisure activities along with their families showed high preventive behaviors. In contrast, those who spent their leisure time with friends of the opposite gender had low levels of precautionary behaviors [43].

Social norms

Only 5 studies showed significant positive associations between social norms and ACPG [26,30,31,54,60]. One of the studies, which used data from 2 cross-sectional surveys (n=2,000 in survey 1; and 2,003 in survey 2) in France, reported that social norms were significantly associated with ACPG (B = 0.13, $p < 0.001$ for survey 1; B = 0.33, $p < 0.001$ for survey 2) [54].

Trust

This intermediary social determinant subcategory is related to 2 concepts: trust in overnment and trust in social institutions (e.g., health workers, media, and hospitals). A study that used data from 2 cross-sectional studies (n=2,000 in survey 1; and 2,003 in survey 2) in France showed that trust in government (β = 0.07, $p < 0.01$ for survey 1; β = 0.08, $p < 0.01$ for survey 2) was significantly associated with ACPG [54]. Another study in Brazil found that trust in government (B = −1.200; 95% CI, −1.600 to −0.940), health workers (B = 1.100; 95% CI, −0.770 to 1.500), and media (B = 0.550; 95% CI, 0.280 to 0.820) were significantly associated with ACPG. Meanwhile, trust in hospitals did not show a significant association [38].

Psychosocial well-being

Only 1 study in Belgium showed that people who had low psychosocial well-being, including anxiety (B = 1.85; 95% CI, 0.62 to 3.09), depression (B = 2.99; 95% CI, 1.72 to 4.26), anger (B = 2.74; 95% CI, 1.28 to 4.21), and social isolation (B = 2.82; 95% CI, 1.58 to 4.05) reported less ACPG [61].

Social support

Social support was another determinant that significantly affected people's ACPG [44,61]. Depending on the source (friends/ family), social support decreased or increased adherence to self-quarantine at home. Thus, perceived social support from one's family reduced the likelihood of poor adherence to stay-at-home orders (OR, 0.874; 95% CI, 0.803 to 0.950). However, the association between perceived social support from friends and adherence to stay-at-home orders was not significant (OR, 0.926; 95% CI, 0.849 to 1.010) [44].

Discussion

Although excellent progress has been made in vaccination, the best way to deal with this pandemic is adherence to preventive guidelines [66,67]. Successful implementation of the guidelines requires substantial engagement from citizens and communities.

ACPG Status

This review study aimed to identify the social determinants of ACPG in the general population. Our findings show that the status of ACPG varied in different communities. In some studies, adherence was high on average, while other studies reported moderate or low adherence. Interestingly, the findings of the review study indicated that higher-income countries such as the USA, France, and Canada had higher levels of adherence than low- and middle-income countries such as Uganda, Nigeria, and Indonesia. These differences may be related to various individual, communities, socio-cultural, economic, and structural factors.

Social Determinants of Health and ACPG

Structural social determinants

Contextual factors

The results of our review showed that at the level of structural social determinants, political inclinations and polarization were associated with ACPG. One study in the USA found that Democrats were 1.76 times more likely than Republicans to wear a face mask and 1.45 times more likely to avoid public spaces or crowds [6]. Participants identified as independent were less likely to wear a face mask than Republicans, though they were 1.23 times more likely to avoid public spaces or crowds [6]. One explanation for this finding is that people who have different political inclinations within a politicized society may follow different sources of information and guidance about COVID-19. Hence, they react differently towards risks, governmental preventive guidelines, and the necessity of adhering to preventive behaviors. This finding may also reflect different approaches and reactions of various political groups about collective strategies (as opposed to individual efforts) in society to promote health outcomes.

Our results also indicate that compact development and geographical areas were associated with ACPG [25,62]. People who live in developed areas may have better access to online shopping options and health information, which minimizes their traveling needs and affects their protective behaviors, respectively.

Local economic endowments were another structural

social determinant of ACPG in our study [34]. In societies with low levels of economic development, the health share of the gross domestic product and the level of government health expenditures are often low. Therefore, these countries seem to face many problems, such as providing and equally distributing hygiene materials (e.g., face masks, disinfectants, and detergents) and improving access to health care to prevent and control this pandemic.

Moreover, we found that governments' communication and transparency of information flow were associated with ACPG. One explanation for this finding is that a clear and strong relationship between the government and populace, regardless of economic development and gross domestic product, can increase trust in society and convince people to engage in more ACPG. Although government communication, as the main source of social influence, can significantly affect the adoption of preventive behaviors, it may negatively affect the further spread of disease in society. These findings are consistent with the results of other studies that addressed the role of socio-economic factors in preventive behaviors [68–70] and emphasized the necessity for comprehensive and health-oriented approaches by governments, especially in conditions of limited resources. Furthermore, our findings indicate that conspiracy beliefs are a substantial barrier to ACPG. In this respect, messages from authorities and local governments denouncing or enhancing conspiracy beliefs may be effective not only as a strategy for pandemic management by the state, but also for attitudes and behaviors at the individual level. For example, in communities with a conspiracy theory-based approach to the pandemic, the government may prioritize political decisions over health decisions. Therefore, instead of focusing on optimal pandemic management at home and emphasizing quarantine, the government may seek to maintain its political position and authority in the world and manage health within a political framework. Furthermore, in communities where conspiracy beliefs regarding the pandemic are predominant, people are less likely to engage in COVID-19 preventive behaviors. This finding aligns with previous studies that found associations between conspiracy beliefs and reluctance to follow health guidelines [71–73].

Socio-economic position

Some of the included studies showed significant associations between socio-economic position or its indicators and ACPG. Socio-economic position may affect ACPG in several ways and engender differential exposures to COVID-19. People with low education may not have sufficient knowledge about the disease and preventive health behaviors [74]. The knowledge and skills acquired through high education levels may improve people's cognitive assessment and perceptions of health messages about COVID-19, enabling them to use those messages in practice [15]. Furthermore, lower-income people usually work in temporary and unstable jobs that make it impossible to work remotely, even in the COVID-19 pandemic [75]. They may also experience some difficulties in obtaining the necessary preventive equipment such as face masks, gloves, disinfectants, and detergents, thereby not following the stay-at-home order and preventive guidelines properly. These people may live in small, unsanitary, and crowded homes, which reduces the possibility of having adequate personal space and maintaining social distance. This finding suggests that the government should support programs by providing packages for individuals of low socio-economic and educational status to help increase ACPG in this population.

Many studies emphasized gender differences in compliance with protective guidelines [24,35,38,46,53,54,60], finding that men were less likely to follow these guidelines than women. This finding may be related to gender roles, norms, and social rules that determine men's and women's responsibilities, expectations, opportunities, limitations, and behaviors in society [76]. Due to masculinity stereotypes, men often pretend that they are immune against disease, deny illness or weakness, present themselves as invulnerable, engage in risky behaviors, and are unwilling to seek health care services [76]. Gender stereotypes and differential expectations about men's role in society, linked to their primary duties in providing their families' livelihood and the necessity of maintaining their jobs and earning income, lead to a greater presence in society than that of women. Thus, men may underestimate the risk of contracting COVID-19 and pay less attention to preventive guidelines such as staying at home. This finding highlights the necessity of gender-based educational programs about COVID-19 preventive guidelines as one of the most important policies, in which men's and women's roles and responsibilities are clarified separately.

Race or ethnicity, as another indicator of socio-economic position acting as a social stratifier [15], was associated with ACPG [6,24,33]. A study in the USA reported that African-Americans and Hispanics were more likely to wash their hands regularly than White people; however, African-Americans were less likely to stay home than individuals belonging to other races [24]. One explanation for this finding is that the value of health behaviors in different societies and the degree to which health is considered a collective social concern may differ among ethnic groups and communities. People's attitudes and behaviors are guided by the culture, implicit or explicit social values,

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and customs within a community, which may affect the adoption of COVID-19 preventive behaviors.

However, some of the included studies that assessed socio-economic position or its indicators did not find any significant associations with ACPG [23,47,48,54,62]. This inconsistency may have several reasons, such as heterogeneity in the studied populations, the use of various instruments for measurements, and measurement errors. In this sense, some studies measured socio-economic position at the county or country level and used aggregated measures, while some others measured this variable at the individual level.

Intermediary Social Determinants

Individual characteristics

Our review study showed that patterns of ACPG were different based on age and marital status. Although some studies showed that ACPG was higher among young people [41], other research found that ACPG increased with age [55]. This inconsistency might be due to social context and shared beliefs in different societies. One explanation is that high-risk perceptions and more perceived vulnerability among the elderly may lead to higher adherence. Conversely, the common belief that young people will not contract COVID-19 may lead to less ACPG. Regarding marital status, the included studies reported higher ACPG among married people than among single people. Since married people may consider themselves responsible for the health of their spouses and children, they are more likely to follow preventive guidelines than single people. Some studies also showed that smokers and users of alcohol or drugs were less likely to adhere to preventive guidelines. However, a study reported a non-significant association between smoking behavior and ACPG [46]. This finding suggests the necessity of paying particular attention to these at-risk people for COVID-19 prevention interventions.

We found an inconsistent association between COVID-19 risk perceptions and ACPG. Although some studies showed significant positive associations between COVID-19 risk perceptions and ACPG, a study in Ethiopia surprisingly reported that people who had higher levels of risk perception were less likely to adhere to preventive guidelines. Another study found no association in this regard. A plausible explanation for this inconsistency might be the use of various tools to measure the variables, differences in the study populations, and discrepancies in when the studies were conducted during the COVID-19 pandemic. Risk perception as a subjective judgment can help people find ways to cope with the COVID-19 pandemic. However, the dynamic properties of risk perception may vary during different pandemic stages, thereby affecting people's levels of protective behavior. This finding suggests that continuing interventions are necessary to enhance risk perceptions and correct misperceptions.

Our review study showed that providing timely and accurate information to society is necessary to address the COVID-19 pandemic successfully. The source of information was also associated with ACPG [48]. During the pandemic, various sources of information and powerful tools such as online social networks may create patterns of misinformation that have been dubbed an "infodemic" [68,77]. Misinformation and disinformation can result in low ACPG and reduce effective public health responses to the epidemic. A study in Uganda found that village leaders had an important role in providing COVID-19 information and that people who received information about COVID-19 preventive behaviors from village leaders were more likely to adhere to those behaviors [48]. This finding highlights the role of opinion leaders for the future effective implementation of health information interventions in communities.

Material circumstances

Living conditions, quality of housing, and place of living were associated with ACPG in our review study. Due to the nature of COVID-19 and its rapid transmission, limited access to some facilities (such as tap water, hot water, bathrooms, and toilets inside the house) creates some obstacles for ACPG, especially among people who are in lower socio-economic positions. According to the literature, people who live in shelters or crowded suburbs cannot wash their hands regularly due to insufficient access to tap water and sanitation at home [8,9]. Furthermore, living in low-quality housing without adequate space and facilities may reduce adherence to stay-at-home orders. A study in Mexico reported that 3.4 million people in the Mexican population did not have sufficient and proper space in their house to maintain a physical distance, especially if there was a family member with suspected or confirmed COVID-19 at home. In addition, 6.9 million people did not have adequate access to necessary housing facilities such as running water and sanitation. Another finding is that 13.9% had dirt floors, and 58.8% cooked their food with wood or charcoal. Therefore, the possibility of preventive measures such as regular hand-washing was minimal [78].

Work conditions (i.e., the work type, work environment, and providing sick leave) were other factors associated with ACPG in our study. One explanation is that people who work in high-risk conditions (such as health workers) may follow

preventive guidelines more closely regarding higher risk perception and communication. Moreover, a supportive work environment based on a mutual understanding between the employer and employees can enhance the motivation and commitment of people to engage more actively in preventive behaviors to protect not only their health but also that of others. People who have temporary, informal, and non-governmental jobs often do not have enough support from their employers to take sick leave, access to the necessary protective equipment (such as gloves, masks, or alcohol), or reduced working hours in the COVID-19 pandemic [79]. These conditions may affect their intention and ability to implement preventive guidelines. These employees are at risk of contracting COVID-19 at their workplace, but they may also transmit the virus to others in the community [77]. Our finding suggests the need to apply educational interventions to inform employers about the role of working conditions and the benefits of providing support for their employees in adhering to the COVID-19 guidelines and stopping the spread of the virus at their workplaces and in the community.

Psychosocial conditions

Two of the included studies found that capacity and coping appraisal were major predictors of adherence to social distancing and stay-at-home orders [30,32]. These findings suggest that interventional programs for capacity building and improving coping are necessary for effective adherence to preventive guidelines in the community.

As another intermediary social determinant, social norms were also positively associated with ACPG [26,30,31,54,60]. This finding indicates that people's perceptions of attitude and behaviors of others, especially those in their social networks, can affect their adoption of protective behaviors in a community. Planning interventions that target people's social networks and opinion leaders in communities can encourage people to engage in more ACPG.

Two studies assessed the role of trust in government and social institutions in ACPG [38,54]. Although a study in the USA reported that people who had more trust in government were more likely to report more protective behaviors [54], Storopoli et al. [38] in Brazil showed a negative association between trust in the government and ACPG. However, Storopoli et al. [38] also found a significant interaction between vulnerability and trust in the government in relation to ACPG. The magnitude of the association between trust in the government and ACPG can increase or decrease based on levels of perceived vulnerability. This finding highlights that divergences in governmental policies in an emergency like the COVID-19 pandemic can harm people's health. Policy-makers should actively provide valid information, build trust, and increase community engagement to enhance ACPG.

During the COVID-19 pandemic, people may experience various mental health problems such as stress, anxiety, and depression, affecting ACPG. Beeckman et al. [61] reported that psychosocial well-being was negatively associated with ACPG. Our finding underscores the necessity of delivering psychosocial interventions for the community, which may help people cope with emerging challenges and enhance their protective behaviors.

Social support was another intermediary social determinant of ACPG [44,61]. Support from family and friends can buffer people's psychological stress caused by the fear of becoming sick and losing their job and income. Family support also may provide a safe and pleasant environment at home, especially during the lockdown period, which can increase people's resiliency in terms of following stay-at-home orders. To improve ACPG, steps should be taken to strengthen encouraging and supportive relationships between people and their family members.

The WHO conceptual framework emphasizes the interconnectedness of SDH, which play a decisive role during health-compromising conditions such as the COVID-19 pandemic. Although our goal was not to focus on indirect associations between social determinants and ACPG, and the included studies did not consider such relationships, it is nonetheless possible that the identified ACPG-related factors (from both the structural and intermediary levels) may be interrelated. For example, contextual factors such as fatalism and conspiracy beliefs can differently affect people's ACPG based on their income, education, occupation, gender, race/ethnicity, and socio-economic status in general. As people with low education levels may be more strongly affected by fatalism and conspiracy theories, they may have lower COVID-19 risk perceptions, which in turn affects their tendency to engage in ACPG. Furthermore, differences in socio-economic positions can result in different exposures and vulnerabilities to health-damaging conditions (e.g., COVID-19). In this vein, people's education level can affect their occupation, which in turn determines their income level and also socio-economic status. Socio-economic status can affect people's leisure activities, working conditions (especially the possibility of telework), and living place, which in turn each can play an important roles in people's strategies for coping with the COVID-19 pandemic and their adherence to protective guidelines. Hence, future studies are suggested to assess both direct and indirect associations between social determinants and ACPG.

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The limitations of the current review are as follows. First, non-English and unpublished studies were not included in this study. Second, although the applied search strategy was broad, some articles may have been overlooked. Third, measurements of ACPG and its social determinants were not consistent across the included studies. This heterogeneity precluded us from performing a meta-analysis.

Conclusion

According to our findings, ACPG is a complex set of behaviors that are affected by various factors on different levels, including sociodemographic and individual lifestyle factors, social and community networks, living and working conditions, and the socio-economic and political context. Both structural and intermediary social determinants play a vital role in whether people follow COVID-19 protective guidelines. Our findings indicated that most determinants of ACPG were factors outside the health system. Therefore, effective management of this pandemic requires efforts to strengthen intersectoral collaboration and interventions beyond the reach of the health sector, particularly SDH. Governments and authorities should also make social policies to create an environment where people have fewer barriers to ACPG.

Supplementary Material

Table S1. Characteristics of related preliminary studies reviewed in the present study in detail ($n = 41$). Supplementary data are available at https://doi.org/10.24171/j.phrp.2021.0180.

Notes

Ethics Approval
Not applicable.

Conflicts of Interest
The authors have no conflicts of interest to declare.

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Availability of Data
All data extracted and analyzed during this study are included in this published article. For other data, these may be available through the corresponding author upon reasonable request.

Authors' Contributions
Conceptualization: all authors; Data curation: ZJS, YS, SA, MS, NRG; Formal analysis: ZJS, YS, SA; Investigation: all authors; Methodology: all authors; Project administration: ZJS; Resources: all authors; Supervision: YS, SA; Validation: all authors; Visualization: all author; Writing–original draft: ZJS, YS, SA; Writing–review & editing: all authors.

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References

1. World Health Organization (WHO). Coronavirus disease 2019 (COVID-19): situation report, 86. Geneva: WHO; 2020.
2. Markel H, Stern A, Cetron M. Nonpharmaceutical interventions implemented by us cities during the 1918–1919 influenza pandemic. Int J Infect Dis 2008;12:e432.
3. Jefferson T, Foxlee R, Del Mar C, et al. Physical interventions to interrupt or reduce the spread of respiratory viruses: systematic review. BMJ 2008;336:77–80.
4. Lee A, Cho J. The impact of epidemics on labor market: identifying victims of the Middle East Respiratory Syndrome in the Korean labor market. Int J Equity Health 2016;15:196.
5. Rangel JC, Ranade S, Sutcliffe P, et al. COVID-19 policy measures: advocating for the inclusion of the social determinants of health in modelling and decision making. J Eval Clin Pract 2020;26:1078–80.
6. Bruine de Bruin W, Saw HW, Goldman DP. Political polarization in US residents' COVID-19 risk perceptions, policy preferences, and protective behaviors. J Risk Uncertain 2020;61:177–94.
7. Dryhurst S, Schneider CR, Kerr J, et al. Risk perceptions of COVID-19 around the world. J Risk Res 2020;23:994–1006.
8. Lima NN, de Souza RI, Feitosa PW, et al. People experiencing homelessness: their potential exposure to COVID-19. Psychiatry Res 2020;288:112945.
9. Patel JA, Nielsen FB, Badiani AA, et al. Poverty, inequality and COVID-19: the forgotten vulnerable. Public Health 2020;183:110–1.
10. Bellato A. A commentary on psychological factors affecting pro-social behaviors: what can we do to increase compliance with the regulations of physical distancing during the COVID-19 pandemic? Soc Sci Humanit Open 2020 May 5 [Epub]. http://doi.org/10.2139/ssrn.3584414.
11. Raisi-Estabragh Z, McCracken C, Bethell MS, et al. Greater risk of severe COVID-19 in Black, Asian and Minority Ethnic populations is not explained by cardiometabolic, socioeconomic or behavioural factors, or by 25(OH)-vitamin D status: study of 1326 cases from the UK Biobank. J Public Health (Oxf) 2020;42:451–60.
12. Renzaho AM. The need for the right socio-economic and cultural fit in the COVID-19 response in sub-Saharan Africa: examining demographic, economic political, health, and socio-cultural differentials in COVID-19 morbidity and mortality. Int J Environ Res Public Health 2020;17:3445.
13. Thakur N, Lovinsky-Desir S, Bime C, et al. The structural and social determinants of the racial/ethnic disparities in the U.S. COVID-19 pandemic: what's our role? Am J Respir Crit Care Med 2020;202:943–9.
14. Shah M, Sachdeva M, Dodiuk-Gad RP. COVID-19 and racial disparities. J Am Acad Dermatol 2020;83:e35.

15. Solar O, Irwin A. A conceptual framework for action on the social determinants of health. Social determinants of health discussion paper 2 (policy and practice). Geneva: World Health Organization; 2010.
16. Missoni E, Armocida B, Formenti B. Face masks for all and all for face masks in the COVID-19 pandemic: community level production to face the global shortage and shorten the epidemic. Disaster Med Public Health Prep 2021;15:e29–33.
17. World Health Organization (WHO). Commission on social determinants of health. Geneva: WHO; 2008.
18. Driedger SM, Maier R, Furgal C, et al. Factors influencing H1N1 vaccine behavior among Manitoba Metis in Canada: a qualitative study. BMC Public Health 2015;15:128.
19. Ahmad T, Khan M, Haroon, et al. COVID-19: zoonotic aspects. Travel Med Infect Dis 2020;36:101607.
20. Mamoon D. Health and economic outcomes of COVID 19. J Econ Soc Thought 2020;7:41–54.
21. Takian A, Raoofi A, Kazempour-Ardebili S. COVID-19 battle during the toughest sanctions against Iran. Lancet 2020;395:1035–6.
22. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 2010;8:336–41.
23. Pollak Y, Dayan H, Shoham R, et al. Predictors of non-adherence to public health instructions during the COVID-19 pandemic. Psychiatry Clin Neurosci 2020;74:602–4.
24. Alsan M, Stantcheva S, Yang D, et al. Disparities in coronavirus 2019 reported incidence, knowledge, and behavior among US adults. JAMA Netw Open 2020;3:e2012403.
25. Hamidi S, Zandiatashbar A. Compact development and adherence to stay-at-home order during the COVID-19 pandemic: a longitudinal investigation in the United States. Landsc Urban Plan 2021;205:103952.
26. Hagger MS, Smith SR, Keech JJ, et al. Predicting social distancing intention and behavior during the COVID-19 pandemic: an integrated social cognition model. Ann Behav Med 2020;54:713–27.
27. Zhai W, Liu M, Peng ZR. Social distancing and inequality in the United States amid COVID-19 outbreak. Environ Plan A Econ Space 2021;53:3–5.
28. Galasso V, Pons V, Profeta P, et al. Gender differences in COVID-19 attitudes and behavior: panel evidence from eight countries. Proc Natl Acad Sci U S A 2020;117:27285–91.
29. Taylor S, Paluszek MM, Rachor GS, et al. Substance use and abuse, COVID-19-related distress, and disregard for social distancing: a network analysis. Addict Behav 2021;114:106754.
30. Smith PH, Branscum PW. Feasibility, utility, and limitations of a rapid community behavioral diagnosis for social distancing during the 2020 coronavirus pandemic. Am J Health Promot 2021;35:77–83.
31. Bogg T, Milad E. Demographic, personality, and social cognition correlates of coronavirus guideline adherence in a U.S. sample. Health Psychol 2020;39:1026–36.
32. Al-Hasan A, Yim D, Khuntia J. Citizens' adherence to COVID-19 mitigation recommendations by the government: a 3-country comparative evaluation using web-based cross-sectional survey data. J Med Internet Res 2020;22:e20634.
33. Hearne BN, Nino MD. Understanding how race, ethnicity, and gender shape mask-wearing adherence during the COVID-19 pandemic: evidence from the COVID impact survey. J Racial Ethn Health Disparities 2021;1–8.
34. Wright AL, Sonin K, Driscoll J, et al. Poverty and economic dislocation reduce compliance with COVID-19 shelter-in-place protocols. J Econ Behav Organ 2020;180:544–54.
35. Margraf J, Brailovskaia J, Schneider S. Behavioral measures to fight COVID-19: an 8-country study of perceived usefulness, adherence and their predictors. PLoS One 2020;15:e0243523.
36. Jimenez T, Restar A, Helm PJ, et al. Fatalism in the context of COVID-19: perceiving coronavirus as a death sentence predicts reluctance to perform recommended preventive behaviors. SSM Popul Health 2020;11:100615.
37. Wise T, Zbozinek TD, Michelini G, et al. Changes in risk perception and self-reported protective behaviour during the first week of the COVID-19 pandemic in the United States. R Soc Open Sci 2020;7:200742.
38. Storopoli J, Braga da Silva Neto WL, Mesch GS. Confidence in social institutions, perceived vulnerability and the adoption of recommended protective behaviors in Brazil during the COVID-19 pandemic. Soc Sci Med 2020;265:113477.
39. Faria de Moura Villela E, Lopez RV, Sato AP, et al. COVID-19 outbreak in Brazil: adherence to national preventive measures and impact on people's lives, an online survey. BMC Public Health 2021;21:152.
40. Bezerra AC, Silva CE, Soares FR, et al. Factors associated with people's behavior in social isolation during the COVID-19 pandemic. Cien Saude Colet 2020;25(suppl 1):2411–21.
41. Chan EY, Huang Z, Lo ES, et al. Sociodemographic predictors of health risk perception, attitude and behavior practices associated with health-emergency disaster risk management for biological hazards: the case of COVID-19 pandemic in Hong Kong, SAR China. Int J Environ Res Public Health 2020;17:3869.
42. Nasirzadeh M, Aligol M. Assessment of knowledge, attitude, and factors associated with the preventive behaviors of COVID-19 in Qom, Iran, in 2020. Qom Univ Med Sci J 2020;14:50–7.
43. Kim YJ, Cho JH. Correlation between preventive health behaviors and psycho-social health based on the leisure activities of South Koreans in the COVID-19 crisis. Int J Environ Res Public Health 2020;17:4066.
44. Paykani T, Zimet GD, Esmaeili R, et al. Perceived social support and compliance with stay-at-home orders during the COVID-19 outbreak: evidence from Iran. BMC Public Health 2020;20:1650.
45. Tong KK, Chen JH, Yu EW, et al. Adherence to COVID-19 precautionary measures: applying the health belief model and generalised social beliefs to a probability community sample. Appl Psychol Health Well Being 2020;12:1205–23.
46. Al-Sabbagh MQ, Al-Ani A, Mafrachi B, et al. Predictors of adherence

https://doi.org/10.24171/j.phrp.2021.0180

with home quarantine during COVID-19 crisis: the case of health belief model. Psychol Health Med 2021;1–13.

47. Ilesanmi O, Afolabi A. Perception and practices during the COVID-19 pandemic in an urban community in Nigeria: a cross-sectional study. PeerJ 2020;8:e10038.
48. Amodan BO, Bulage L, Katana E, et al. Level and determinants of adherence to COVID-19 preventive measures in the first stage of the outbreak in Uganda. Int J Environ Res Public Health 2020;17:8810.
49. Iorfa SK, Ottu IF, Oguntayo R, et al. COVID-19 knowledge, risk perception, and precautionary behavior among Nigerians: a moderated mediation approach. Front Psychol 2020;11:566773.
50. Mohamed AA, Elhassan EA, Mohamed AO, et al. Knowledge, attitude and practice of the Sudanese people towards COVID-19: an online survey. BMC Public Health 2021;21:274.
51. Azene ZN, Merid MW, Muluneh AG, et al. Adherence towards COVID-19 mitigation measures and its associated factors among Gondar City residents: a community-based cross-sectional study in Northwest Ethiopia. PLoS One 2020;15:e0244265.
52. Plohl N, Musil B. Modeling compliance with COVID-19 prevention guidelines: the critical role of trust in science. Psychol Health Med 2021;26:1–12.
53. Coroiu A, Moran C, Campbell T, et al. Barriers and facilitators of adherence to social distancing recommendations during COVID-19 among a large international sample of adults. PLoS One 2020;15:e0239795.
54. Raude J, Lecrique JM, Lasbeur L, et al. Determinants of preventive behaviors in response to the COVID-19 pandemic in France: comparing the sociocultural, psychosocial and social cognitive explanations. Front Psychol 2020;11:3345.
55. Cvetkovic VM, Nikolic N, Radovanovic Nenadic U, et al. Preparedness and preventive behaviors for a pandemic disaster caused by COVID-19 in Serbia. Int J Environ Res Public Health 2020;17:4124.
56. Carlucci L, D'Ambrosio I, Balsamo M. Demographic and attitudinal factors of adherence to quarantine guidelines during COVID-19: the Italian model. Front Psychol 2020;11:559288.
57. Kowalski J, Marchlewska M, Molenda Z, et al. Adherence to safety and self-isolation guidelines, conspiracy and paranoia-like beliefs during COVID-19 pandemic in Poland: associations and moderators. Psychiatry Res 2020;294:113540.
58. Yang XY, Gong RN, Sassine S, et al. Risk perception of COVID-19 infection and adherence to preventive measures among adolescents and young adults. Children (Basel) 2020;7:311.
59. Sturman D, Auton JC, Thacker J. Knowledge of social distancing measures and adherence to restrictions during the COVID-19 pandemic. Health Promot J Austr 2021;32:344–51.
60. Gouin JP, MacNeil S, Switzer A, et al. Socio-demographic, social, cognitive, and emotional correlates of adherence to physical distancing during the COVID-19 pandemic: a cross-sectional study. Can J Public Health 2021;112:17–28.
61. Beeckman M, De Paepe A, Van Alboom M, et al. Adherence to the physical distancing measures during the COVID-19 pandemic: a HAPA-based perspective. Appl Psychol Health Well Being 2020;12:1224–43.
62. Moussaoui LS, Ofosu ND, Desrichard O. Social psychological correlates of protective behaviours in the COVID-19 outbreak: evidence and recommendations from a nationally representative sample. Appl Psychol Health Well Being 2020;12:1183–204.
63. Allington D, Dhavan N. The relationship between conspiracy beliefs and compliance with public health guidance with regard to COVID-19. London: Centre for Countering Digital Hate; 2020.
64. Kasjono HS, Amalia R, Nugroho NM, et al. Study on physical distancing compliance towards corona virus risk (COVID-19). Eur J Mol Clin Med 2020;7:2236–42.
65. Truong N, Asare AO. Assessing the effect of socio-economic features of low-income communities and COVID-19 related cases: an empirical study of New York City. Glob Public Health 2021;16:1–16.
66. Young BE, Ong SW, Kalimuddin S, et al. Epidemiologic features and clinical course of patients infected with SARS-CoV-2 in Singapore. JAMA 2020;323:1488–94.
67. The Lancet. COVID-19: learning from experience. Lancet 2020;395:1011.
68. Adedimeji A, Sinayobye JD, Asiimwe-Kateera B, et al. Social contexts as mediator of risk behaviors in Rwandan men who have sex with men (MSM): implications for HIV and STI transmission. PLoS One 2019;14:e0211099.
69. Astrom AN, Rise J. Socio-economic differences in patterns of health and oral health behaviour in 25 year old Norwegians. Clin Oral Investig 2001;5:122–8.
70. Turrell G, Kavanagh AM. Socio-economic pathways to diet: modelling the association between socio-economic position and food purchasing behaviour. Public Health Nutr 2006;9:375–83.
71. Dunn AG, Surian D, Leask J, et al. Mapping information exposure on social media to explain differences in HPV vaccine coverage in the United States. Vaccine 2017;35:3033–40.
72. Jolley D, Douglas KM. The effects of anti-vaccine conspiracy theories on vaccination intentions. PLoS One 2014;9:e89177.
73. Thorburn S, Bogart LM. Conspiracy beliefs about birth control: barriers to pregnancy prevention among African Americans of reproductive age. Health Educ Behav 2005;32:474–87.
74. Do BN, Tran TV, Phan DT, et al. Health literacy, ehealth literacy, adherence to infection prevention and control procedures, lifestyle changes, and suspected COVID-19 symptoms among health care workers during lockdown: online survey. J Med Internet Res 2020;22:e22894.
75. International Labour Organization (ILO). Working from home: estimating the worldwide potential. Geneva: ILO; 2020.
76. Sen G, Ostlin P, George A. Unequal, unfair, ineffective and inefficient. Gender inequity in health: why it exists and how we can change it. Final report to the WHO Commission on Social Determinants of Health. Geneva: World Health Organization; 2007.
77. Vaezi A, Javanmard SH. Infodemic and risk communication in the era of CoV-19. Adv Biomed Res 2020;9:10.

78. Diaz de Leon-Martinez L, de la Sierra-de la Vega L, Palacios-Ramirez A, et al. Critical review of social, environmental and health risk factors in the Mexican indigenous population and their capacity to respond to the COVID-19. Sci Total Environ 2020;733:139357.
79. SoleimanvandiAzar N, Irandoost SF, Ahmadi S, et al. Explaining the reasons for not maintaining the health guidelines to prevent COVID-19 in high-risk jobs: a qualitative study in Iran. BMC public health 2021;21:1–15.

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Original Article

Factors influencing acceptance of the COVID-19 vaccine in Malaysia: a web-based survey

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ABSTRACT

Objectives: The coronavirus disease 2019 (COVID-19) pandemic has set a precedent for the fastest-produced vaccine as a result of global collaboration and outreach. This study explored Malaysians' acceptance of the COVID-19 vaccine and its associated factors.
Methods: A cross-sectional anonymous web-based survey was disseminated to Malaysian adults aged ≥18 years old via social media platforms between July 10, 2020 and August 31, 2020.
Results: In the analysis of 4,164 complete responses, 93.2% of participants indicated that they would accept the COVID-19 vaccine if it was offered for free by the Malaysian government. The median out-of-pocket cost that participants were willing to pay for a COVID-19 vaccine was Malaysian ringgit (MYR) 100 (interquartile range [IQR], 100) if it was readily available and MYR 150 (IQR, 200) if the supply was limited. Respondents with a low likelihood of vaccine hesitancy had 13 times higher odds of accepting the COVID-19 vaccine (95% confidence interval [CI], 8.69 to 19.13). High perceived risk and severity were also associated with willingness to be vaccinated, with adjusted odds ratios of 2.22 (95% CI, 1.44 to 3.41) and 2.76 (95% CI, 1.87 to 4.09), respectively. Age and ethnicity were the only independent demographic characteristics that predicted vaccine uptake.
Conclusion: Public health strategies targeting perceived risk, perceived susceptibility and vaccine hesitancy could be effective in enhancing vaccine uptake.

Keywords: COVID-19; COVID-19 vaccines; SARS-CoV-2 vaccine; Surveys and questionnaires

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Introduction

It has been over a year since coronavirus disease 2019 (COVID-19) emerged as the greatest global health crisis of the century, with wide-reaching economic, social, and environmental impacts. From its humble origins as a novel cluster of pneumonia cases in China, the number of current infections worldwide as of May 10, 2021 stands at 157.9 million, with a global death toll of nearly 3.3 million [1]. In Malaysia, the first reported case of COVID-19 occurred on January 25, 2020, marking the beginning of the first wave of COVID-19 infections in Malaysia

[2]. Buoyed by the emergence of several clusters, the rate of infections began to escalate rapidly. Since then, the country has undergone 2 additional waves; the second started on February 27, 2020 and an ongoing third wave started on September 8, 2020. Various stages of movement control orders (MCOs) have since been implemented by the Malaysian government in an attempt to contain the outbreak. Thus far, the third wave has proved to be the most severe, with daily infections reaching a record high of 5,725 on January 29, 2021 [3]. Only with the reintroduction of the MCO restrictions on January 11 did the rate of infections start to show a gradual decline. As of May 8, 2021, the number of cumulative infections in Malaysia reached 444,484, with 1,700 deaths [4].

Since the announcement in early November 2020 by Pfizer-BioNTech that the COVID-19 vaccine was 90% effective [5], the United Kingdom and United States (US) responded swiftly by authorising the emergency use of this vaccine, which is also known as the Comirnaty COVID-19 mRNA vaccine. This was followed by approval for emergency use by the World Health Organization (WHO) a month later [6]. The Malaysian government similarly mounted a prompt response with the implementation of the national COVID-19 immunisation plan across 3 phases, with the first beginning on February 24, 2021 and lasting until April [7]. The target population for the first phase are front-liners, particularly those in the medical profession. Subsequently, the second phase (April to August 2021) involved senior citizens aged 65 and above, high-risk groups, and disabled, and the third phase (May to February 2022) will cover both citizens and non-citizens aged 18 years and above. Based on latest estimates, it is predicted that approximately 60% to 75% of the population needs to be vaccinated in order to confer effective herd immunity against COVID-19 transmission [8,9]. Our national target is 80% of the population [10]. Hence, public acceptance and the role of the public will be of great consequence for achieving the intended goal of herd immunity. Nevertheless, polls on COVID-19 vaccine acceptance have exposed a perturbing trend in Malaysia. During the first wave in April 2020, a relatively high acceptance rate of 85% to 94% was demonstrated in polls conducted by an international market research company and a research team from Malaysia, respectively [11,12]. However, by December 2020, in the midst of the third wave and impending vaccination rollout, acceptance levels declined to 67%, a stark contrast from the earlier values [13].

Despite having standard monitoring mechanisms in place, uncertainties regarding safety profile and effectiveness remain the primary concerns. Extensive publicity highlighting adverse events in the early stages [14,15] and during the initial vaccination rollout [16] may have triggered negative perceptions and unfounded fears, ultimately contributing to reduced vaccine uptake. Several studies during previous influenza pandemics had adopted health behavioural theories to examine predictors of vaccination intent [17–19]. During the influenza pandemic in 2009, post-pandemic public polls reported poor uptake of the pandemic influenza vaccine in the general public, high-risk groups, and healthcare workers [20,21]. These failures stemmed from a breakdown in perceptions of risk, susceptibility, and vulnerability in the population. Therefore, this study aimed to provide a pre-emptive understanding of factors influencing acceptance of the COVID-19 vaccine amongst the Malaysian population. This will serve to guide interventions for future pandemic preparedness planning.

Materials and Methods

Study Population and Sampling

We conducted a cross-sectional anonymous survey using the Research Electronic Data Capture platform to disseminate a web-based self-administered questionnaire. This survey was done between July 10, 2020 and August 31, 2020. The survey was disseminated via various social media platforms such as Instagram, Twitter, LinkedIn, Facebook, WhatsApp, and Telegram. The target population was Malaysian adults aged 18 years old and above. All respondents were informed that their participation was anonymous and voluntary at the beginning of the survey. Consent was implied if the participants started answering the questionnaire.

Study Instrument

The questionnaire in this study was adapted from published literature during the previous H1N1 pandemic [22]. Questions were modified to fit the context of COVID-19 pandemic in accordance with the objective of this study. Furthermore, a few additional questions were adopted from the SAGE Working Group on Vaccine Hesitancy to assess the possibility of vaccine hesitancy [23].

During the process of questionnaire development, local experts, including healthcare professionals and academicians, proofread and validated the content. The questionnaire was developed in English and subsequently translated into Bahasa Malaysia and Mandarin. Pilot testing was done before study commencement, and the questionnaire was modified according to the feedback until no more amendments were needed. The final version of the questionnaire can be found in Supplementary Material 1. The questionnaire comprised questions that assessed (1) sociodemographic characteristics

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and COVID-19 experience; (2) vaccine hesitancy; (3) perceptions of risk and seriousness; (4) acceptability of the COVID-19 vaccine; (5) willingness to pay; and (6) attitudes towards the COVID-19 vaccine.

Sociodemographic characteristics and COVID-19 experience

The first part of the questionnaire collected basic sociodemographic data on age, sex, ethnicity, education level, monthly household income, occupation, and living arrangements (e.g., living with elderly individuals, children, and/or pregnant women). The respondents were also asked to indicate whether they or their family and friends had been infected with COVID-19 previously.

Vaccine hesitancy

All respondents were asked 4 items to assess vaccine hesitancy. Three items were assessed on a 5-point Likert-type scale. For the fourth item, respondents were asked to respond to the following statement "Have you ever declined vaccination for your child?" A simplified option of yes/no/not applicable was used for this item. Responses suggestive of vaccine hesitancy are shown in Table 1. These responses are given a score of 1 for each item, with a maximum score of 4. A score of 2 or more is considered to indicate a likelihood of vaccine hesitancy.

Perceptions of risk and seriousness

Perceptions of risk and seriousness were measured using 3 items with responses on a 5-point Likert-type scale. Participants were asked about the risk level they perceived for themselves, the perceived risk for the general community in Malaysia, and the perceived seriousness of the disease if they contracted the infection.

Acceptability of the COVID-19 vaccine

One item assessed respondents' perceived acceptability of the COVID-19 vaccine. The respondents were asked to choose yes, no, or unsure to describe their intention if a COVID-19 vaccine was made available to Malaysians for free. Respondents who answered no or unsure were prompted for reasons for refusal, while respondents who answered yes were asked about the maximum acceptable number of doses.

Willingness to pay

The willingness to pay for a COVID-19 vaccine under the circumstances of sufficient and limited supply was measured using 2 items. Both items were open-ended questions, where participants were allowed to input any amount between Malaysian ringgit (MYR) 0 and MYR 1,500 (approximately USD 360).

Attitudes towards the COVID-19 vaccine

The last part of the questionnaire contained 7 items assessing the attitudes of respondents towards a COVID-19 vaccine. All items were measured on a 5-point Likert-type scale.

Statistical Analysis

The responses were analysed using descriptive and inferential statistics. All categorical variables were expressed as frequencies and percentages, while continuous variables were expressed as means with standard deviations or medians with interquartile ranges (IQRs) depending on the distribution of data. For inferential analysis, we studied the factors associated with acceptance of COVID-19 vaccination. Logistic regression was used to assess statistical associations in univariate and multivariate analyses. Variables with a p-value < 0.05 in the univariate analyses were included in the multivariate logistic regression analysis to identify independent predictors of COVID-19 vaccine uptake. Odds ratio (ORs) and 95% confidence intervals (95% CIs) were calculated. All statistical analyses were performed using R version 3.6.3, with the level of significance set at 5%.

In the analysis, responses regarding the level of agreement or risk level were collapsed into 3 levels (agree, not sure, disagree or low risk, medium risk, high risk). Under the vaccine hesitancy section, the level of agreement was dichotomised into agree (consisting of strongly agree and agree) or disagree (consisting of strongly disagree, disagree, and not sure) due to the small number of responses for not sure. Respondents

Table 1. Responses suggestive of vaccine hesitancy

Statement	Responses suggestive of vaccine hesitancy
My religion/physiology/culture recommends against vaccination.	Agree or strongly agree
Some groups or influential people are against vaccination for different reasons. Do you agree or disagree with these groups of people?	Agree or strongly agree
It is important for me to get recommended vaccines for myself and my children.	Disagree or strongly disagree
Have you ever declined vaccination for your children?	Yes

who answered at least 2 out of the 4 questions pointing towards vaccine hesitancy were considered more likely to be vaccine-hesitant.

Results

Background Characteristics

In total, 4,164 complete responses were received during the survey period. Demographic profiles and COVID-19 experiences of the respondents are summarised in Table 2. The majority of the respondents were women (71.2%), with a median age of 37.0 years (IQR, 14 years), of Malay ethnicity (54.7%) and possessed at least tertiary education (74.5%). Slightly over half of respondents had an average monthly household income of over MYR 5,000 (58.4%), while the remainder earned less than MYR 5,000 (41.6%). Approximately one-third (31.2%) of the respondents were healthcare workers with the remainder being the general public (68.8%). A total of 61.7% lived with elderly individuals, children, and/or pregnant women. Nearly all respondents (99.6%) did not have a previous COVID-19 infection, whereas a small fraction of the respondents (6.5%) reported having family members or friends who had contracted COVID-19.

Vaccine Hesitancy

In total, 137 (3.3%) respondents were identified as being more likely to have vaccine hesitancy sentiments. Although Malaysia is a multicultural and multi-ethnic country, most respondents (91.6%) did not think that their religion, philosophy, or culture was against vaccination. The majority (94.1%) agreed with the importance of receiving the recommended vaccination for themselves and their children. Among 2,809 respondents with children, only a minority stated that they would refuse vaccination for their children. Furthermore, only 7% of the respondents agreed with the views of the vaccine-hesitant population (Table 3).

Perceptions of Risk and Seriousness

The respondents perceived that there was a higher risk of COVID-19 infection among the general Malaysian population than for themselves (Table 4). Nearly half (49.5%) of the respondents ranked Malaysian residents to be at high risk of becoming infected with COVID-19 during this pandemic. However, the self-perceived risk of contracting COVID-19 was more evenly distributed across the different risk levels. Interestingly, the respondents had high perceptions of severity. Almost two-thirds of the respondents perceived that their health would be seriously affected if they were infected with COVID-19.

Acceptability of the COVID-19 Vaccine and Willingness to Pay

The acceptance rate of the COVID-19 vaccine was generally high at 93.2%, while the remaining respondents answered either no (2.1%) or unsure (4.7%) if they were offered the COVID-19 vaccine for free by the Malaysian government. The median willingness to pay for a COVID-19 vaccine was 50% higher if the supply was limited than if it was readily available, with values of MYR 150 (IQR, 200) and MYR 100 (IQR, 100), respectively.

Among the 3,882 participants who responded yes for COVID-19 vaccine intent, 1,702 (43.8%) felt that the number of doses did not matter to them. The proportion of participants who would accept more than a single dose of the COVID-19 vaccine was rather high, with only 262 of them

Table 2. Background characteristics and their associations with COVID-19 vaccine acceptance

Characteristic	Results (*n* = 4,164)
Demographic profile	
Age (y)	37.0 (31.0–45.0)
Sex	
Male	1,200 (28.8)
Female	2,964 (71.2)
Ethnicity	
Malay	2,276 (54.7)
Chinese	1,309 (31.4)
Indian	285 (6.8)
Others	294 (7.1)
Highest education level	
Up to high school education/technical skills/diploma or equivalent	1,061 (25.5)
Tertiary education	3,103 (74.5)
Average monthly household income	
< MYR 5,000	1,731 (41.6)
≥ MYR 5,000	2,433 (58.4)
Live with elderly/children/pregnant woman	
Yes	2,570 (61.7)
No	1,594 (38.2)
Occupation	
Healthcare workers	1,298 (31.2)
Non-healthcare workers	2,866 (68.8)
COVID-19 experience	
History of contracting COVID-19 infection	
Yes	16 (0.4)
No	4,148 (99.6)
Known any family members or friends infected with COVID-19	
Yes	272 (6.5)
No	3,892 (93.5)

Data are presented as median (interquartile range) or *n* (%).
COVID-19, coronavirus disease 2019; MYR, Malaysian ringgit.

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Table 3. Determinants of vaccine hesitancy among the respondents

Statement	Result (*n* = 4,164)
My religion/philosophy/culture recommends against vaccination	
Agree	348 (8.4)
Disagree	3,816 (91.6)
Some groups or influential people are against vaccination for different reasons. Do you agree or disagree with these groups of people?	
Agree	290 (7.0)
Disagree	3,874 (93.0)
It is important for me to get recommended vaccines for myself and my children	
Agree	3,917 (94.1)
Disagree	247 (5.9)
Have you ever declined vaccination for your children?	
Yes	21 (0.5)
No	2,788 (67.0)
Not applicable	1,355 (32.5)
Vaccine hesitancy	
Probable	137 (3.3)
Not likely	4,027 (96.7)

Data are presented as *n* (%).

Table 4. Respondents' perceived risk and severity

Perception of risk and severity	Result (*n* = 4,164)
How likely is it for a Malaysian resident to get infected by COVID-19 during this pandemic?	
High	2,061 (49.5)
Medium	1,615 (38.8)
Low	488 (11.7)
What is the risk for you to get infected by COVID-19 during this pandemic?	
High	1,491 (35.8)
Medium	1,448 (34.8)
Low	1,225 (29.4)
If you were infected with COVID-19, how seriously do you think it would affect your health?	
Severe	2,768 (66.5)
Moderate	1,052 (25.3)
Mild	344 (8.3)

Data are presented as *n* (%).
COVID-19, coronavirus disease 2019.

(6.7%) choosing 1 dose as the maximum acceptable dose. However, very few ($n = 36$, 0.9%) would accept a maximum of 4 doses. As for the others, the maximum number of acceptable doses for the COVID-19 vaccine ranged between 2 ($n = 1{,}023$, 26.4%) and 3 ($n = 859$, 22.1%) doses (Figure 1).

For the respondents who had negative responses or were unsure of their COVID-19 vaccine intent, the top 3 concerns were the adequacy of vaccine testing (77.7%), its effectiveness (63.8%), and side effects (57.1%) (Table 5).

Factors Associated with Acceptance of the COVID-19 Vaccine

Table 6 summarises the univariate and multivariate analyses of factors associated with acceptance of the COVID-19 vaccine. Stepwise multivariate regression analysis (backward method) was performed, and the variables selected were age, race, vaccine hesitancy sentiments, perceived population risk of contracting COVID-19 and risk to health. In the final model, variables that were important indicators of vaccine acceptance were added to the multivariate regression model. The Hosmer-Lemeshow test was used to test the goodness of fit of the model ($p = 0.582$, $\chi^2 = 4.702$). All variables were checked for interaction and multicollinearity. The variance inflation factor (VIF), which was used for collinearity analysis, indicated low correlations among the investigated variables (VIF < 2). Older participants were less

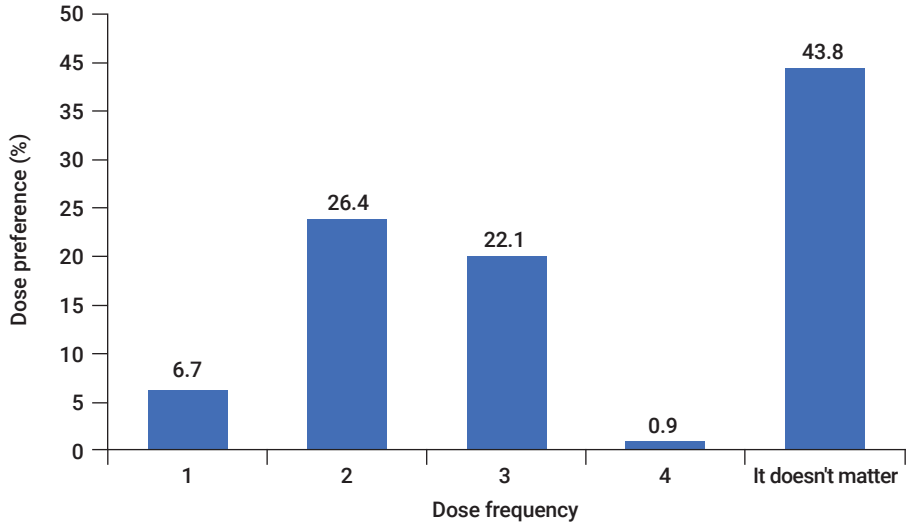

Figure 1. Maximum acceptable number of doses if the vaccination needs to be received in stages for those who accepted the coronavirus disease 2019 (COVID-19) vaccine.

Table 5. Reasons for refusing the COVID-19 vaccine

Reason	Result (*n* = 282)
I am concerned that the vaccine has not been tested adequately	219 (77.7)
I am concerned regarding the effectiveness of the vaccine	180 (63.8)
I am afraid of the side effects	161 (57.1)
I am concerned that taking the COVID-19 vaccine will cause me to get the disease	47 (16.7)
I think my chances of being infected are low	42 (14.9)
I am afraid of pain	21 (7.4)
COVID-19 will only cause a mild illness	21 (7.4)

Data are presented as *n* (%).
COVID-19, coronavirus disease 2019.

likely to accept the COVID-19 vaccine. With every 1-year increase in age, there was a 3% lower likelihood of accepting the vaccine (0.97; 95% CI, 0.96 to 0.98). In terms of ethnicity, the odds of being willing to accept the COVID-19 vaccine among Malays was 2.4 and 1.9 times higher than that among Chinese and Indians, respectively. The associations between COVID-19 vaccination intent and other sociodemographic factors (e.g., sex, education level, monthly household income, occupation, and living arrangement) were not statistically significant. A low likelihood of vaccine hesitancy sentiments (adjusted odds ratio [AOR], 12.89; 95% CI, 8.69 to 19.13) showed the strongest association with acceptance of the COVID-19 vaccine. Additionally, respondents who perceived a high risk for the general community to contract COVID-19 were more than 2 times as likely to be willing to receive the COVID-19 vaccine than those with a low-risk perception (AOR, 2.22; 95% CI, 1.44 to 3.41). Although the self-perceived risk of COVID-19 infection was associated with COVID-19 vaccination intent in the univariate analysis, it was not significant when adjusted for other variables. Participants who perceived their health would be seriously affected if they were infected with COVID-19 had significantly higher odds of accepting the COVID-19 vaccine than those who perceived a low level of severity (AOR, 2.76; 95% CI, 1.87 to 4.09). However, previous COVID-19 experience did not influence the acceptance of COVID-19 vaccination.

Attitude towards the COVID-19 Vaccine

The participants were asked if they were concerned about adverse events, and 68.9% reported that they could readily accept the mild side effects of the COVID-19 vaccine. The respondents agreed that cost of the COVID-19 vaccine (53.9%) and *halal* certification (43.7%) were important considerations. Comparatively, only 1,285 (30.9%) felt that the country of origin was important when deciding whether to receive the COVID-19 vaccine. The majority (57.6%) believed that the vaccine will stop virus transmission, and 2,646 (63.5%) disagreed with the statement that only high-risk populations require vaccination. On a positive note, the participants had strong trust in the Malaysian government, with 88.2% expressing confidence in receiving the COVID-19 vaccine if the government advocated doing so (Table 7).

Discussion

Our study showed that Malaysians generally had higher levels of acceptance of the COVID-19 vaccine than respondents from many countries [24–27]. This finding is further supported by Wong et al. [11], who reported a 94.3% rate of COVID-19 vaccination intent among Malaysians. According to a global

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Table 6. Univariate and multivariate logistic regression of factors associated with acceptance of the COVID-19 vaccine

Characteristic	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p*	AOR	95% CI	*p*
Age (y)	0.96	0.95–0.97	< 0.001	0.97	0.96–0.98	< 0.001*
Sex						
Female	1 (reference)			1 (reference)		
Male	0.74	0.58–0.96	0.023*	1.10	0.82–1.49	0.633
Ethnicity						
Malay	1 (reference)			1 (reference)		
Chinese	0.42	0.33–0.55	< 0.001*	0.39	0.29–0.52	< 0.001*
Indian	0.40	0.27–0.62	< 0.001*	0.47	0.29–0.77	0.004*
Others	1.00	0.58–1.89	0.706	1.05	0.57–2.07	0.808
Education level						
Secondary education and below	1 (reference)					
Tertiary education	0.85	0.64–1.13	0.27			
Average monthly household income						
< MYR 5,000	1 (reference)					
≥ MYR 5,000	0.86	0.67–1.11	0.248			
Live with elderly, children, or pregnant woman						
No	1 (reference)					
Yes	1.21	0.95–1.54	0.126			
Occupation						
Non-healthcare workers	1 (reference)					
Healthcare workers	1.25	0.95–1.64	0.113			
History of contracted COVID-19						
No	1 (reference)					
Yes	0.51	0.14–3.24	0.296			
Known any family members of friends infected with COVID-19						
No	1 (reference)					
Yes	1.26	0.76–2.25	0.394			
Likelihood of vaccine hesitancy sentiments						
High	1 (reference)			1 (reference)		
Low	15.8	12.2–20.64	< 0.001*	12.92	8.70–19.18	< 0.001*
How likely it is for a Malaysian resident to get infected by COVID-19 during this pandemic						
Low	1 (reference)			1 (reference)		
Medium	2.17	1.59–2.95	< 0.001*	1.38	0.93–2.04	0.028
High	3.94	2.84–5.47	< 0.001*	2.02	1.29–3.14	< 0.001*
What level of risk do you think you have of catching COVID-19 during this pandemic?						
Low	1 (reference)			1 (reference)		
Medium	1.81	1.36–2.41	< 0.001*	1.27	0.90–1.79	0.248
High	2.42	1.79–3.30	< 0.001*	1.20	0.81–1.78	0.433
If you were infected with COVID-19, how seriously do you think it would affect your health?						
Low	1 (reference)			1 (reference)		
Medium	1.88	1.30–2.69	< 0.001*	1.26	0.82–1.92	0.023
High	3.52	2.49–4.92	< 0.001*	2.28	1.50–3.41	< 0.001*

COVID-19, coronavirus disease 2019; OR, odds ratio; CI, confidence interval; AOR, adjusted odds ratio; MYR, Malaysian ringgit.
$R^2 = 0.140$, variance inflation factor < 2, No interactions among covariates. Hosmer-Lemeshow goodness of fit test: $\chi^2 = 4.7023$, df = 6, $p = 0.5825$.
*$p < 0.05$.

Table 7. Attitude towards the COVID-19 vaccine

Statement	Result (*n* = 4,164)
I can readily accept the mild side effects of the COVID-19 vaccine.	
Agree	2,867 (68.9)
Not sure	714 (17.1)
Disagree	583 (14.0)
The COVID-19 vaccine will stop the virus transmission.	
Agree	2,397 (57.6)
Not sure	1,230 (29.5)
Disagree	537 (12.9)
Only high-risk groups such as children, pregnant women, elderly and those with underlying medical conditions need to be vaccinated with the COVID-19 vaccine.	
Agree	1,069 (25.7)
Not sure	449 (10.8)
Disagree	2,646 (63.5)
I am confident in taking the COVID-19 vaccine if it is advocated by the Malaysian government.	
Agree	3,674 (88.2)
Not sure	333 (8.0)
Disagree	157 (3.8)
The country of origin of the COVID-19 vaccine will influence my decision to take it.	
Agree	1,285 (30.9)
Not sure	1,031 (24.8)
Disagree	1,848 (44.4)
The COVID-19 vaccine needs to be certified halal before I will take it.	
Agree	1,818 (43.7)
Not sure	516 (12.4)
Disagree	1,830 (43.9)
The cost of the vaccine will affect my decision to take it.	
Agree	2,245 (53.9)
Not sure	807 (19.4)
Disagree	1,112 (26.7)

Data are presented as *n* (%).
COVID-19, coronavirus disease 2019.

survey involving 13,426 respondents from 19 countries, country-specific acceptance rates ranged between 54.9% and 88.6% [26]. However, these studies were done during the peak of the pandemic period. Hence, the acceptance rate would be likely to change if this study is repeated at a different stage of the pandemic [28]. This could likely be attributed to factors modulating vaccine hesitancy, including confidence in the healthcare system, health professionals, and policy-makers [23]. During the period when this survey was conducted, Malaysia had just entered the recovery movement control order phase, with the reopening of various economic sectors. The daily number of cases reported was trending towards single digits, with a general positive view on how the Malaysian government had tackled the COVID-19 pandemic [29]. Thus, vaccine acceptance rates were relatively high with government advocacy. This is consistent with several published studies reporting a significant positive association between trust in the government and vaccine uptake [23,30,31]. Several months later, in December, a public survey by the Ministry of Health Malaysia reported that the vaccine acceptance rate was 67%, in significant contrast to previous results [32]. By then, Malaysia had entered its third wave and was rife with pandemic fatigue, with palpable strain on the healthcare system and economy. Daily infections surged to 4 digits and continued on an upwards trend. Therefore, this highlights the need to capitalise on positive momentum to retain public confidence for a smooth and successful vaccination rollout in the future.

Vaccine hesitancy was named by the WHO as one of the top 10 threats to global health [33]. It is defined as delay or refusal of vaccinations despite availability and is influenced by complacency, convenience, and confidence. Similar to many countries, Malaysia has seen a rise in vaccine hesitancy in recent years [34,35]. As a Southeast Asian country, Malaysia has rich social, cultural, traditional, and

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religious elements that play a prominent role in influencing health behaviours. The vaccine hesitancy survey questions focused primarily on contextual, individual, and group influences, taking into account local literature highlighting the importance of religious and socio-cultural influences on vaccine hesitancy in Malaysia [36–38]. Nevertheless, only a small proportion of the study participants agreed that their religion and culture were against vaccination. In the National Health and Morbidity Survey 2016, concerns that the vaccines were not *halal* were cited as one of the reasons for vaccine hesitancy [39]. Nearly half of our study respondents wanted the COVID-19 vaccine to be certified as *halal* before agreeing to take it. This highlights the central role of religious authorities in promoting COVID-19 vaccination. After the influenza pandemic of 2008, few studies were done in Malaysia regarding vaccination hesitancy and uptake during the pandemic. Our findings showed that those whose answers implied vaccine hesitancy had a lower likelihood of accepting the vaccine. This is consistent with findings from many studies showing vaccine hesitancy to be a main contributor to poor vaccine uptake [40–42]. This is especially relevant in the midst of the COVID-19 pandemic fuelled with uncertainties, which are further accentuated by social media misinformation. Conspiracy theories have dominated social media, ranging from assertions that the COVID-19 pandemic is a hoax, that COVID-19 was spread on purpose [43] or more recently, that the COVID vaccine contains a microchip [44]. A study by Mohd Azizi et al. [38] found that the internet was the main source of information about vaccines in Malaysia and that misinformation contributed to vaccine reluctance. To put these findings into perspective, a week into the launch of the national COVID-19 immunisation plan in Malaysia, only 6.1% of the targeted 80% of the population had registered for the vaccine [45].

Multiple health behavioural theories and published studies have indicated individuals with high perceived risk and perceived seriousness had a higher likelihood of accepting the vaccine [46–48]. Recent studies on acceptance of the COVID-19 vaccine also found positive associations between vaccination intent and perceived susceptibility or perceived severity [24,25,49–51]. Although our study showed similar findings, the association between perceived personal risk level and acceptance of the COVID-19 vaccine was not statistically significant in the multivariate analysis. Interestingly, it was the perceived risk of the general community to be infected with COVID-19 that predicted vaccine acceptance among the participants. A cross-sectional survey of 1,159 Malaysians on their intent to receive the COVID-19 vaccine found that the majority (85.4%) were worried about the possibility of contracting COVID-19, but only 59.3% perceived their risk of infected with COVID-19 to be high [11]. These connections may be complex. For instance, individuals who are healthy or adhere to preventive measures (i.e., wearing a mask and physical distancing) may perceive their risk of contracting COVID-19 infection to be low, but still prefer to be vaccinated in view of the risk of community transmission. Nevertheless, we found that participants with high perceived severity were more likely to obtain the COVID-19 vaccine. Our findings highlighted the importance of increasing perceived risk and severity for COVID-19 among the public, as these beliefs may result in higher vaccine uptake. Some past public health programs targeting these beliefs have been successful in increasing vaccine uptake [52–54].

Published studies have suggested that COVID-19 vaccine acceptance can be predicted by various sociodemographic factors [24,25,27,49–51]. In our study, only age and ethnicity were found to be significant predictors of acceptance. Both Malik et al. [27] and Al-Mohaithef and Padhi [24] found that older individuals were more likely to accept the COVID-19 vaccine.

However, our findings showed otherwise. This is a cause for concern considering the current evidence indicating that the elderly population is at higher risk of severe infections [55–57]. With the WHO and Malaysian government recommending the elderly population as a priority group to receive the COVID-19 vaccine [58,59], strategies need to be in place to ensure good vaccine uptake among the elderly. Interestingly, our study showed no significant difference in vaccine acceptance between the healthcare and non-healthcare worker groups, unlike in other studies [60]. This could be attributed to the study period, since the questionnaire was administered at a time when public fear was still predominant with no indication of a cure or vaccine. However, with more information available in tandem with the global COVID-19 vaccination rollout, acceptance levels will change. This may be particularly true among healthcare workers who depend on published scientific evidence to determine their intent to vaccinate. A study by Shekhar et al. [61] on COVID-19 vaccine acceptance among healthcare workers in the US in October to November 2020 found only one-third (36.0%) of respondents to be agreeable for vaccination immediately. In contrast, non-healthcare workers may be influenced by widely available information—be it misinformation, disinformation, or accurate information—that is easily accessible via social media. According to the report of the SAGE Working Group in Vaccine Hesitancy, religion and culture were identified as a determinant influencing vaccine uptake [23]. This may

explain the difference in vaccine acceptance between the ethnic groups in our study. It is important to note that the population reflected by our respondents differs from the general Malaysian population. Based on statistics compiled by the Department of Statistics Malaysia, the median age of the Malaysian population is 29.2 years, with a slight male predominance (51.5% vs. 48.5%) [62]. Furthermore, the racial distribution of the Malaysian population is predominantly Malay (69.6%), followed by Chinese (22.6%), Indian (6.8%), and others (1.0%).

Over the past year, the pandemic has taken a considerable toll on the economic welfare of nations and their inhabitants. While high-income countries are able to procure excess doses for their citizens, this is inversely seen in lower- to middle-income countries [63]. Therefore, willingness to pay may be a strategic advantage for health systems facing budget constraints. Our study results imply that with limited availability, people may be more inclined to pay a higher price for the vaccine. Healthcare in Malaysia is divided into the government-funded system and the private sector. Perhaps, this could be a positive indicator that the private healthcare sector could play a greater role in the later parts of the national COVID-19 immunisation program. This situation is reminiscent of the influenza vaccine, which is readily available at private clinics and hospitals in Malaysia for a fee depending on the type [64]. Among numerous elements driving public confidence in vaccines, copious significance is placed on the safety and effectiveness of vaccines [49,50]. The recent information surrounding adverse events in the ongoing COVID-19 vaccine rollout may have a further impact on vaccine acceptance. Although only 14% of the study participants were unable to accept mild side effects of the COVID-19 vaccine, concerns about the adequacy of vaccine testing, vaccine effectiveness, and vaccine safety were the top reasons for participants who refused or were unsure about receiving the COVID-19 vaccine. While 57.6% of the study participants believed that the COVID-19 vaccine would help stop the virus transmission, some participants also were concerned about the cost and *halal* status of the COVID-19 vaccine. In adjunct to various concerns regarding the prospective vaccine, we asked respondents about the maximum number of acceptable doses to understand whether the number of doses would be a potential deterrent. Many of the respondents felt that the number of doses did not matter, likely due to their heightened perceived susceptibility and severity. Other studies centred on non-pandemic vaccines such as hepatitis B found that fewer doses were associated with better completion rates. It was also reported that an accelerated dosing schedule increased adherence. A study during the early stages of the COVID-19 pandemic in China similarly showed that there was a preference for fewer doses. With the current COVID-19 vaccination being mostly a 2-dose schedule, this may be one less problem affecting vaccine acceptance. Unfortunately, our study did not explore how additional vaccine characteristics would affect the public's COVID-19 vaccination intent. It is recommended that future research should explore the key attributes influencing the public's willingness to be vaccinated.

This study has a few limitations. Firstly, the study employed convenience sampling, and the nature of a web-based online survey also limits the participation of those without internet access or low digital literacy. Hence, we acknowledge limitations in replicating the demographic distribution to reflect the broader Malaysian population. Secondly, as participation in this survey was voluntary, there may have been some level of self-selection bias since the survey may have received more attention from those who were concerned about the COVID-19 pandemic and vaccine. Thirdly, this was a cross-sectional study collecting the public's responses during a specific time frame. Therefore, the responses are only reflective of the information available during that time. The study did not explore other details (e.g., vaccine attributes and disease determinants) that could affect vaccine acceptance among the public. Next, our study assessed the COVID-19 vaccination intent with the assumption that the vaccine would be free. The acceptance level might be lower if out-of-pocket payments are incurred. Additionally, as this survey was conducted anonymously, we were unable to rule out the possibility of multiple entries from the same respondent. Last but not least, the use of a 5-point Likert scale for responses to survey questions may have resulted in some form of response bias. Merging the responses into 2 or 3 groups (whichever is applicable) could have resulted in some loss in the statistical interpretation of the findings on an ordinal scale.

Conclusion

In conclusion, most participants were willing to receive the COVID-19 vaccine. Willingness to receive the COVID-19 vaccine was affected by factors including age, race, perceived community risk to COVID-19 infection, perceived severity, and the absence of vaccine hesitancy sentiments. If the real-world acceptance level is similar to the findings of this study, Malaysia will be able to achieve herd immunity through its COVID-19 vaccination program. Further studies are warranted to explore the relative importance of various vaccine-related, contextual, and individual or group determinants associated with acceptance of the COVID-19

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vaccine. Future public health strategies targeting these factors could help to increase vaccine uptake.

Supplementary Material

Supplementary Material 1. Acceptance and perception on the COVID-19 vaccination (immunization) in the general population of Malaysia. Supplementary data are available at https://doi.org/10.24171/j.phrp.2021.0085.

Notes

Ethics Approval

This study was registered with the National Medical Research Registry (NMRR-20-1089-55153). Ethical approval for this study was obtained from the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia (KKM/NIHSEC/ P20-1333 (4)). Participation in this survey was voluntary. All methods were performed in accordance with the Declaration of Helsinki. No personal identifiers were collected in the survey. Informed consent of the participants was implied when the participants started answering the questionnaire, as participation in the study was voluntary. The study was conducted anonymously; hence no personal identifiers were collected. Before answering the survey, all respondents were informed regarding the need to publish the results. We have obtained permission from the Director General of Health Malaysia to publish this article.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Availability of Data

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Authors' Contributions

Conceptualization: JFWL, YLW; Data curation: JFWL, CTL; Formal analysis: JFWL, CTL, HST; Investigation: JFWL; Methodology: JFWL, YLW; Project administration: JFWL; Writing–original draft: JFWL; Writing–review & editing: all authors.

Additional Contributions

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References

1. John Hopkins University (JHU). COVID-19 dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU) [Internet]. Baltimore: JHU; 2020 [cited 2021 May 10]. Available from: https://coronavirus.jhu.edu/map.html.
2. DG of Health. KPK Press statement 25 January 2020-Detection of new cases confirmed infected with 2019 novel coronavirus (2019-nCoV) in Malaysia [Internet]. General of Health Malaysia; 2020 [cited 2021 Jan 5]. Available from: https://kpkesihatan.com/2020/01/25/kenyataan-akhbar-kpk-25-januari-2020-pengesanan-kes-baharu-yang-disahkan-dijangkiti-2019-novel-coronavirus-2019-ncov-di-malaysia/.
3. DG of Health. KPK Press statement 29 January 2021-Current situation of coronavirus infection 2019 (COVID-19) in Malaysia [Internet]. General of Health Malaysia; 2021 [cited 2021 Mar 7]. Available from: https://kpkesihatan.com/2021/01/29/kenyataan-akhbar-kpk-29-januari-2021-situasi-semasa-jangkitan-penyakit-coronavirus-2019-covid-19-di-malaysia/.
4. DG of Health. KPK Press statement 10 May 2021-Current situation of coronavirus infection 2019 (COVID-19) in Malaysia [Internet]. General of Health Malaysia; 2021 [cited 2021 May 28]. Available from: https://kpkesihatan.com/2021/05/10/kenyataan-akhbar-kpk-10-mei-2021-situasi-semasa-jangkitan-penyakit-coronavirus-2019-covid-19-di-malaysia/.
5. Pfizer. Pfizer and BioNTech announce vaccine candidate against covid-19 achieved success in first interim analysis from phase 3 study [Internet]. New York: Pfizer; 2020 [cited 2021 Mar 8]. Available from: https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-announce-vaccine-candidate-against.
6. World Health Organization (WHO). WHO issues its first emergency use validation for a COVID-19 vaccine and emphasizes need for equitable global access [Internet]. Geneva: WHO; 2020 [cited 2021 Mar 11]. Available from: https://www.who.int/news/item/31-12-2020-who-issues-its-first-emergency-use-validation-for-a-covid-19-vaccine-and-emphasizes-need-for-equitable-global-access.
7. The special committee for ensuring access to COVID-19 vaccine supply (JKJAV). National COVID-19 immunisation programme [Internet]. Putrajaya, Malaysia: JKJAV; 2021 [cited 2021 Nov 8]. Available from: https://www.vaksincovid.gov.my/pdf/Program_Imunisasi_COVID-19_Kebangsaan_Versi_Bahasa_Inggeris.pdf.
8. Billah MA, Miah MM, Khan MN. Reproductive number of coronavirus: a systematic review and meta-analysis based on global level evidence. PLoS One 2020;15:e0242128.
9. Anderson RM, Vegvari C, Truscott J, et al. Challenges in creating herd immunity to SARS-CoV-2 infection by mass vaccination. Lancet 2020;396:1614–6.
10. PM: vaccination vital for herd immunity. The Star [Internet]. 2021 Feb 22 [cied 2021 Mar 8]. Available from: https://www.thestar.com.my/news/nation/2021/02/22/pm-vaccination-vital-for-herd-immunity.
11. Wong LP, Alias H, Wong PF, et al. The use of the health belief model to assess predictors of intent to receive the COVID-19 vaccine and willingness to pay. Hum Vaccin Immunother 2020;16:2204–14.

12. Ipsos. Global attitudes : COVID-19 vaccines [Internet]. Sarajevo: Ipsos; 2021 [cited 2021 Apr 5]. Available from: https://www.ipsos.com/en-ba/global-attitudes-covid-19-vaccine-january-2021.
13. World Health Organization (WHO). COVID-19 in Malaysia situation report 30 [Internet]. Geneva: WHO; 2021 [cited 2021 May 28]. Available from: https://www.who.int/malaysia/internal-publications-detail/covid-19-in-malaysia-situation-report-30.
14. Visontay E. Oxford University Covid vaccine trial put on hold due to possible adverse reaction in participant. The Guardian [Internet]. 2020 Sep 9 [cited 2021 Jan 25]. Available from: https://www.theguardian.com/world/2020/sep/09/oxford-university-astrazeneca-covid-vaccine-trial-put-on-hold-due-to-adverse-reaction-in-participant.
15. Herper M. Johnson & Johnson Covid-19 vaccine study paused due to unexplained illness in participant. STAT [Internet]. 2020 Oct 12 [cited 2021 Apr 5]. Available from: https://www.statnews.com/2020/10/12/johnson-johnson-covid-19-vaccine-study-paused-due-to-unexplained-illness-in-participant/.
16. Glover RE, Urquhart R, Lukawska J, et al. Vaccinating against covid-19 in people who report allergies. BMJ 2021;372:n120.
17. Shahrabani S, Benzion U, Yom Din G. Factors affecting nurses' decision to get the flu vaccine. Eur J Health Econ 2009;10:227–31.
18. Allison MA, Reyes M, Young P, et al. Parental attitudes about influenza immunization and school-based immunization for school-aged children. Pediatr Infect Dis J 2010;29:751–5.
19. Hu Y, Wang Y, Liang H, et al. Seasonal influenza vaccine acceptance among pregnant women in Zhejiang province, China: evidence based on health belief model. Int J Environ Res Public Health 2017;14:1551.
20. Jimenez-Garcia R, Rodriguez-Rieiro C, Hernandez-Barrera V, et al. Negative trends from 2008/9 to 2011/12 seasons in influenza vaccination coverages among high risk subjects and health care workers in Spain. Vaccine 2014;32:350–4.
21. Chor JS, Ngai KL, Goggins WB, et al. Willingness of Hong Kong healthcare workers to accept pre-pandemic influenza vaccination at different WHO alert levels: two questionnaire surveys. BMJ 2009; 339:b3391.
22. Seale H, Heywood AE, McLaws ML, et al. Why do I need it? I am not at risk! Public perceptions towards the pandemic (H1N1) 2009 vaccine. BMC Infect Dis 2010;10:99.
23. World Health Organisation (WHO). Report of the SAGE Working Group on Vaccine Hesitancy [Internet]. Geneva: WHO; 2014 [cited 2021 Apr 5]. Available from: https://www.who.int/immunization/sage/meetings/2014/october/1_Report_WORKING_GROUP_vaccine_hesitancy_final.pdf.
24. Al-Mohaithef M, Padhi BK. Determinants of COVID-19 vaccine acceptance in Saudi Arabia: a web-based national survey. J Multidiscip Healthc 2020;13:1657–63.
25. Fu C, Wei Z, Pei S, et al. Acceptance and preference for COVID-19 vaccination in health-care workers (HCWs) [Preprint]. Posted 2020 Apr 14. medRxiv 2020.04.09.20060103. https://doi.org/10.1101/2020.04.09.20060103.
26. Lazarus JV, Ratzan SC, Palayew A, et al. A global survey of potential acceptance of a COVID-19 vaccine. Nat Med 2020;27:225–8.
27. Malik AA, McFadden SM, Elharake J, et al. Determinants of COVID-19 vaccine acceptance in the US. EClinicalMedicine 2020;26:100495.
28. SteelFisher GK, Blendon RJ, Ward JR, et al. Public response to the 2009 influenza A H1N1 pandemic: a polling study in five countries. Lancet Infect Dis 2012;12:845–50.
29. Malaysia ranks 4th in global survey on public approval of Covid-19 crisis management. FMT [Internet]. 2020 May 8 [cited 2021 Jan 25]. Available from: https://www.freemalaysiatoday.com/category/nation/2020/05/08/malaysia-ranks-4th-in-global-survey-on-public-approval-of-covid-19-crisis-management/.
30. Fu LY, Zimet GD, Latkin CA, et al. Associations of trust and healthcare provider advice with HPV vaccine acceptance among African American parents. Vaccine 2017;35:802–7.
31. Lee C, Whetten K, Omer S, et al. Hurdles to herd immunity: distrust of government and vaccine refusal in the US, 2002-2003. Vaccine 2016;34:3972–8.
32. Zahiid SJ. Health Ministry survey shows a third of Malaysians still fear, doubt Covid-19 vaccine. Malay Mail [Internet]. 2020 Dec 31 [cited 2021 Mar 9]. Available from: https://www.malaymail.com/news/malaysia/2020/12/31/health-ministry-survey-shows-a-third-of-malaysians-still-fear-doubt-covid-1/1936319.
33. World Health Organisation (WHO). Ten threats to global health in 2019 [Internet]. Geneva: WHO; 2019 [cited 2021 Jan 25]. Available from: https://www.who.int/vietnam/news/feature-stories/detail/ten-threats-to-global-health-in-2019.
34. Arikiah P. Why childhood vaccination continues to be a divisive issue in Malaysia. cna [Internet]. 2019 Apr 14 [cited 2021 Jan 5]. Available from: https://www.channelnewsasia.com/news/asia/malaysia-childhood-vaccination-immunisation-debatable-11389462.
35. Wong LP, Wong PF, AbuBakar S. Vaccine hesitancy and the resurgence of vaccine preventable diseases: the way forward for Malaysia, a Southeast Asian country. Hum Vaccin Immunother 2020;16:1511–20.
36. Zainal Abidin Z, Hanafiah Juni M, Ibrahim F, et al. Adherence towards different vaccines of childhood immunization of under five year old children. Malays J Med Health Sci 2017;13:43–50.
37. Ahmad NA, Jahis R, Kuay LK, et al. Primary immunization among children in Malaysia: reasons for incomplete vaccination. J Vaccines Vaccin 2017;8:358.
38. Mohd Azizi FS, Kew Y, Moy FM. Vaccine hesitancy among parents in a multi-ethnic country, Malaysia. Vaccine 2017;35:2955–61.
39. Institute for Public Health, National Institutes of Health. National health and morbidity survey 2016: maternal and child health. Volume two: maternal and child health findings [Internet]. Kuala Lumpur, Malaysia: Ministry of Health Malaysia; 2016 [cited 2021 Apr 5]. Available from: https://iku.moh.gov.my/images/IKU/Document/REPORT/2016/NHMS2016ReportVolumeII-MaternalChildHealthFindingsv2.pdf.
40. de Figueiredo A, Simas C, Karafillakis E, et al. Mapping global trends in vaccine confidence and investigating barriers to vaccine uptake:

a large-scale retrospective temporal modelling study. Lancet 2020;396:898–908.

41. Quinn SC, Jamison AM, An J, et al. Measuring vaccine hesitancy, confidence, trust and flu vaccine uptake: results of a national survey of White and African American adults. Vaccine 2019;37:1168–73.
42. Kohl S. Vaccine confidence and vaccination delivery in the European Union. Eur J Hosp Pharm 2019;26:51–4.
43. Uscinski JE, Enders AM, Klofstad C, et al. Why do people believe COVID-19 conspiracy theories? Harvard Kennedy Sch Misinformation Rev [Internet]. 2020 Apr [cited 2021 Apr 5]. Available from: https://doi.org/10.37016/mr-2020-015.
44. Ball P, Maxmen A. The epic battle against coronavirus misinformation and conspiracy theories. Nature 2020;581:371–4.
45. Carvalho M. Only 6.1% of target 80% have registered for Covid-19 vaccine so far, says Khairy. The Star [Internet]. 2021 Mar 1 [cited 2021 Mar 9]. Available from: https://www.thestar.com.my/news/nation/2021/03/01/only-61-of-target-80-have-registered-for-covid-19-vaccine-so-far-says-khairy.
46. Ling M, Kothe EJ, Mullan BA. Predicting intention to receive a seasonal influenza vaccination using Protection Motivation Theory. Soc Sci Med 2019;233:87–92.
47. Rajamoorthy Y, Radam A, Taib NM, et al. Willingness to pay for hepatitis B vaccination in Selangor, Malaysia: a cross-sectional household survey. PLoS One 2019;14:e0215125.
48. Rajamoorthy Y, Radam A, Taib NM, et al. The relationship between perceptions and self-paid hepatitis B vaccination: a structural equation modeling approach. PLoS One 2018;13:e0208402.
49. Reiter PL, Pennell ML, Katz ML. Acceptability of a COVID-19 vaccine among adults in the United States: how many people would get vaccinated? Vaccine 2020;38:6500–7.
50. Harapan H, Wagner AL, Yufika A, et al. Acceptance of a COVID-19 vaccine in Southeast Asia: a cross-sectional study in Indonesia. Front Public Health 2020;8:381.
51. Harapan H, Wagner AL, Yufika A, et al. Willingness-to-pay for a COVID-19 vaccine and its associated determinants in Indonesia. Hum Vaccin Immunother 2020;16:3074–80.
52. Reiter PL, Katz ML, Bauermeister JA, et al. Increasing human papillomavirus vaccination among young gay and bisexual men: a randomized pilot trial of the outsmart HPV intervention. LGBT Health 2018;5:325–9.
53. McRee AL, Shoben A, Bauermeister JA, et al. Outsmart HPV: acceptability and short-term effects of a web-based HPV vaccination intervention for young adult gay and bisexual men. Vaccine 2018;36:8158–64.
54. Graffigna G, Palamenghi L, Boccia S, et al. Relationship between citizens' health engagement and intention to take the COVID-19 vaccine in Italy: a mediation analysis. Vaccines (Basel) 2020;8:576.
55. Sim BLH, Chidambaram SK, Wong XC, et al. Clinical characteristics and risk factors for severe COVID-19 infections in Malaysia: a nationwide observational study. Lancet Reg Health West Pac 2020;4:100055.
56. Li J, Huang DQ, Zou B, et al. Epidemiology of COVID-19: a systematic review and meta-analysis of clinical characteristics, risk factors, and outcomes. J Med Virol 2021;93:1449–58.
57. Chidambaram V, Tun NL, Haque WZ, et al. Factors associated with disease severity and mortality among patients with COVID-19: a systematic review and meta-analysis. PLoS One 2020;15:e0241541.
58. Malaysia agrees to buy 12.8 million doses of Pfizer's COVID-19 vaccine. cna [Internet]. 2020 Nov 27 [cited 2021 Jan 25]. Available from: https://www.channelnewsasia.com/news/asia/malaysia-covid-19-pfizer-vaccine-coronavirus-13651672.
59. World Health Organization (WHO). Roadmap for prioritizing population groups for vaccines against COVID-19 [Internet]. Geneva: WHO; 2020 [cited 2021 Nov 8]. Available from: https://www.who.int/immunization/sage/meetings/2020/october/Session03_Roadmap_Prioritization_Covid-19_vaccine.pdf.
60. Dror AA, Eisenbach N, Taiber S, et al. Vaccine hesitancy: the next challenge in the fight against COVID-19. Eur J Epidemiol 2020;35:775–9.
61. Shekhar R, Sheikh AB, Upadhyay S, et al. COVID-19 vaccine acceptance among health care workers in the United States. Vaccines (Basel) 2021;9:119.
62. Department of Statistics Malaysia. Current population estimates, Malaysia, 2020 [Internet]. Putrajaya, Malaysia: Department of Statistics Malaysia; 2020 [cited 2021 Jan 15]. Available from: https://www.dosm.gov.my/v1/index.php?r=column/cthemeByCat&cat=155&bul_id=OVByWjg5YkQ3MWFZRTN5bDJiaEVhZz09&menu_id=L0pheU43NWJwRWVSZklWdzQ4TlhUUT09.
63. Collins K, Holder J. See how rich countries got to the front of the vaccine line. The New York Times [Internet]. 2021 Mar 31 [cited 2021 May 18]. Available from: https://www.nytimes.com/interactive/2021/03/31/world/global-vaccine-supply-inequity.html.
64. Yusof TA. 200,000 influenza vaccines available within the next two months. New Straits Times [Internet]. 2020 Jan 18 [cited 2021 May 18]. Available from: https://www.nst.com.my/news/nation/2020/01/557596/200000-influenza-vaccines-available-within-next-two-months.

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Original Article

Prevalence and correlates of highly caffeinated beverage consumption among Korean adolescents

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ABSTRACT

Objectives: The purposes of this study were to (1) examine the multi-year prevalence of highly caffeinated beverage (HCB) consumption, (2) identify sex differences in the prevalence, and (3) investigate relationships between HCB consumption and behavioral characteristics in a nationally representative sample of Korean adolescents.
Methods: Data from the Korea Youth Risk Behavior Web-based Survey (2014–2017) were analyzed.
Results: HCB consumption was higher in 2017 than 2014 (23.9% vs. 12.0%), and higher among boys than girls (17.2% vs. 13.1%). HCB drinkers were more likely to (1) be boys, (2) be overweight or obese, (3) use alcohol and tobacco, (4) consume soda at least once per week, (5) consume sweetened beverages at least once per week, (6) have seriously considered suicide during the past 12 months, and (7) have attempted suicide during the past 12 months ($p < 0.05$ for all).
Conclusion: Effective programs to curb HCB consumption among Korean adolescents need to be established.

Keywords: Adolescent; Behavior; Beverages; Caffeine

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Introduction

The consumption of highly caffeinated beverages (HCBs), often referred to as "energy drinks," is an issue of growing concern [1]. Although HCBs are advertised as providing various benefits, such as improved energy and performance, they may cause respiratory disorders, seizures, and insomnia [2]. Despite these health risks, caffeine is one of the most widely used psychoactive substances in the world [3], including in South Korea (hereafter, Korea) [4,5]. Caffeine consumption

has steadily grown in Korea [4,5]. The majority of HCBs available today first entered the Korean market in 2010 [4,5], and according to a 2013 estimate, HCBs have since grown to an industry worth approximately 90 million United States dollars (USD) [5]. One study found that Koreans consume an estimated 67.8 to 102.6 mg of caffeine per day from all food sources [6], but that study used data from before HCBs became popular in Korea. The prevalence of coffee consumption was reported to be 52.3% [7], but the prevalence of HCB consumption remains unclear despite these products' popularity in Korea.

Adolescents are vulnerable to HCB abuse, as HCBs are readily accessible, relatively inexpensive, and have a sweet flavor that is more appealing to younger consumers than coffee [1,8]. Adolescents who consume HCBs may be at higher risk of caffeine intoxication than adults [9]. Korean adolescents may be particularly vulnerable to HCB abuse and caffeine intoxication, as many rely on HCBs to stay awake or focus on studying [10]. The Korean government attempted to limit adolescents' caffeine intake by restricting advertisements, requiring warning labels, and banning the sale of HCBs on school grounds [11]. However, the effectiveness of those policies remains unclear, as no studies to date have examined changes in Korean adolescents' HCB consumption over multiple years.

Past studies [12,13] found that Korean adolescents who consumed HCBs were at greater risk of stress, anxiety, and depression. Unlike the psychological health problems associated with HCB consumption, relatively little attention has been given thus far to the relationship between HCB consumption and behavioral factors (e.g., physical activity, sleep, suicidal behavior, and alcohol and tabaco use). Furthermore, the data on sex differences in the multi-year prevalence of HCB consumption are sparse, and little is known about the multi-year prevalence of HCB consumption among Korean adolescents. The purposes of this study were to (1) examine the multi-year prevalence of HCB consumption from 2014 to 2017, (2) identify, if any, sex differences in the multi-year prevalence, and (3) investigate relationships between HCB consumption and behavioral characteristics using a nationally representative sample of Korean adolescents.

Materials and Methods

Survey and Participants

Since 2005 the Korea Youth Risk Behavior Web-based Survey (KYRBS) has been conducted by the Korea Centers for Disease Control and Prevention (now known as the Korea Disease Control and Prevention Agency) every year. Because the KYRBS has collected HCB-related information since 2014, we combined 4 data sets of KYRBS from 2014 to 2017. The KYRBS uses a self-administered questionnaire and 2-stage sampling. In the first stage, each school (including middle and high schools) was selected as a primary sampling unit (PSU). In the second stage, a classroom of each grade was chosen within a PSU using the systematic sampling method. The probability of selection was 14% of total middle and high schools and 2% of total students [14]. The KYRBS team obtained online consent from all participants. This research received Institutional Review Board approval from Touro University (IRB No: PH0219).

This data set includes a representative sample of middle and high school students in Korea (n = 267,907) from the following years: (1) 2014 (n = 72,060; 97.2% response rate); (2) 2015 (n = 68,043; 96.7% response rate); (3) 2016 (n = 65,528; 96.4% response rate); and (4) 2017 (n = 62,276; 95.8% response rate) [14]. The exclusion criteria were (1) students needing special education services or (2) students with reading difficulties.

Independent Variables

The school level of participants was grouped into middle and high school. Students responded to academic achievement with 5 options, and we combined these options into 3 responses: (1) low (i.e., low or middle-low), (2) middle, and (3) high (i.e., high or middle-high) [15]. The household income of each student was provided using 5 options, which we combined into 3 levels: (1) low (i.e., very low or low), (2) middle, and (3) high (i.e., very high or high) [15].

Participants provided information on their weekly expenditures with 6 options, from 0 ≤ 10,000 Korean won (KRW) (equivalent to 0 ≤ USD 8.92) to ≥ 150,000 KRW (USD 133.80) and regrouped into 3 levels: (1) < 50,000 KRW (equivalent to < USD 44.66), (2) 50,000 to 99,999 KRW (USD 44.66–89.32), and (3) ≥ 100,000 KRW (≥ USD 89.33). The education level of their parents was divided into 3 groups: ≤ middle school; high school; and ≥ college.

Self-reported weight and height were used for the assessment of body mass index (BMI), which was calculated as weight in kilograms divided by height in meters squared. We used the 2017 Korean National Growth Chart sex-specific BMI-for-age percentile cutoffs. The nutritional status of participants were grouped into 4 levels: (1) underweight (BMI < 5th percentile), (2) normal weight (5th ≤ BMI < 85th percentile), (3) overweight (85th ≤ BMI < 95th percentile), and (4) obese (BMI ≥ 95th percentile) [16].

Weekly exercise for ≥ 60 minutes was originally answered with 8 options from 0 to 7 days for the last 7 days. We regrouped these responses into 3 categories: (1) none, (2) 1 to 2 days, and (3) ≥ 3 days [15]. The responses for weekly vigorous exercise

for ≥20 minutes were originally categorized into 6 groups. We recoded them into 3 levels: (1) none, (2) 1 to 2 days, and (3) ≥3 days. Tobacco use of participants during their lifetime was dichotomized as "never" versus "ever."

The National Sleep Foundation recommends that adolescents sleep for 8 to 10 hours per night [17]. We dichotomized participants as meeting or not meeting this recommendation. Participants described whether they felt fatigue relief after sleep with 5 options, from "not enough at all" to "more than enough." We recoded these responses into 3 groups: (1) "not enough/not enough at all," (2) "fair," and (3) "more than enough/enough." The following information of participants was dichotomized as "no" or "yes": (1) having seriously considered suicide during the last year and (2) having attempted suicide during the last year.

Alcohol use of participants during their lifetime was assessed to compare users with nonusers. Weekly intake frequency of soda and sweetened beverages (excluding soda and HCBs) was categorized into 7 options, from never to ≥3 times per day for the last 7 days. We recoded them into 3 groups: (1) 0 times, (2) 1 to 2 times, and (3) ≥3 times per week.

Dependent Variable

Information on HCB consumption was elicited by the following question, "During the past 7 days, how frequently did you drink highly caffeinated beverages?" with 7 levels: (1) never, (2) 1 to 2 times per week, (3) 3 to 4 times per week, (4) 5 to 6 times per week, (5) 1 time per day, (6) 2 times per day, and (7) 3 times or more per day. Using these responses, we dichotomized participants into HCB drinkers and HCB nondrinkers.

Statistical Analysis

We implemented the Cramer V test to examine the statistical significance of differences in behavioral characteristics between HCB drinkers and nondrinkers. We calculated the prevalence of HCB intake from 2014 to 2017 with 95% confidence intervals. Graphical plots were created by survey year and sex. We performed multiple logistic regression to examine behavioral factors associated with HCB intake with adjustment for school year, household income of family level, weekly expenditure, and academic achievement based on previous studies [18–20]. We conducted a complete case analysis except all records with any missing information on the variables of our interest. We used STATA ver. 14 (STATA Press, College Station, TX, USA) for statistical analyses, and took the sample weights into consideration by using the *svy* command for the complex survey design.

Results

The final data set included 267,907 middle and high school students. Their mean age was 15.0 years (standard deviation, 1.7 years) and 51.2% of them were boys. Among the male participants, 17.2% were HCB drinkers (Table 1). Merely 24.1% of male participants met the daily recommendation of 8 to 10 hour sleep duration. Male participants had the highest proportion of normal weight (72.7%), followed by obesity (10.2%), overweight (8.7%), and underweight (8.4%). Negligible associations were found between HCB consumption and the independent variables. However, HCB consumption was weakly associated with soda intake (Cramer V = 0.190) and sweetened beverage intake (Cramer V = 0.155) (Table 1).

Among female participants, only 13.1% were HCB drinkers (Table 2). The majority of female participants (87.3%) did not meet the daily recommendation of sleep duration (8 to 10 hours per night). More than three-fourths of female participants were in the normal weight category (78.8%), followed by overweight (8.5%), obesity (6.4%), and underweight (6.3%). The magnitude of the associations between HCB consumption and the independent variables was negligible. However, there were weak associations between HCB consumption and soda consumption (Cramer V = 0.148) and sweetened beverage consumption (Cramer V = 0.144) (Table 2).

Among the total participants, the prevalence of HCB consumption was 1.8%p higher in 2016 (13.8%) than in 2014 (12.0%) (Figure 1). The prevalence increased by 10.1%p between 2016 (13.8%) and 2017 (23.9%). This gap was considerably higher for male participants (11.7%p compared with female participants (8.5%p) in this short time period. In 2017, HCB consumption was more prevalent in male participants (26.7%) than in female participants (20.9%).

In the overall sample, higher odds of HCB consumption were related to male sex, overweight or obesity, alcohol consumption, and tobacco use ($p < 0.05$ for all) (Table 3). Moreover, HCB consumption showed significantly relationships with (1) >60 minutes of physical activity 1 to 2 days per week, (2) >1 time per week of soda consumption, (3) >1 time per week of sweetened baverage consumption ($p < 0.05$ for all), (4) feeling less than enough fatigue relief after sleep, (5) having seriously considered suicide during the last 12 months, and (6) having attempted suicide during the last 12 months ($p < 0.05$ for all). Lower odds of HCB consumption were associated with high school maternal education level and underweight ($p < 0.05$ for both).

Among male participants, HCB drinkers were more likely to be obese, drink alcohol, and use tobacco ($p < 0.05$ for all). Additionally, higher odds of HCB consumption were associated with (1) ≥60 minutes of physical activity 1 to 2 days per week,

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Table 1. Characteristics of boys by highly caffeinated beverage consumption, Korea Youth Risk Behavior Web-based Survey 2014–2017

Characteristic	Total (n = 137,101) (%)	Drinker (n = 23,600) (%)	Nondrinker (n = 113,501) (%)	Effect size[a)]	p
School type					
Middle school	46.6	43.8	47.2	0.026	< 0.001
High school	53.4	56.2	52.8		
Academic achievement					
Low	34.0	38.6	33.1	0.045	< 0.001
Middle	27.3	26.2	27.5		
High	38.7	35.2	39.5		
Household income					
Low	16.0	17.3	15.7	0.026	< 0.001
Middle	44.6	41.9	45.2		
High	39.4	40.9	39.1		
Weekly expenditure					
< 50,000 KRW (< USD 44.66)	85.1	78.8	86.4	0.087	< 0.001
50,000–99,999 KRW (USD 44.66–89.32)	9.8	12.7	9.2		
≥ 100,000 KRW (≥ USD 89.33)	5.1	8.5	4.4		
Paternal education					
≤ Middle school	3.0	3.4	2.9	0.013	0.001
High school	33.4	32.4	33.6		
≥ College	63.7	64.2	63.5		
Maternal education					
≤ Middle school	2.4	2.7	2.3	0.015	< 0.001
High school	41.1	39.7	41.4		
≥ College	56.5	57.6	56.3		
BMI[b)]					
Underweight	8.4	8.0	8.5	0.019	< 0.001
Normal weight	72.7	72.1	72.8		
Overweight	8.7	8.8	8.6		
Obese	10.2	11,1	10.0		
Alcohol use					
Never	54.4	45.9	56.1	0.077	< 0.001
Ever	45.6	54.1	43.9		
Tobacco use					
Never	75.9	68.7	77.4	0.076	< 0.001
Ever	24.1	31.3	22.6		
Weekly physical activity for ≥ 60 min					
None	27.4	24.5	28.0	0.030	< 0.001
1–2 days	30.1	31.6	29.8		
≥ 3 days	42.5	43.9	42.2		
Weekly vigorous exercise for ≥ 20 min					
None	14.0	12.5	14.3	0.021	< 0.001
1–2 days	36.4	36.3	36.4		
≥ 3 days	49.6	51.2	49.3		
Weekly frequency of soda consumption					
0 times	18.4	8.3	20.5	0.190	< 0.001
1–2 times	46.7	38.0	48.5		
≥ 3 times	34.9	53.8	31.0		

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Table 1. Continued

Characteristic	Total (n = 137,101) (%)	Drinker (n = 23,600) (%)	Nondrinker (n = 113,501) (%)	Effect size[a)]	p
Weekly frequency of sweetened beverage consumption					
0 times	14.4	6.0	16.2	0.155	< 0.001
1–2 times	40.8	33.7	42.3		
≥ 3 times	44.8	60.4	41.6		
Meeting sleep duration recommendations (8–10 h)					
Not met	75.9	78.5	75.4	0.028	< 0.001
Met	24.1	21.5	24.7		
Feeling fatigue relief after sleep					
Not enough/not enough at all	34.8	40.8	33.5	0.060	< 0.001
Fair	33.2	31.8	33.4		
Very enough/enough	32.1	27.5	33.1		
Seriously considered suicide during last 12 mo					
No	90.1	85.3	91.1	0.073	< 0.001
Yes	9.9	14.7	8.9		
Suicide attempt during last 12 mo					
No	97.9	95.7	98.4	0.072	< 0.001
Yes	2.1	4.3	1.6		

Use of weighted data with adjustment for the complex survey design. The percentages may not add to 100 because of rounding errors.
KRW, Korean won; USD, United States dollar; BMI, body mass index.
[a)]Phi effect sizes were considered negligible if < 0.1, weak if between 0.1 and < 0.2, moderate if between 0.2 and < 0.4, and strong if ≥ 0.4. [b)]Underweight (BMI < 5th percentile), normal weight (5th percentile ≤ BMI < 85th percentile), overweight (85th percentile ≤ BMI < 95th percentile), and obese (BMI ≥ 95th percentile).

(2) ≥ 20 minutes of vigorous exercise ≥ 3 days per week, (3) ≥ 1 time per week of soda consumption, (4) > 1 time per week of sweetened beverage consumption, (5) not meeting the recommendation for an 8–10 hour sleep duration, (6) insufficient fatigue relief after sleep, (7) having seriously considered suicide during the last 12 months, and (8) having attempted suicide during the last 12 months ($p < 0.05$ for all). Lower odds of HCB consumption were correlated with underweight ($p < 0.05$ for all).

Among female HCB drinkers, higher odds of HCB consumption were related to being obese, drinking alcohol, and using tobacco ($p < 0.05$ for all). In girls, HCB consumption was correlated with (1) > 60 minutes of physical activity 1 to 2 days per week, (2) > 1 time per week of soda consumption, (3) > 1 time per week of sweetened beverage consumption, (4) insufficient fatigue relief after sleep, (5) having seriously considered suicide during the last 12 months, and (6) having attempted suicide during the last 12 months ($p < 0.05$ for all). Lower odds of HCB consumption were correlated with high school maternal education ($p < 0.05$) (Table 3).

Discussion

The current study examined the multi-year prevalence of HCB consumption from 2014 to 2017 in a nationally representative sample of adolescents in Korea. This might be the only study to date to explore sex differences in the multi-year prevalence of HCB consumption among Korean adolescents. Moreover, this might be among the first studies to investigate associations between HCB consumption and behavioral factors using the multi-year KYRBS data. This study revealed that more male participants consumed HCB than female participants. HCB consumption was related to unhealthy behaviors (e.g., alcohol intake, tobacco use, sweetened beverage consumption, and insufficient sleep) and mental health problems (e.g., considering or attempting suicide). We identified that HCB intake was associated with simultaneous health risk behaviors and problems. Therefore, we need to intervene on HCB consumption and concurrent multiple health risk behaviors and problems together, especially targeting Korean male adolescents.

Overall, the HCB consumption prevalence was higher in boys than in girls (17.2% vs. 13.1%), which aligns with prior research findings [13,21]. In 2017, the HCB consumption prevalence was 26.7% for boys and 20.9% for girls. These rates are nearly twice as high as the reported prevalence (12.2%) in a previous study of Korean adolescents in both boys and girls in 2015 [13]. The present study found a rapid

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Table 2. Characteristics of girls by highly caffeinated beverage consumption, Korea Youth Risk Behavior Web-based Survey 2014–2017

Characteristic	Total (n = 130,806) (%)	Drinker (n = 17,014) (%)	Nondrinker (n = 113,792) (%)	Effect size[a)]	p
School type					
Middle school	46.6	45.6	46.8	0.008	0.090
High school	53.4	54.4	53.3		
Academic achievement					
Low	33.5	38.6	32.7	0.042	< 0.001
Middle	29.4	28.0	29.6		
High	37.1	33.4	37.7		
Household income					
Low	16.5	17.9	16.3	0.025	< 0.001
Middle	49.6	46.4	50.1		
High	33.9	35.7	33.6		
Weekly expenditure					
< 50,000 KRW (< USD 44.66)	86.5	82.2	87.2	0.053	< 0.001
50,000–99,999 KRW (USD 44.66–89.32)	10.0	12.4	9.6		
≥ 100,000 KRW (≥ USD 89.33)	3.5	5.5	3.2		
Paternal education					
≤ Middle school	2.7	3.2	2.7	0.012	0.004
High school	35.3	34.6	35.3		
≥ College	62.0	62.1	62.0		
Maternal education					
≤ Middle school	2.5	3.0	2.5	0.018	< 0.001
High school	44.8	42.7	45.1		
≥ College	52.7	54.3	52.5		
BMI[b)]					
Underweight	6.3	6.0	6.4	0.016	< 0.001
Normal weight	78.8	77.7	78.9		
Overweight	8.5	9.1	8.4		
Obese	6.4	7.3	6.3		
Alcohol use					
Never	64.6	56.4	65.8	0.066	< 0.001
Ever	35.4	43.6	34.2		
Tobacco use					
Never	91.6	86.9	92.2	0.064	< 0.001
Ever	8.4	13.1	7.8		
Weekly physical activity for ≥ 60 min					
None	44.6	41.5	45.1	0.024	< 0.001
1–2 days	33.9	35.8	33.7		
≥ 3 days	21.5	22.7	21.3		
Weekly vigorous exercise for ≥ 20 min					
None	34.1	32.1	34.4	0.016	< 0.001
1–2 days	41.5	42.8	41.4		
≥ 3 days	24.3	25.1	24.2		
Weekly frequency of soda consumption					
0 times	29.3	17.8	31.0	0.148	< 0.001
1–2 times	48.9	45.5	49.4		
≥ 3 times	21.8	36.7	19.6		

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Table 2. Continued

Characteristic	Total (*n* = 130,806) (%)	Drinker (*n* = 17,014) (%)	Nondrinker (*n* = 113,792) (%)	Effect size[a)]	*p*
Weekly frequency of sweetened beverage consumption					
0 times	16.1	7.7	17.4	0.144	< 0.001
1–2 times	45.0	36.1	46.3		
≥ 3 times	38.9	56.3	36.3		
Meeting sleep duration recommendations (8–10 h)					
Not met	87.3	88.1	87.1	0.010	0.004
Met	12.7	11.9	12.9		
Feeling fatigue relief after sleep					
Not enough/not enough at all	48.2	55.6	47.1	0.059	< 0.001
Fair	31.6	28.6	32.1		
Very enough/enough	20.1	15.9	20.8		
Seriously considered suicide during last 12 mo					
No	85.2	78.3	86.2	0.075	< 0.001
Yes	14.8	21.8	13.8		
Suicide attempt during last 12 mo					
No	96.9	93.8	97.3	0.067	< 0.001
Yes	3.1	6.2	2.7		

Use of weighted data with adjustment for the complex survey design. The percentages may not add to 100 because of rounding errors.
KRW, Korean won; USD, United States dollar; BMI, body mass index.
[a)]Phi effect sizes were considered negligible if < 0.1, weak if between 0.1 and < 0.2, moderate if between 0.2 and < 0.4, and strong if ≥ 0.4. [b)]Underweight (BMI < 5th percentile), normal weight (5th percentile ≤ BMI < 85th percentile), overweight (85th percentile ≤ BMI < 95th percentile), and obese (BMI ≥ 95th percentile).

(13.8% to 23.9%) rise in HCB consumption from 2016 to 2017, despite governmental policies to limit access to HCBs for adolescents [11] in Korea. Although it remains necessary to perform a longitudinal analysis that compares HCB use before and after policy implementation and evaluates the effectiveness of the government policies, the present study indicates that overall, current policies to reduce HCB consumption of Korean adolescents are not as efficacious as initially anticipated. The government of Korea should consider enforcing tougher policies that would reduce HCB use among adolescents since HCBs are likely to be even more popular in the adolescent population. Considering the higher rate of HCB consumption in boys than girls, there is an urgent need to develop sex-specific programs to curb HCB use, especially in boys.

For both sexes, HCB drinkers had higher odds of alcohol and tobacco use than HCB nondrinkers. This result is in accord with the previous literature [19,22], which has shown that adolescents mix HCBs with alcohol and that this risky behavior is related to other unhealthy behaviors (e.g., higher alcohol consumption, drunk driving, and unprotected sex). HCB drinkers had higher odds of feeling unrested after sleep and having suicidal thoughts and suicide attempts. Furthermore, more HCB users than nonusers did not meet the recommended sleep duration in boys (78.5% vs. 75.4%), but this trend was not found in girls. However, the magnitude of the association was negligible. This result aligns with prior research, which has found a relationship between HCB consumption and shorter sleep duration among adolescents [21]. The present study found that HCB use was related to suicidal behavior. Given that suicide remains the leading cause of death among Korean adolescents [23], it is important for middle and high schools in Korea to identify effective strategies to address the early stages of HCB use among students. Additional research is needed to determine causal links between HCB consumption and sleep quality and sleep duration among adolescents.

In both sexes, HCB drinkers had higher odds of (1) being obese, (2) drinking soda at least once a week, and (3) drinking sweetened beverages at least once a week. These findings are consistent with previous evidence that the sugar content and the resulting sweet flavor are associated with HCB consumption [24,25]. Those findings also suggest that for adolescents who consume HCBs, the sugar content and its subsequent impact on weight may mask any weight-loss effect expected from the caffeine content [26]. Thus, HCB abuse should be considered a vital determinant of obesity as well as caffeine abuse. Since the transition

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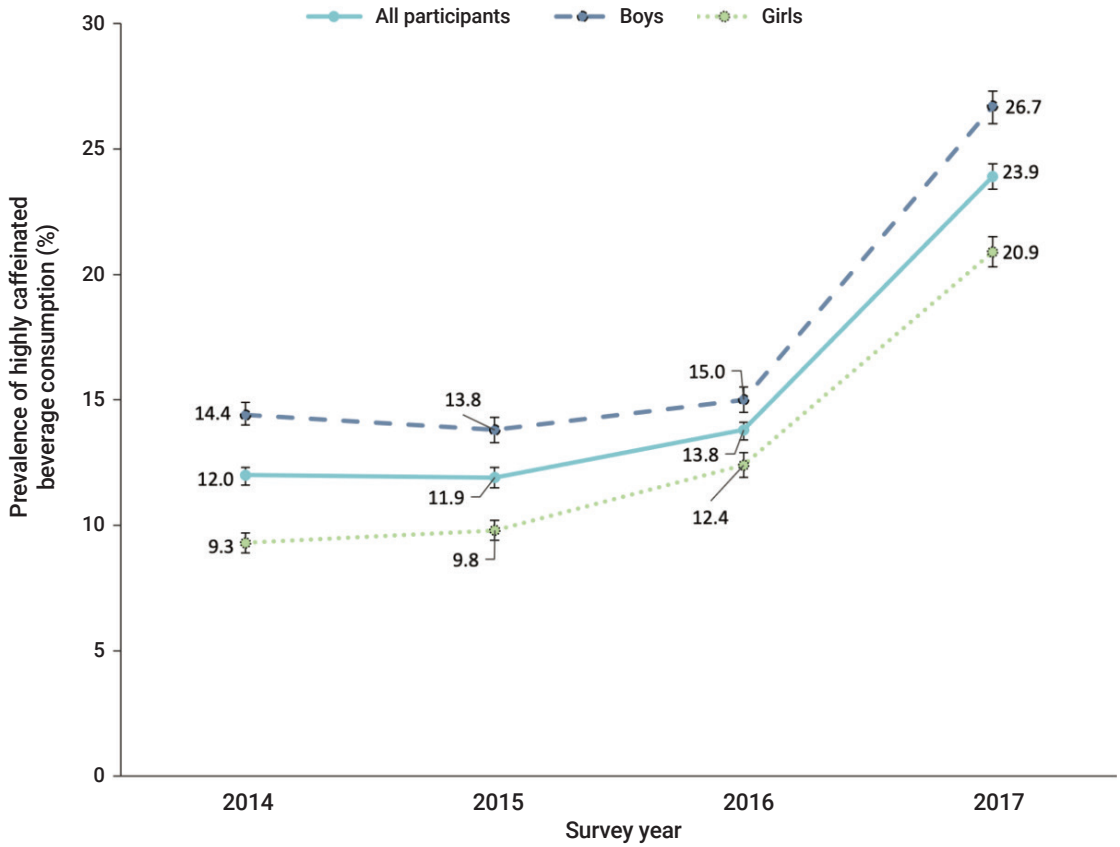

Figure 1. Prevalence (%) of highly caffeinated drink consumption by survey year among all participants (n = 267,907), using weighted data for the complex survey design.

from adolescence to adulthood is a stage of particular risk for obesity and weight gain [22], health professionals in middle and high schools should develop health education programs. These programs should help their students become aware of the health effects of HCB consumption, which may consequently lead to less intake of them.

The adolescents in this study showed some sex differences in the relationship between HCB consumption and vigorous exercise. Among boys, in comparison with nondrinkers, HCB drinkers had higher odds of reporting ≥20 minutes of vigorous exercise ≥3 days per week. Considering that boys expect higher energy and better athletic performance from caffeine [27], they may believe that HCBs improve their workouts. Consequently, this may result in HCB use for vigorous-intensity exercise. An association between HCB consumption and vigorous exercise was not found in girls. Prior research has shown that girls were less likely to use caffeine for athletic performance [27]. Given research findings that caffeine may increase blood pressure and the risk of myocardial infarction during exercise [28], the aforementioned finding of the present study highlights the need to develop tailored school-based education programs. These programs should focus on discouraging HCB consumption and encouraging a healthy diet (e.g., drinking water) during workouts especially in boys.

Another notable finding was that girls with mothers having a high school education had lower odds of HCB consumption than those with mothers having a middle school education or less. Evidence indicates that the maternal education level is related to health behaviors of their children and that mothers play a vital role in preventing and treating obesity in their children [29]. Research has shown that mothers with lower education levels make more unhealthy foods available at home [29], whereas mothers with higher education levels feed their children nutritious foods and limit their children's access to unhealthy foods [30]. The result of this study indicates the need for health educators in Korea to provide mothers with health education programs that help them become aware of the health consequences of HCB consumption. Future studies should consider the important role that mothers play in reducing HCB consumption, and more rigorous experimental studies focusing on this topic are needed to establish a causal link between maternal education level and HCB use.

Table 3. Multiple logistic regression analysis of highly caffeinated beverage consumption, Korea Youth Risk Behavior Web-based Survey 2014–2017

Variable	All (*n* = 267,907)	Boy (*n* = 137,101)	Girl (*n* = 130,806)
Sex			
Girl	Reference	-	-
Boy	1.25 (1.20–1.31)***	-	-
Paternal education			
≤ Middle school	Reference	Reference	Reference
High school	0.92 (0.83–1.02)	0.92 (0.80–1.06)	0.91 (0.78–1.06)
≥ College	0.95 (0.85–1.05)	0.96 (0.84–1.10)	0.93 (0.79–1.09)
Maternal education			
≤ Middle school	Reference	Reference	Reference
High school	0.88 (0.79–0.98)*	0.91 (0.79–1.06)	0.84 (0.72–0.98)*
≥ College	0.99(0.88–1.10)	1.00 (0.86–1.16)	0.97 (0.83–1.13)
BMI[a)]			
Underweight	0.90 (0.84–0.96)**	0.90 (0.82–0.98)*	0.91 (0.82–1.00)
Normal	Reference	Reference	Reference
Overweight	1.07 (1.01–1.13)*	1.06 (0.98–1.14)	1.09 (1.00–1.18)*
Obese	1.22 (1.15–1.29)***	1.21 (1.12–1.30)***	1.24 (1.13–1.37)***
Alcohol use			
Never	Reference	Reference	Reference
Ever	1.17 (1.13–1.22)***	1.16 (1.10–1.22)***	1.19 (1.13–1.26)***
Tobacco use			
Never	Reference	Reference	Reference
Ever	1.11 (1.06–1.16)***	1.10 (1.04–1.16)**	1.11 (1.02–1.21)*
Weekly physical activity for ≥ 60 min			
None	Reference	Reference	Reference
1–2 days	1.10 (1.06–1.15)***	1.14 (1.07–1.21)***	1.08 (1.02–1.14)**
≥ 3 days	1.04 (1.00–1.09)	1.06 (1.00–1.12)	1.03 (0.96–1.11)
Weekly vigorous exercise for ≥ 20 min			
None	Reference	Reference	Reference
1–2 days	1.04 (0.99–1.09)	1.05 (0.97–1.13)	1.04 (0.98–1.10)
≥ 3 days	1.05 (1.00–1.11)	1.08 (1.01–1.16)*	1.02 (0.94–1.09)
Weekly frequency of soda consumption			
0 times	Reference	Reference	Reference
1–2 times	1.41 (1.35–1.48)***	1.55 (1.44–1.67)***	1.33 (1.25–1.42)***
≥ 3 times	2.32 (2.20–2.44)***	2.71 (2.51–2.92)***	1.99 (1.85–2.13)***
Weekly frequency of sweetened beverage consumption			
0 time	Reference	Reference	Reference
1–2 times	1.61 (1.52–1.71)***	1.78 (1.63–1.95)***	1.45 (1.33–1.57)***
≥ 3 times	2.35 (2.21–2.49)***	2.37 (2.17–2.59)***	2.33 (2.14–2.54)***
Meeting sleep duration recommendations (8–10 h)			
Not met	1.04 (0.99–1.09)	1.06 (1.01–1.13)*	1.01 (0.94–1.09)
Met	Reference	Reference	Reference
Feeling fatigue relief after sleep			
Not enough/not enough at all	1.22 (1.17–1.28)***	1.18 (1.12–1.25)***	1.29 (1.20–1.38)***
Fair	1.07 (1.02–1.12)**	1.05 (0.99–1.11)	1.11 (1.03–1.19)**
Very enough/enough	Reference	Reference	Reference
Seriously considered suicide during last 12 mo			
No	Reference	Reference	Reference
Yes	1.11 (1.05–1.16)***	1.08 (1.00–1.16)*	1.13 (1.06–1.20)***

(Continued to the next page)

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Table 3. Continued

Variable	All (n = 267,907)	Boy (n = 137,101)	Girl (n = 130,806)
Suicide attempt during last 12 mo			
No	Reference	Reference	Reference
Yes	1.44 (1.31–1.58)***	1.62 (1.39–1.87)***	1.31 (1.16–1.49)***

Data are presented as adjusted odds ratio (95% confidence interval). Odds ratio adjusted for school year, family level household income, weekly expenditure, and academic achievement. Use of weighted data with adjustment for the complex survey design.
BMI, body mass index.
[a)]Underweight (BMI < 5th percentile), normal weight (5th percentile ≤ BMI < 85th percentile), overweight (85th percentile ≤ BMI < 95th percentile), and obese (BMI ≥ 95th percentile).
*p < 0.05, **p < 0.01, ***p < 0.001.

This study has limitations. First, although efforts were made to include and control for known confounders, there are unmeasured confounders (e.g., types of HCBs, nutrient content of HCBs, and access to HCBs) that could potentially influence the association between independent variables and HCB consumption. Second, this study used self-reported data. Since adolescents have been shown to under-report their body weight and over-report their height [31], the BMI percentiles computed in this study may have differed slightly from those made using direct anthropometric measurements. In addition, the study findings might have been confounded by unintentional recall bias. Third, this study relied on BMI percentiles to assign weight categories. Although BMI percentiles are commonly used to predict adiposity in children and adolescents, they cannot account for individuals' body composition (e.g., amount of fat mass vs. fat-free mass) or fat distribution (e.g., abdominal vs. non-abdominal fat). Finally, this study was not a longitudinal analysis, despite having used multiple years of data. Therefore, the numbers reported herein reflect correlation, but not necessarily causation. Despite these limitations, this study provides data on the prevalence of HCB consumption and its behavioral correlates among Korean adolescents. This study also found significant growth in HCB consumption between 2016 and 2017, despite the Korean government's efforts to curb adolescents' caffeine abuse. New strategies are needed to effectively curb HCB consumption among the adolescent population. Longitudinal studies are needed to further investigate HCB consumption among Korean adolescents.

Notes

Ethics Approval
This study was approved by the Touro University Institutional Review Board (IRB No: PH0219).

Conflicts of Interest
The authors have no conflicts of interest to declare.

Funding
None.

Availability of Data
Data can be made available through the authors.

Authors' Contributions
Conceptualization: HKK, JS, JL; Data analysis: HKK, JS, SC, JL; Methodology: JS, JL, SC; Validation: all authors; Visualization: HKK, JS, SC, JPC, JL; Writing–original draft: HKK, JS, SC, JL; Writing–review & editing: JPC, JC, GC.

References

1. Reissig CJ, Strain EC, Griffiths RR. Caffeinated energy drinks: a growing problem. Drug Alcohol Depend 2009;99:1–10.
2. Wolk BJ, Ganetsky M, Babu KM. Toxicity of energy drinks. Curr Opin Pediatr 2012;24:243–51.
3. Shabir A, Hooton A, Tallis J, et al. The influence of caffeine expectancies on sport, exercise, and cognitive performance. Nutrients 2018;10:1528.
4. Ko G. Energy drink market status and regulatory trend. KHIDI Brief 2014;154:1–8. Korean.
5. Lim H. Survey on safety of energy drink. Consumer safety. Seoul: Korea Consumer Agency; 2013. Korean.
6. Lim HS, Hwang JY, Choi JC, et al. Assessment of caffeine intake in the Korean population. Food Addit Contam Part A Chem Anal Control Expo Risk Assess 2015;32:1786–98.
7. Shin J, Kim SY, Yoon J. Status of coffee intake in South Korea: analysis of 2007-2009 Korea National Health and Nutrition Examination Survey. Korean J Community Living Sci 2016;27:83–93. Korean.
8. Heckman MA, Weil J, Gonzalez de Mejia E. Caffeine (1,3,7-trimethylxanthine) in foods: a comprehensive review on consumption, functionality, safety, and regulatory matters. J Food Sci 2010;75:R77–87.
9. Seifert SM, Schaechter JL, Hershorin ER, et al. Health effects of energy drinks on children, adolescents, and young adults. Pediatrics 2011;127:511–28.
10. Ryu SH. Energy drink consumption status and associated factors among male and female high school students in Deajon area. Korean J Food Nutr 2016;29:899–910. Korean.
11. Korean Ministry of Food and Drug Safety. Health functional food code. Cheongju: Korean Ministry of Food and Drug Safety; 2019.
12. Jin MJ, Yoon CH, Ko HJ, et al. The relationship of caffeine intake with depression, anxiety, stress, and sleep in Korean adolescents. Korean

J Fam Med 2016;37:111–6.
13. Ra JS, Yun HK, Kim HS, et al. Associated factors on energy drink consumption among Korean high school students. J Korean Soc Sch Health 2017;30:48–58. Korean.
14. Korea Centers for Disease Control and Prevention (KCDC). The Korea youth risk behavior web-based survey user's guide. Cheongju: KCDC; 2019. Korean.
15. Kim Y, Kawachi I. School- and individual-level predictors of weight status misperception among Korean adolescents: a national online survey. PLoS One 2016;11:e0154826.
16. Kim JH, Yun S, Hwang SS, et al. The 2017 Korean National Growth Charts for children and adolescents: development, improvement, and prospects. Korean J Pediatr 2018;61:135–49.
17. Hirshkowitz M, Whiton K, Albert SM, et al. National Sleep Foundation's updated sleep duration recommendations: final report. Sleep Health 2015;1:233–43.
18. Bulut B, Beyhun NE, Topbas M, et al. Energy drink use in university students and associated factors. J Community Health 2014;39:1004–11.
19. Larson N, DeWolfe J, Story M, et al. Adolescent consumption of sports and energy drinks: linkages to higher physical activity, unhealthy beverage patterns, cigarette smoking, and screen media use. J Nutr Educ Behav 2014;46:181–7.
20. Larson N, Laska MN, Story M, et al. Sports and energy drink consumption are linked to health-risk behaviours among young adults. Public Health Nutr 2015;18:2794–803.
21. Sampasa-Kanyinga H, Hamilton HA, Chaput JP. Sleep duration and consumption of sugar-sweetened beverages and energy drinks among adolescents. Nutrition 2018;48:77–81.
22. Azagba S, Langille D, Asbridge M. An emerging adolescent health risk: caffeinated energy drink consumption patterns among high school students. Prev Med 2014;62:54–9.
23. Kwak CW, Ickovics JR. Adolescent suicide in South Korea: risk factors and proposed multi-dimensional solution. Asian J Psychiatr 2019;43:150–3.
24. Bunting H, Baggett A, Grigor J. Adolescent and young adult perceptions of caffeinated energy drinks: a qualitative approach. Appetite 2013; 65:132–8.
25. Kim EJ, Cheong HS. Study on perceptions and intake of caffeine-containing favorite foods by rural and urban middle school students in Kyungnam. Korean J Food Cook Sci 2014;30:650–62. Korean.
26. Williams RD Jr, Housman JM, Odum M, et al. Energy drink use linked to high-sugar beverage intake and BMI among teens. Am J Health Behav 2017;41:259–65.
27. Temple JL, Dewey AM, Briatico LN. Effects of acute caffeine administration on adolescents. Exp Clin Psychopharmacol 2010;18:510–20.
28. Hartley TR, Sung BH, Pincomb GA, et al. Hypertension risk status and effect of caffeine on blood pressure. Hypertension 2000;36:137–41.
29. Feng Y, Ding L, Tang X, et al. Association between maternal education and school-age children weight status: a study from the China Health Nutrition Survey, 2011. Int J Environ Res Public Health 2019;16:2543.
30. Choi HJ, Lee HJ, Jang HB, et al. Effects of maternal education on diet, anemia, and iron deficiency in Korean school-aged children. BMC Public Health 2011;11:870.
31. Bae J, Joung H, Kim JY, et al. Validity of self-reported height, weight, and body mass index of the Korea Youth Risk Behavior Web-based Survey questionnaire. J Prev Med Public Health 2010;43:396–402.

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Original Article

Laboratory investigations of herpes simplex virus-1 and -2 clinical samples in Korea

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ABSTRACT

Objectives: Herpes simplex virus (HSV) infections have been reported in 60% to 95% of the adult population worldwide, making them one of the most common infectious conditions globally. HSV-1 and HSV-2 cause severe disease in immunocompromised patients. Therefore, the aim of this study was to provide information that could be used to reduce the incidence of genital herpes caused by HSV-1 and HSV-2.
Methods: From September 2018 to December 2020, 59,381 specimens were collected from outpatients across primary and secondary hospitals in Korea who requested U2Bio (Korea) to conduct molecular biological testing of their samples for sexually transmitted infections. In this study, the positivity rates of HSV-1 and HSV-2 were analyzed according to age, sex, and specimen type.
Results: In the age-specific analysis of HSV-1, the highest positivity rate (0.58%) was observed in patients under 19 years of age, whereas the lowest positivity rate (0.08%) was observed in patients aged over 70 years. In the age-specific analysis of HSV-2, the highest positivity rate (2.53%) was likewise observed in patients under 19 years of age.
Conclusion: Our study identified differences in the infection rates of HSV-1 and HSV-2 depending on patients' sex and age. These differences will be useful for improving disease prevention and control measures for HSV-1 and HSV-2.

Keywords: Human herpesvirus 1; Human herpesvirus 2; Korea; Sexually transmitted diseases

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Introduction

Herpes simplex virus (HSV) infections are among the most widespread infectious conditions worldwide, affecting 60% to 95% of the adult population [1]. HSV is the most common sexually transmitted infection (STI) in the United States [2]. According to Burn Aschner et al. [3], 67% of the worldwide population is infected with HSV-1 by 49 years of age; many individuals in

developing countries are infected early in childhood [3].

In the United States, between 2015 and 2016, the prevalence of HSV-1 and HSV-2 among people between 14 and 49 years of age was 47.8% and 11.9%, respectively [4]. During the period from October 2014 to March 2015 in Ghana, the prevalence rates of HSV-1 and HSV-2 among females were 99.2% and 78.4%, respectively [5]. These results indicate that the global spread of HSV-1 and HSV-2 is high and attention-worthy [6].

HSV-1 and HSV-2, which are double-stranded DNA viruses that typically infect humans [7], are related to many diseases and can cause rare but severe after-effects, such as meningitis and neonatal herpes [8]. Moreover, HSV infection during pregnancy is related to miscarriage, premature birth, and congenital and neonatal herpes, and it can cause severe infections in newborns owing to intrauterine vertical metastasis. In many cases, contact with HSV-infected genital secretions can lead to a high risk of mortality and neurodevelopmental disorders during vaginal delivery [1].

HSV infection can also function as a co-factor for the acquisition and transmission of other sexually contagious infections, including human immunodeficiency virus, syphilis, hepatitis C virus, and human papillomavirus [9]. HSV-1 and HSV-2 also cause blindness and severe infectious diseases in immunocompromised patients [10]. In the United States, the proportion of individuals co-infected with HSV-1 and HSV-2 decreased from 14.6% in 1988–1994 to 10.5% in 1999–2004 [11]. Co-infection with HSV-1 and HSV-2 severely affects the dynamics of patients with clinical genital herpes compared with infection with HSV-2 only [12].

Vaccines that prevent genital herpes infections affect public health [13]. However, vaccines intended to prevent HSV-2 genital herpes have not been successful to date [13]. Therefore, the aim of this study was to provide information to support the development of vaccines that would be useful for protection against genital herpes caused by HSV-1 and HSV-2 and to provide information that could be used to safeguard public health and reduce the incidence of genital herpes caused by HSV-1 and HSV-2.

Materials and Methods

Materials

From September 2018 to December 2020, 59,381 specimens were collected from outpatients across primary and secondary hospitals in Korea who requested U2Bio (Seoul, Korea) to conduct molecular biological testing of their samples for STIs. The specimens were classified into swab, urine, and other (catheter, pus, and tissue) samples. The study protocol was approved by the Institutional Review Board of Dankook University (IRB No. 2021-04-002).

Nucleic Acid Extraction

The collected clinical specimens were stored at −70°C until DNA isolation for multiplex polymerase chain reaction (mPCR). DNA for the mPCR assay was extracted using an ExiPrep Dx Bacteria Genomic DNA kit (Bioneer, Daejeon, Korea) according to the manufacturer's instructions. The concentrations of the extracted DNA samples were measured using the AccuPower STI8B-Plex Real-Time PCR kit (Bioneer).

Real-Time PCR Analysis

Real-time PCR analysis was performed using the AccuPower STI8B-Plex Real-Time PCR kit with an Exicycler 96 Real-Time Quantitative Thermal Block (Exicycler 96; Bioneer), according to the manufacturer's protocol. The amplification protocol comprised 1 cycle at 95°C for 5 minutes and 45 cycles at 95°C for 5 seconds and 55°C for 5 seconds. The threshold cycle was determined according to the manufacturer's instructions. Four pathogens—*Trichomonas vaginalis, Mycoplasma hominis*, HSV-1, and HSV-2—were evaluated. In this study, we analyzed HSV-1 and HSV-2. The real-time PCR target genes used and their product sizes are listed in Table 1.

Statistical Analysis

SAS ver. 9.4 (SAS Institute Inc., Cary, NC, USA) was used to perform all statistical analyses, including descriptive statistical analysis and frequency analysis. Statistical significance was set at $p < 0.05$.

Results

In total, 59,381 specimens were tested for HSV-1 and HSV-2 infections between August 2018 and December 2020, and 1,429 (2.4%) of them tested positive.

In the age-specific analysis of HSV-1, the highest positivity rate (0.58%, 6/1,026) was observed in patients under 19 years of age, followed by those aged 20 to 29 years (0.50%, 80/16,076) (Figure 1). The lowest HSV-1 positivity rate (0.08%, 2/2,370) was observed in patients aged over 70 years (Figure 1). In the age-specific analysis of HSV-2, the highest positivity rate (2.53%, 26/1,026) was observed in patients under 19 years of age, followed by those aged 20 to 29 years (2.33%, 375/16,076). The lowest HSV-2-positivity rate (1.76%, 196/11,119) was observed in patients aged 40 to 49 years (Figure 1). The positivity rate

Table 1. Target genes and their product sizes for real-time polymerase chain reaction

Pathogen	Target gene	Product size (bp)
Herpes simplex virus type 1	*us4*	111
Herpes simplex virus type 2	*Gg*	86

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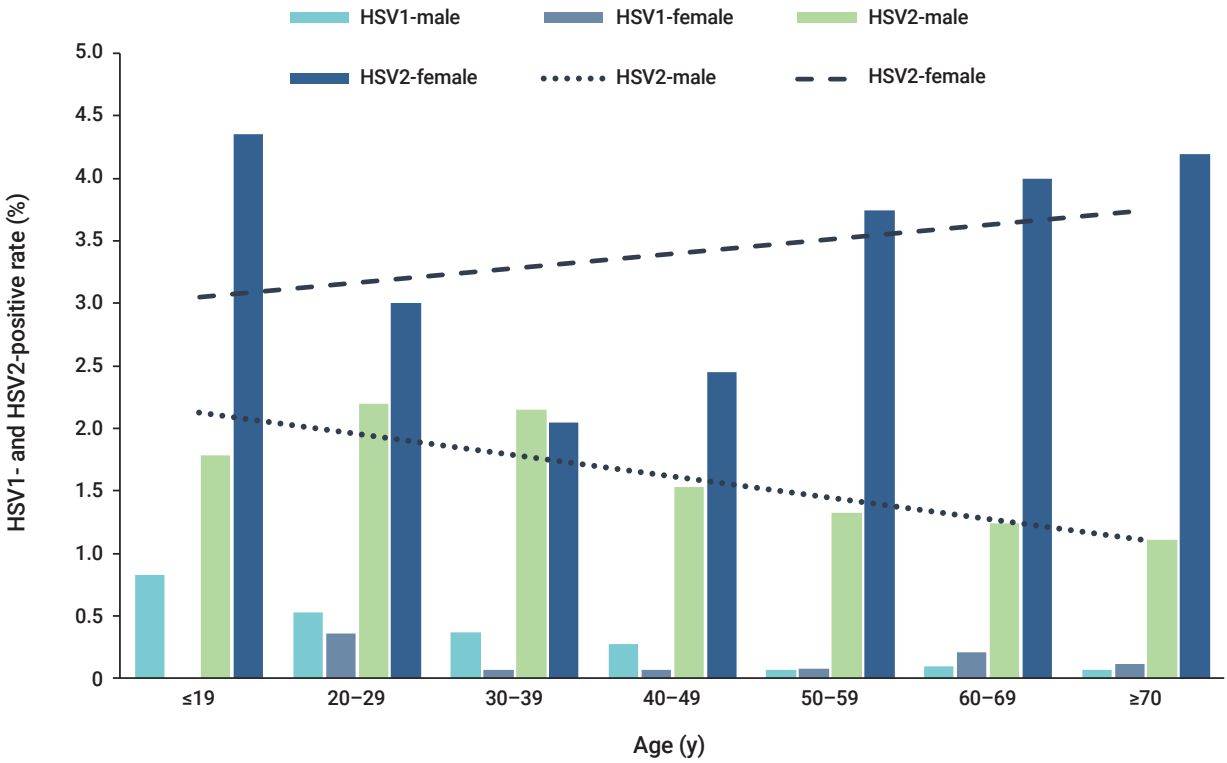

Figure 1. Herpes simplex virus (HSV)-1 and HSV-2 positivity rates according to age and sex.
The HSV-2 positivity rate was higher than the HSV-1 positivity rate. The positivity rate of HSV was higher in females than in males.

of HSV-1 showed a significant association with age ($p = 0.007$) (Table 2). Similarly, the positivity rate of HSV-2 was also significantly associated with age ($p = 0.026$) (Table 2). Distinct patterns of infection were observed in different age groups.

The results of the specimen-specific positivity rate analysis showed that in males, the highest HSV-1-positivity rate was found in urine specimens (0.66%, 5/760), and the highest HSV-2-positivity rate was found in swab specimens (5.92%, 45/760) (Table 3). In females, the highest HSV-1-positivity rate was found in swab specimens (0.23%, 15/6,665), and the highest HSV-2-positivity rate was found in swab specimens (3.81%, 254/6,665) (Table 3). To summarize, the highest positivity rate was observed in swab specimens of both males and females. The HSV-2-positivity rate was higher than that of HSV-1 during the study period. HSV-1 and HSV-2 co-infection ($n = 5/59,381$) was observed.

Table 2. Age distribution of the positivity rate of HSV-1 and HSV-2 and correlation between age and the positivity rate of HSV-1 and HSV-2 between 2018 and 2020

Age (y)	HSV-1	HSV-2
≤ 19 ($n = 1,026$)	6 (0.58)	26 (2.53)
20–29 ($n = 16,076$)	80 (0.50)	375 (2.33)
30–39 ($n = 15,644$)	49 (0.31)	333 (2.13)
40–49 ($n = 11,119$)	25 (0.22)	196 (1.76)
50–59 ($n = 8,474$)	6 (0.07)	175 (2.07)
60–69 ($n = 4,672$)	6 (0.13)	98 (2.10)
≥ 70 ($n = 2,370$)	2 (0.08)	52 (2.19)
p	0.007*	0.026*

Data are presented as n (%).
HSV, herpes simplex virus.
*$p < 0.05$.

Discussion

The study analyzed the positivity rates of HSV-1 and HSV-2 infections according to age, sex, and specimen type from September 2018 to December 2020. The highest positivity rates for both HSV-1 and HSV-2 were observed in the specimens of patients under 19 years of age. The HSV-2 positivity rate was higher in females than in males.

HSV-1 prevalence tends to increase with age, and most incident cases occur in childhood and adolescence. Moreover, the shapes of age-specific HSV-2 and HSV-1 prevalence graphs differ primarily in terms of whether they show the expected patterns of an STI (HSV-2) rather than a non-STI (HSV-1) [8]. The prevalence of HSV-2 was previously reported to range from 34% to 79% among clinic- and community-based 15-

Table 3. Positivity rates of HSV-1 and HSV-2 according to the specimen type and sex between 2018 and 2020

Specimen	Male			Female		
	Total (*n*)	HSV-1	HSV-2	Total (*n*)	HSV-1	HSV-2
Swab	760	5 (0.66)	45 (5.92)	6,665	15 (0.23)	254 (3.81)
Urine	38,905	127 (0.33)	699 (1.80)	5,986	5 (0.08)	145 (2.42)
Other	6,168	22 (0.36)	99 (1.61)	897	0	13 (1.45)
Total	45,833	154 (0.34)	843 (1.84)	13,548	20 (0.15)	412 (3.04)

Data are presented as *n* (%).
HSV, herpes simplex virus.

to 24-year-old individuals in Eastern Africa and from 46% to 66% in high-risk populations [14,15].

Sexually acquired genital HSV-1 infections are common in young females and males with active sex lives [16]. According to Issakwisa et al. [16], the infection rates are higher in males than in females [16]. Our study also showed that HSV-1 infection was more common in males than in females. The age-specific HSV-2 prevalence is usually higher in females than in males, as well as in individuals with high-risk sexual behaviors [14,17]. This result appears to be consistent across multiple geographic sites, and females seem to show a higher risk of HSV-2 acquisition than males [8].

Severe HSV-1 and HSV-2 co-infections, with high mortality and morbidity rates, have been observed in newborns [18]. HSV-1 and HSV-2 co-infection were observed in this study; however, further research is needed to verify this finding.

This study has some limitations. First, it was conducted in the tests performed by a single organization, and it did not represent all regions in Korea. Additionally, the 3-year study period was relatively short, making it difficult to identify trends in HSV-1 and HSV-2 infections. Second, the sample data were anonymous, and the residence of the patients was not specified. Third, it was a retrospective study rather than a prospective study, and the results were not analyzed according to patients' clinical characteristics.

The prevalence of HSV-2 and HSV-1 is highly variable, and it depends on many factors, including country, area of residence, population subgroup, sex, and age [10]. Therefore, age-specific or age-adjusted prevalence among similar populations should be analyzed to compare the prevalence of HSV infections across geographic areas or between countries. Despite these limitations, we found distinct infection patterns in different age groups. We expect that this information will assist in the development and implementation of targeted behavioral interventions to reduce genital herpes infections caused by HSV-1 and HSV-2.

Conclusion

Our study identified differences in the infection rates of HSV-1 and HSV-2 according to sex and age. The characterization of these differences will be useful for describing the dynamics and risk factors of HSV-1 and HSV-2, especially for improving disease prevention and control measures. We also expect that this study will provide information that can be used to safeguard public health and reduce the incidence of genital herpes caused by HSV-1 and HSV-2.

Notes

Ethics Approval
This study was approved by the Dankook University Institutional Review Board (IRB No. 2021-04-002).

Conflicts of Interest
The authors have no conflicts of interest to declare.

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None.

Availability of Data
The datasets are not publicly available but are available from the corresponding author upon reasonable request.

Authors' Contributions
Conceptualization: all authors; Data curation: EJO; Formal analysis: YSY; Investigation: all authors; Methodology: all authors; Project administration: JKK; Resources: all authors; Software: all authors; Supervision: JKK; Validation: all authors; Visualization: all author; Writing–original draft: EJO, JKK; Writing–review & editing: all authors.

References

1. Marchi S, Trombetta CM, Gasparini R, et al. Epidemiology of herpes simplex virus type 1 and 2 in Italy: a seroprevalence study from 2000 to 2014. J Prev Med Hyg 2017;58:E27–33.
2. Roberts CM, Pfister JR, Spear SJ. Increasing proportion of herpes simplex virus type 1 as a cause of genital herpes infection in college students. Sex Transm Dis 2003;30:797–800.
3. Burn Aschner C, Knipe DM, Herold BC. Model of vaccine efficacy against HSV-2 superinfection of HSV-1 seropositive mice demonstrates protection by antibodies mediating cellular cytotoxicity. NPJ Vaccines 2020;5:35.
4. McQuillan G, Kruszon-Moran D, Flagg EW, et al. Prevalence of herpes simplex virus type 1 and type 2 in persons aged 14-49: United States, 2015-2016. NCHS Data Brief 2018;(304):1–8.

5. Debrah O, Agyemang-Yeboah F, Asmah RH, et al. SERO-prevalence of herpes simplex virus type 1 and type 2 among women attending routine Cervicare clinics in Ghana. BMC Infect Dis 2018;18:378.
6. Looker KJ, Magaret AS, May MT, et al. Global and regional estimates of prevalent and incident herpes simplex virus type 1 infections in 2012. PLoS One 2015;10:e0140765.
7. Koganti R, Yadavalli T, Shukla D. Current and emerging therapies for ocular herpes simplex virus type-1 infections. Microorganisms 2019;7:429.
8. Smith JS, Robinson NJ. Age-specific prevalence of infection with herpes simplex virus types 2 and 1: a global review. J Infect Dis 2002;186 Suppl 1:S3–28.
9. Agyemang-Yeboah F, Debrah O, Timmy-Donkoh E, et al. Co-infection prevalence of herpes simplex virus types 1 and 2 with human papillomavirus and associated risk factors among asymptomatic women in Ghana. Int J Infect Dis Ther 2018;3:45–51.
10. Bernstein DI, Cardin RD, Smith GA, et al. The R2 non-neuroinvasive HSV-1 vaccine affords protection from genital HSV-2 infections in a guinea pig model. NPJ Vaccines 2020;5:104.
11. Perkins D, Chong H, Irvine B, et al. Genital co-infection with herpes simplex viruses type 1 and 2: comparison of real-time PCR assay and traditional viral isolation methods. J Cell Mol Med 2007;11:581–4.
12. Xu F, Schillinger JA, Sternberg MR, et al. Seroprevalence and coinfection with herpes simplex virus type 1 and type 2 in the United States, 1988-1994. J Infect Dis 2002;185:1019–24.
13. Egan K, Hook LM, Naughton A, et al. Herpes simplex virus type 2 trivalent protein vaccine containing glycoproteins C, D and E protects guinea pigs against HSV-1 genital infection. Hum Vaccin Immunother 2020;16:2109–13.
14. Torrone EA, Morrison CS, Chen PL, et al. Prevalence of sexually transmitted infections and bacterial vaginosis among women in sub-Saharan Africa: an individual participant data meta-analysis of 18 HIV prevention studies. PLoS Med 2018;15:e1002511.
15. Mehta SD, Nandi D, Agingu W, et al. Vaginal and penile microbiome associations with HSV-2 in women and their male sex partners. J Infect Dis 2020 Aug 21 [Epub]. https://doi.org/10.1093/infdis/jiaa529.
16. Issakwisa HM, Mbwile GR, Mbwanji GF, et al. Seroprevalence of herpes simplex virus type 1 among people living with HIV in Mbeya, Tanzania. BMC Infect Dis 2020;20:577.
17. Dargham SR, Nasrallah GK, Al-Absi ES, et al. Herpes simplex virus type 2 seroprevalence among different national populations of Middle East and North African men. Sex Transm Dis 2018;45:482–7.
18. Kimberlin D. Herpes simplex virus, meningitis and encephalitis in neonates. Herpes 2004;11 Suppl 2:65A–76A.

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Original Article

Prevalence of plasmid-mediated AmpC β-lactamases among uropathogenic *Escherichia coli* isolates in southwestern Iran

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ABSTRACT

Objectives: This study was undertaken to evaluate AmpC β-lactamase-producing *Escherichia coli* urine isolates and to characterize the frequency of plasmid-mediated AmpC (pAmpC)-encoding genes.
Methods: Antimicrobial susceptibility tests were performed using the disk diffusion technique. AmpC β-lactamase production was assessed with a phenotypic inhibitor-based method. The presence of 6 pAmpC-encoding cluster genes was detected by multiplex polymerase chain reaction (PCR).
Results: The proportion of antibiotic resistance of *E. coli* isolates ranged from 7.4% to 90.5%, and more than half (51.6%) of the total isolates were multidrug-resistant (MDR). Among the 95 *E. coli* isolates, 60 (63.2%) were found to be cefoxitin-resistant, but only 14 (14.7%) isolates were confirmed as AmpC β-lactamase-producers. In the PCR assay, pAmpC-encoding genes were found in 15 (15.8%) isolates, and bla_{DHA} was the most prevalent type. However, bla_{FOX}, bla_{MOX}, and bla_{ACC} genes were not detected in the isolates.
Conclusion: Our findings contributed valuable information concerning antibiotic resistance, confirmatory phenotypic testing for AmpC production, and pAmpC β-lactamase gene content in *E. coli* isolates in southwestern Iran. The level of MDR recorded in AmpC-producing strains of this study was worrying; therefore, implementing strong infection control approaches to reduce the MDR burden is recommended.

Keywords: AmpC; *Escherichia coli*; Multidrug resistance; Urinary tract infections

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Introduction

Escherichia coli is the most common cause of urinary tract infections worldwide. The increasing rates of antibiotic resistance among *E. coli* strains are worrying and have limited the empiric

treatment options for these infections [1]. Beta-lactam antibiotics are of substantial importance in the treatment of infections due to their broad-spectrum antibacterial activity and selective toxicity, but their extensive usage over recent decades has led to resistance to them [2]. The production of AmpC β-lactamase enzymes, which confer resistance to a wide range of β-lactam antibiotics, excluding carbapenems and fourth-generation cephalosporins, is one of the key mechanisms of bacterial resistance to these types of antibiotics [3]. AmpC-type β-lactamases are in the C group of Ambler and their common genotypes include bla_{FOX}, bla_{MOX}, bla_{CIT}, bla_{DHA}, bla_{EBC}, and bla_{ACC}. Originally, these genes were transferred chromosomally, but they can also be disseminated by plasmids or other mobile elements [4]. The acquisition of plasmid-mediated AmpC (pAmpC) β-lactamases genes by organisms such as *E. coli* has prompted major concerns because it leads to the emergence and wide dissemination of multidrug-resistant (MDR) strains that are clinically and epidemiologically very important [5]. The phenotypic diagnosis of AmpC-mediated resistance is difficult due to misleading results and may lead to treatment failure. In addition, the Clinical and Laboratory Standards Institute (CLSI) has not introduced any technique for the phenotypic detection of AmpC production in micro-organisms [6]. Molecular tests such as polymerase chain reaction (PCR) to identify the presence of pAmpC genes, along with phenotypic methods, are essential. However, they are not routinely performed in clinical microbiology laboratories [7]. Awareness of the prevalence of AmpC β-lactamase-producing micro-organisms could be very valuable for achieving more accurate epidemiological results, as well as controlling their spread. Hence, this study was designed to assess the frequency of pAmpC β-lactamases in *E. coli* isolates causing urinary tract infections, utilizing both phenotypic and genotypic methods.

Materials and Methods

Study Setting and Bacterial Isolation

In a 7-month period (from August 2020 to March 2021), 95 consecutive non-repetitive urine isolates of *E. coli* were obtained from clinical diagnostic laboratories and medical centers affiliated with Abadan University of Medical Sciences in southwestern Iran. Isolates were accurately identified through routine microbiological diagnostic tests [8]. The confirmed isolates were stored in a trypticase soy broth (Merck Co., Darmstadt, Germany) containing 20% glycerol at −70°C until antibiograms and molecular tests.

Antibiotic Susceptibility Testing

Antibiograms of the confirmed *E. coli* isolates for 10 standard antibiotics (Roscoe, Taastrup, Denmark), including tetracycline (30 µg), amoxicillin (25 µg), cefoxitin (30 µg), piperacillin/tazobactam (100/10 µg), cefpodoxime (30 µg), cephalothin (30 µg), ceftriaxone (30 µg), amikacin (30 µg), ceftizoxime (30 µg), colistin (10 µg), were carried out using the standard disk diffusion method as recommended by the CLSI [9]. The *E. coli* ATCC 25922 strain was used for quality control. In this study, 8 different classes of antibiotics including penicillins; first-, second-, and third-generation cephalosporins; tetracyclines; aminoglycosides; polymyxins; and β-lactamase inhibitors were used. Isolates that were resistant to at least 1 agent in 3 or more classes of antimicrobials were considered MDR.

Screening and Confirmatory Testing of AmpC Production

All isolates were first screened for the probable production of AmpC β-lactamases by placing a cefoxitin disk (30 µg) on Mueller-Hinton agar (Merck Co.) [10]. Isolates that conferred an inhibition zone diameter of <18 mm were considered potential producers of AmpC and subjected to the confirmatory phenotypic test. Screening-positive AmpC producers were confirmed by an inhibitor-based method on a disk containing boronic acid [11]. Briefly, a lawn culture of the tested isolates was made on a Mueller-Hinton agar plate using 0.5 McFarland solutions. Two disks of cefoxitin (30 µg) with and without phenylboronic acid (400 µg) was placed onto the agar surface and the results were interpreted. If the growth inhibition zone around the antibiotic with phenylboronic acid compared to the disk containing only cefoxitin was 5 mm or greater, the isolate was considered to be an AmpC producer.

Detection of pAmpC Genes

The genomic DNA of the isolates was extracted using a commercial extraction kit (SinaClon BioScience Co., Tehran, Iran) following the manufacturer's instructions. The detection of 6 different families of pAmpC β-lactamases, including bla_{FOX}, bla_{MOX}, bla_{CIT}, bla_{DHA}, bla_{EBC}, and bla_{ACC}, was performed as previously described by Perez-Perez and Hanson [12]. All primers were synthesized and provided by SinaClon (SinaClon BioScience Co.).

Ethics Approval

This research was approved by the local ethics committee of the Abadan University of Medical Sciences (No. IR.ABADANUMS.REC.1399.070), Abadan, Iran, and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all the participants.

Results

In this study, the highest antibiotic resistance was observed first towards amoxicillin (90.5%) and then to cephalothin (81.1%). Of the 95 *E. coli* isolates tested, 60 (63.2%) were resistant to cefoxitin, while 9 (9.5%) showed intermediate resistance. Alternatively, of 69 (72.6%) isolates insensitive to cefoxitin, 58 (61.1%), 55 (57.9%), and 52 (54.7%) isolates were resistant to ceftriaxone, cefpodoxime, and ceftizoxime, respectively. The isolates showed the highest susceptibility to colistin (92.6%), followed by piperacillin/tazobactam (82.1%) and amikacin (62.1%) (Table 1). Among the all studied isolates, 49 (51.6%) exhibited MDR phenotypes, with 8 different profiles. The group VII resistance pattern of strains (ceftizoxime, cefoxitin, ceftriaxone, cefpodoxime, amoxicillin, cephalothin) was the most prevalent (20.4%) (Table 2). Of all 95 *E. coli* isolates investigated for β-lactamases, 60 (63.2%) were suspected to be AmpC producers by the disk agar diffusion cefoxitin screening test. After performing the confirmatory phenotypic test, the frequency of confirmed isolates producing AmpC β-lactamase was determined to be 14.7% (14/95). Concerning the antibiogram results, the resistance rate of AmpC β-lactamase-producing strains to all antimicrobial agents was higher than that of 81 AmpC-negative strains (Figure 1). Multiplex PCR for pAmpC genes revealed that 8 (8.4%), 4 (4.2%), and 3 (3.2%) of *E. coli* strains tested positive for the bla_{DHA}, bla_{CIT}, and bla_{EBC} genes, respectively. The other 3 genotypes (bla_{MOX}, bla_{FOX}, and bla_{ACC}) were not detected in any strains (Table 3).

Discussion

The growing frequency of antibiotic resistance as a primary public health concern in developing and undeveloped countries has resulted in the failure to treat various infections, higher handling costs, limited therapeutic choices, and increased mortality and morbidity [13]. pAmpC β-lactamases have become increasingly significant from a therapeutic standpoint, and their identification will be useful for both monitoring and epidemiological and infection control strategies [5]. In this study, the level of antibiotic resistance of *E. coli* isolates ranged from 7.4% to 90.5%. Antimicrobial susceptibility testing revealed that the bacterial isolates studied had relatively high resistance to β-lactam antibiotics (amoxicillin, cephalothin, cefoxitin, ceftriaxone, cefpodoxime, and ceftizoxime). Meanwhile,

Table 1. The antimicrobial susceptibility profile of all isolates ($n = 95$)

Antimicrobials	Resistant (%)	Intermediate (%)	Susceptible (%)
Ceftriaxone	58 (61.1)	7 (7.4)	30 (31.6)
Cefoxitin	60 (63.2)	9 (9.5)	26 (27.4)
Cefpodoxime	55 (57.9)	2 (2.1)	38 (40.0)
Cephalothin	77 (81.1)	4 (4.2)	14 (14.7)
Ceftizoxime	52 (54.7)	4 (4.2)	39 (41.1)
Amikacin	27 (28.4)	9 (9.5)	59 (62.1)
Tetracycline	52 (54.7)	3 (3.2)	40 (42.1)
Amoxicillin	86 (90.5)	0	9 (9.5)
Piperacillin/tazobactam	16 (16.8)	1 (1.1)	78 (82.1)
Colistin	7 (7.4)	0	88 (92.6)

Table 2. Multidrug-resistance patterns of isolates ($n = 49$)

Resistance pattern	Resistance phenotypes	*n* (%)
I	KF, AN, AMX	9 (18.4)
II	CZX, CRO, FOX, TZP	3 (6.1)
III	CZX, FOX, CRO, CPD, TET, AMX	8 (16.3)
IV	CRO, KF, AN, AMX, FOX	5 (10.2)
V	CZX, TZP, FOX, AN, TET, AMX, CPD	7 (14.3)
VI	CZX, CRO, CPD, CS, AMX, TZP, AN, TET	1 (2.0)
VII	CZX, FOX, CRO, CPD, AMX, KF	10 (20.4)
VIII	CZX, FOX, CRO, CPD, TET, AMX, KF, AN, TZP	6 (12.2)

KF, cephalothin; AN, amikacin; AMX, amoxicillin; CZX, ceftizoxime; CRO, ceftriaxone; FOX, cefoxitin; TZP, piperacillin/tazobactam; CPD, cefpodoxime; TET, tetracycline; CS, colistin.

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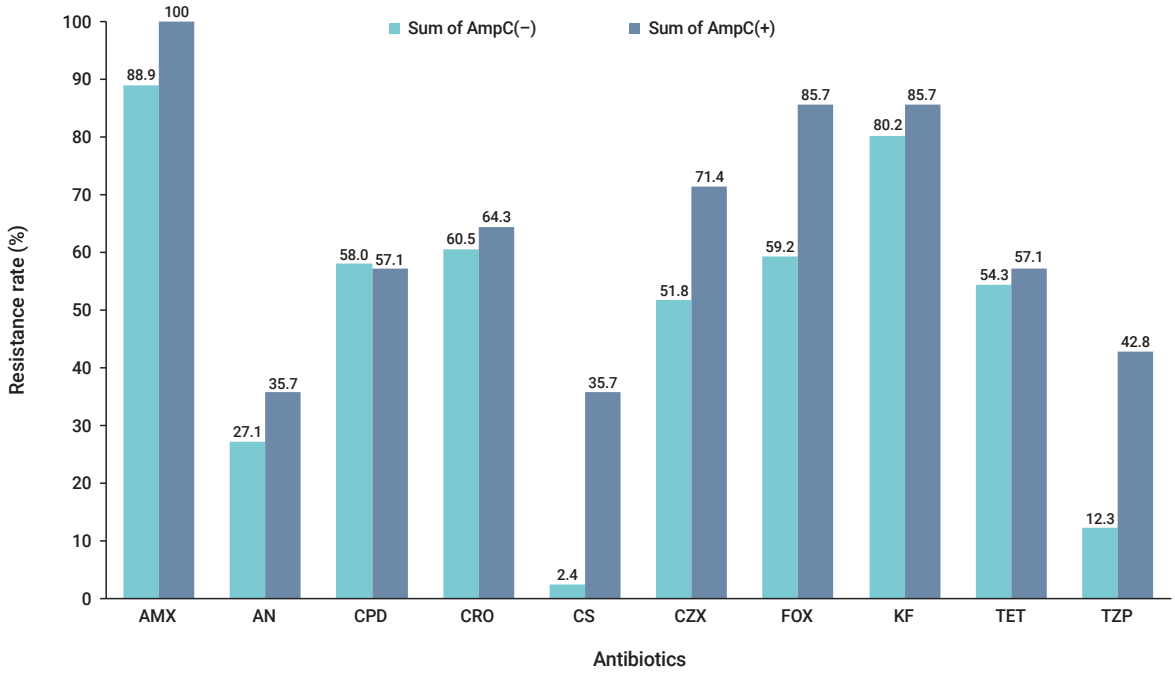

Figure 1. Comparison of antibiotic resistance among AmpC-positive and -negative strains (%).
AMX, amoxicillin; AN, amikacin; CPD, cefpodoxime; CRO, ceftriaxone; CS, colistin; CZX, ceftizoxime; FOX, cefoxitin; KF: cephalothin; TET, tetracycline; TZP, piperacillin/tazobactam.

Table 3. Distribution of plasmid-mediated AmpC β-lactamase genes among *Escherichia coli* strains ($n = 95$)

AmpC positive	*n* (%)
Cefoxitin screening test	60 (63.2)
Confirmatory phenotypic test	14 (14.7)
Multiplex polymerase chain reaction	15 (15.8)
AmpC gene	
bla_{DHA}	8 (8.4)
bla_{CIT}	4 (4.2)
bla_{EBC}	3 (3.2)
bla_{MOX}	0
bla_{FOX}	0
bla_{ACC}	0

they had the highest susceptibility to colistin, piperacillin/tazobactam, and amikacin. Comparable results were reported by some previous studies from Nepal [13], India [14], and Iran [15]. As shown in Figure 1, AmpC producers exhibited significantly higher resistance rates than AmpC-negative strains. This observation extensively corroborated the findings of previous authors, associating AmpC production with increasing resistance to diverse antimicrobial classes [16–18]. Antimicrobial resistance is linked to the increasing spread of MDR strains, and since infections caused by these organisms are extremely difficult to treat, recognition and awareness of their prevalence in the community are crucial [19]. In the present study, almost half of the *E. coli* isolates (49, 51.6%) were found to be MDR, which is in line with the results of other studies carried in Iran [20] and Gabon [1] and contrary to that of Bala et al. [14]. There are several reasons for the reduction in sensitivity towards newer generations of antibiotics, including bacterial production of β-lactam ring hydrolyzing enzymes such as extended-spectrum β-lactamases, AmpC β-lactamases, and metallo-β-lactamases [21]. Although various screening and confirmatory phenotypic methods for AmpC β-lactamase have been introduced, most of them are not suitable for routine use in diagnostic laboratories. However, the inhibitor-based method, which serves as a reliable confirmatory marker with acceptable negative predictive values, has been employed by many researchers to detect AmpC production [17]. As expected, in the present study, screening and confirmatory phenotypic tests yielded different results, and the production of AmpC β-lactamase was confirmed in only 14.7% (14/95) of cefoxitin-resistant isolates. Studies conducted in Spain (14.2%) [22], Nigeria (15.2%) [23], and Iran (15.1%) [5] have reported equivalent frequencies. However, the frequency rate of AmpC production in the present study was lower than those found in other studies conducted in India [14], Bahrain [24], Iran [25], and Egypt [6], which reported rates of 47.1%, 87%, 54.4%, and 73.4%, respectively. There are several reasons

for this discrepancy in the findings, including differences in the diagnostic methods employed, geographical location, study participants, and the study period. Various studies have been conducted on the prevalence of the pAmpC genes at different time points and in different countries, which can provide valuable information about AmpC-type resistance over time and its course. According to the multiplex PCR assay results of this study, 3 types of pAmpC cluster genes (bla_{CIT}, bla_{DHA}, and bla_{DHA}) were detected in 15 isolates (15.8%). The prevalence of the bla_{DHA}, bla_{CIT}, and bla_{EBC} genes in *E. coli* isolates was also found to be 8.4%, 4.2%, and 3.2%, respectively. These results were in accordance with a previous study reported by Kazemian et al. [26], from Iran. Although some studies have reported the coexistence of bla_{DHA}, bla_{EBC}, and bla_{CIT} in *E. coli* isolates [15,25,27], only 1 pAmpC gene family was detected in the strains of our study. Some limitations of this study included the lack of data on the molecular typing of the strains and the sequencing of pAmpC cluster genes. In addition, due to a lack of funding, only the presence of pAmpC genes was targeted, and other potential associates of cefoxitin resistance, such as chromosomal hyperproduction or purine loss mutations, were not investigated.

Conclusion

This is the first study to investigate pAmpC β-lactamases using phenotypic and molecular methods among patients in southwestern Iran, and our research results could provide useful information to support the development of antimicrobial strategies for better infection control in healthcare facilities. In this study, a significant percentage of MDR was observed among AmpC-producing strains. The PCR results also showed that 15.8% of phenotypically confirmed isolates harbored pAmpC β-lactamase genes (bla_{DHA}, bla_{CIT}, and bla_{EBC}), and the most prevalent genotype belonged to bla_{DHA} (8.4%).

Notes

Ethics Approval

This research was approved by the local ethics committee of the Abadan University of Medical Sciences (No. IR.ABADANUMS.REC.1399.070), Abadan, Iran, and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all the participants.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Availability of Data

All data generated or analyzed during this study are included in this published article. For other data, these may be available through the corresponding author upon reasonable request.

Authors' Contributions

Conceptualization: NJ; Data curation: NJ; Formal analysis: NJ; Investigation: all authors; Methodology: KA, ZR; Project administration: NJ; Resources: all authors; Software: all authors; Supervision: NJ; Validation: all authors; Visualization: all author; Writing–original draft: NJ; Writing–review & editing: NJ. All the authors reviewed and approved the final draft, and are responsible for all aspects of the work.

Additional Contributions

This research was derived from the general physician thesis by Zahra Rahmani under the supervision of Dr. N Jomehzadeh, which was approved by Abadan University of Medical Sciences, Abadan, Iran. The authors appreciate all those who contributed directly or indirectly to this research.

References

1. Mouanga Ndzime Y, Onanga R, Kassa Kassa RF, et al. Epidemiology of community origin Escherichia coli and Klebsiella pneumoniae uropathogenic strains resistant to antibiotics in Franceville, Gabon. Infect Drug Resist 2021;14:585–94.
2. Dalhoff A. Selective toxicity of antibacterial agents-still a valid concept or do we miss chances and ignore risks? Infection 2021; 49:29–56.
3. Najjuka CF, Kateete DP, Lodiongo DK, et al. Prevalence of plasmid-mediated AmpC beta-lactamases in Enterobacteria isolated from urban and rural folks in Uganda. AAS Open Res 2020;3:62.
4. Santiago GS, Goncalves D, da Silva Coelho I, et al. Conjugative plasmidic AmpC detected in Escherichia coli, Proteus mirabilis and Klebsiella pneumoniae human clinical isolates from Portugal. Braz J Microbiol 2020;51:1807–12.
5. Saffar H, Asgari Niaraki N, Ghahroudi Tali A, et al. Prevalence of AmpC β-lactamase in clinical isolates of Escherichia coli, Klebsiella spp., and Proteus mirabilis in a Tertiary Hospital in Tehran, Iran. Jundishapur J Microbiol 2016;9:e39121.
6. Helmy MM, Wasfi R. Phenotypic and molecular characterization of plasmid mediated AmpC β-lactamases among Escherichia coli, Klebsiella spp., and Proteus mirabilis isolated from urinary tract infections in Egyptian hospitals. Biomed Res Int 2014;2014:171548.
7. Chakraborty A, Adhikari P, Shenoy S, et al. Characterization of plasmid mediated AmpC producing Escherichia coli clinical isolates from a tertiary care hospital in South India. Indian J Pathol Microbiol 2014;57:255–8.
8. Jomezadeh N, Farajzadeh A, Javaherizadeh H, et al. The prevalence of asymptomatic bacteriuria in infants and children. Pak Pediatr J 2011;35:13–6.
9. Clinical Laboratory Standards Institute (CLSI). Performance standards for antimicrobial susceptibility testing, 30th ed. CLSI supplement 100. Wayne: CLSI; 2020.

10. Polsfuss S, Bloemberg GV, Giger J, et al. Practical approach for reliable detection of AmpC beta-lactamase-producing Enterobacteriaceae. J Clin Microbiol 2011;49:2798–803.
11. Coudron PE. Inhibitor-based methods for detection of plasmid-mediated AmpC beta-lactamases in Klebsiella spp., Escherichia coli, and Proteus mirabilis. J Clin Microbiol 2005;43:4163–7.
12. Perez-Perez FJ, Hanson ND. Detection of plasmid-mediated AmpC beta-lactamase genes in clinical isolates by using multiplex PCR. J Clin Microbiol 2002;40:2153–62.
13. Aryal SC, Upreti MK, Sah AK, et al. Plasmid-mediated AmpC β-lactamase CITM and DHAM genes among gram-negative clinical isolates. Infect Drug Resist 2020;13:4249–61.
14. Bala R, Singh VA, Gupta N, et al. Prevalence, multidrug-resistance and risk factors for AmpC β-lactamases producing Escherichia coli from hospitalized patients. J Infect Dev Ctries 2020;14:1466–9.
15. Robatjazi S, Nikkhahi F, Niazadeh M, et al. Phenotypic identification and genotypic characterization of plasmid-mediated AmpC β-lactamase-producing Escherichia coli and Klebsiella pneumoniae isolates in Iran. Curr Microbiol 2021;78:2317–23.
16. Ibrahim ME, Abbas M, Al-Shahrai AM, et al. Phenotypic characterization and antibiotic resistance patterns of extended-spectrum β-lactamase- and AmpC β-lactamase-producing gram-negative bacteria in a referral hospital, Saudi Arabia. Can J Infect Dis Med Microbiol 2019; 2019:6054694.
17. Akya A, Elahi A, Chegene Lorestani R, et al. Antibiotic resistance and phenotypically and genotypically AmpC beta-lactamases among Escherichia coli isolates from outpatients. J Gorgan Univ Med Sci 2019;20:108–14.
18. Tekele SG, Teklu DS, Tullu KD, et al. Extended-spectrum beta-lactamase and AmpC beta-lactamases producing gram negative bacilli isolated from clinical specimens at International Clinical Laboratories, Addis Ababa, Ethiopia. PLoS One 2020;15:e0241984.
19. Pokharel S, Raut S, Adhikari B. Tackling antimicrobial resistance in low-income and middle-income countries. BMJ Glob Health 2019; 4:e002104.
20. Koshesh M, Mansouri S, Hashemizadeh Z, et al. Identification of extended-spectrum β-lactamase genes and AmpC-β-lactamase in clinical isolates of Escherichia coli recovered from patients with urinary tract infections in Kerman, Iran. Arch Pediatr Infect Dis 2017;5:e37968.
21. Kakoullis L, Papachristodoulou E, Chra P, et al. Mechanisms of antibiotic resistance in important gram-positive and gram-negative pathogens and novel antibiotic solutions. Antibiotics (Basel) 2021; 10:415.
22. Gomara M, Lopez-Calleja AI, Iglesia B, et al. Detection of carbapenemases and other mechanisms of enzymatic resistance to β-lactams in Enterobacteriaceae with diminished susceptibility to carbapenems in a tertiary care hospital. Enferm Infecc Microbiol Clin (Engl Ed) 2018;36:296–301.
23. Ogefere HO, Osikobia JG, Omoregie R. Prevalence of AmpC β-lactamase among Gram-negative bacteria recovered from clinical specimens in Benin City, Nigeria. Trop J Pharm Res 2016;15:1947–53.
24. Joji RM, Al-Mahameed AE, Jishi TA, et al. Molecular detection of plasmid-derived AmpC β-lactamase among clinical strains of Enterobacteriaceae in Bahrain. Ann Thorac Med 2021;16:287–93.
25. Motamedifar M, Mohebi S, Hadadi M, et al. The prevalence of ESBL and AmpC β-lactamases in uropathogenic isolates of Escherichia coli in a tertiary care hospital in Southwest Iran. Gene Rep 2020;20: 100747.
26. Kazemian H, Heidari H, Ghanavati R, et al. Phenotypic and genotypic characterization of ESBL-, AmpC-, and carbapenemase-producing Klebsiella pneumoniae and Escherichia coli Isolates. Med Princ Pract 2019;28:547–51.
27. Mohamudha PR, Harish BN, Parija SC. Molecular description of plasmid-mediated AmpC β-lactamases among nosocomial isolates of Escherichia coli & Klebsiella pneumoniae from six different hospitals in India. Indian J Med Res 2012;135:114–9.

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Brief Report

COVID-19 vaccine safety monitoring in Republic of Korea from February 26, 2021 to October 31, 2021

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ABSTRACT

Objectives: This study aimed to present data on reported adverse events following coronavirus disease 2019 (COVID-19) vaccination in Republic of Korea from February 26 to October 31, 2021, and to determine whether any significant patterns emerged from an analysis of the characteristics of suspected adverse event cases for each type of vaccine.
Methods: Adverse events following COVID-19 vaccination reported by medical doctors and forensic pathologists were analyzed. Cases of suspected anaphylaxis were classified using the Brighton Collaboration definition.
Results: By October 31, 2021, a total of 353,535 (0.45%) adverse events were reported after 78,416,802 COVID-19 vaccine doses. Of the adverse events, 96.4% were non-serious and 3.6% were serious. The most frequently reported adverse events were headache, myalgia, and dizziness. Of the 835 reported deaths after COVID-19 vaccination, 2 vaccine-related deaths were confirmed. Suspected anaphylaxis was confirmed in 454 cases using the Brighton Collaboration definition.
Conclusion: The commonly reported symptoms were similar to those described in clinical trials. Most reported adverse events were non-serious, and the reporting rate of adverse events following COVID-19 vaccination was higher in women than in men (581 vs. 315 per 100,000 vaccinations). Confirmed anaphylaxis was reported in 5.8 cases per 1,000,000 vaccinations.

Keywords: COVID-19; Safety; Vaccines

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Introduction

The first vaccines against coronavirus disease 2019 (COVID-19) introduced in Korea were the AstraZeneca COVID-19 vaccine (ChAdOx1 nCoV-19), a viral vector vaccine, and the Pfizer-BioNTech COVID-19 vaccine (BNT162b2), an mRNA vaccine. These vaccines were approved for use as 2 doses for those aged ≥18 years by the Ministry of Food and Drug Safety on February 10, 2021 and March 5, 2021, respectively, and were recommended by the Korea Advisory

Committee on Immunization Practices (KACIP). Next, the Janssen COVID-19 vaccine (Ad26.COV2.S) and the Moderna COVID-19 vaccine (CX-024414) were approved on April 7 and May 21, 2021, respectively. Thus, 4 COVID-19 vaccines are currently being used in the vaccination campaign in Korea. In accordance with the vaccination plan announced on January 28, 2021, vaccination was started on February 26; however, following European reports of an association between the AstraZeneca COVID-19 vaccine and rare thrombosis with thrombocytopenia syndrome (TTS), the recommended age group eligible for this vaccine was changed to >30 years on April 12, 2021 and then to >50 years on June 29, 2021 [1–3]. At the time of establishing the vaccination plan, adolescents aged ≤17 years were excluded. On August 25, the KACIP recommended vaccination for children aged 12 to 17 years and pregnant women. In Korea, in accordance with the Infectious Disease Control and Prevention Act, doctors and forensic pathologists report adverse events following immunization (AEFI) to the web-based COVID-19 vaccination management system regardless of the clinical severity of the event or the determination of causality. Reported adverse events are classified as serious if they involve hospitalization in the intensive care unit, life-threatening illness, permanent disability, a congenital anomaly, a birth defect, or death.

This study collected and analyzed data on adverse events after COVID-19 vaccination to provide an early warning that the safety of COVID-19 vaccines may require further investigation and to detect any possible new side effects.

Materials and Methods

From February 26, 2021, when COVID-19 vaccination began, to October 31, 2021, 78,416,802 doses were administered in Korea. The characteristics of the 353,535 adverse events reported on the COVID-19 vaccination management system were analyzed by sex, age, and vaccine type. Suspected cases of anaphylaxis were classified into 5 levels using the World Health Organization Brighton Collaboration definition, and cases of levels 1 through 3 were classified as anaphylaxis [4]. Since the current activity was conducted and authorized by the Korea Disease Control and Prevention Agency, the purpose was to disseminate information to the public, and the data are presented in aggregated format, the current study falls under a category of exemptions from the government regulations for ethical board review.

Results

From February 26, 2021 to October 31, 2021, 353,535 adverse events were reported, with a reporting rate of 0.45%. Of these, 340,715 (96.4%) were common adverse events such as myalgia, fever, and headache, and 12,820 cases (3.6%) were serious adverse events such as admission to the intensive care unit or death.

The reporting rate of adverse events per 100,000 vaccinations was 581 for women and 315 for men, corresponding to a rate approximately half of that of women. The reporting rate by age group was highest in the age group of 20 to 29 years (515 per 100,000 doses), and the reporting rate decreased as age increased. The reporting rate among those aged >75 years was 280 per 100,000 doses. The adverse event reporting rate by vaccine type was 522 per 100,000 doses after the AstraZeneca COVID-19 vaccine, 368 per 100,000 doses after the Pfizer-BioNTech COVID-19 vaccine, 623 per 100,000 doses after the Moderna COVID-19 vaccine, and 575 per 100,000 doses after the Janssen vaccine (Table 1).

The AstraZeneca COVID-19 vaccine showed the largest difference in the reporting rate according to age and the dose administered. In particular, the reporting rate of adverse events was very high after the first vaccination in those aged <30 years, whereas it was lower among those aged ≥30 years, and those aged ≥75 years had a relatively low reporting rate compared to the other 2 COVID-19 vaccines (Figure 1). The current status of vaccination by age is presented in the supplementary (Table S1). By October 31, 21,994,707 first doses of the Pfizer-BioNTech COVID-19 vaccine and 22,501,177 second doses were administered. The Pfizer-BioNTech COVID-19 vaccine showed a different pattern from the AstraZenica COVID-19 vaccine in terms of adverse events by age and dose. A high rate of reported adverse events was only observed after the second dose in those aged ≥75 years. Moreover, the adverse event reporting rate by age group was relatively consistent, unlike what was observed for AstraZeneca (Figure 1).

Although the most frequent symptoms were slightly different for each vaccine, the top 3 most frequently reported adverse events were headache, myalgia, and dizziness (Figure 2). The distribution of adverse event symptoms can be found in the supplementary (Table S2).

Of the 1,400 suspected cases of anaphylaxis that were reported, 1,278 cases were evaluated by provincial rapid response teams. Of these, 454 cases were confirmed as anaphylaxis through a case evaluation according to the anaphylaxis pictorial level of certainty algorithm and review by the vaccination damage investigation team, and approximately 5.8 cases per 1,000,000 vaccinations (454 cases out of 78,416,802 doses) were reported. By vaccine type, 4.2 cases per 1,000,000 doses occurred after the AstraZeneca COVID-19 vaccine, 6.6 cases per 1,000,000 doses after the

Table 1. Reports of adverse events after receipt of COVID-19 vaccines, by recipients' sex, age group, and type of vaccine: Republic of Korea, February 26, 2021 to October 31, 2021 (n = 353,535)

Variable	Vaccination dose	Adverse events reported[a] (per 100,000)				
		Sub-total	Non-serious adverse event[b]	Serious adverse event[c]		
				Death	Anaphylaxis	Others
Total	78,416,802	353,535 (451)	340,715 (434)	835 (1)	1,400 (2)	10,585 (13)
Sex						
Female	40,018,486	232,683 (581)	225,463 (563)	319 (1)	959 (2)	5,942 (15)
Male	38,398,316	120,852 (315)	115,252 (300)	516 (1)	441 (1)	4,643 (12)
Age group (y)						
≤ 19	2,207,056	8,998 (408)	8,788 (398)	1 (< 1)	54 (2)	155 (7)
20–29	11,503,735	59,283 (515)	58,018 (504)	18 (< 1)	366 (3)	881 (8)
30–49	24,527,651	117,615 (480)	114,426 (467)	73 (< 1)	605 (2)	2,511 (10)
50–74	33,388,114	148,608 (445)	142,361 (426)	377 (1)	318 (1)	5,552 (17)
≥ 75	6,790,246	19,031 (280)	17,122 (252)	366 (5)	57 (1)	1,486 (22)
AstraZeneca vaccine	20,342,226	106,287 (522)	101,028 (497)	348 (2)	313 (2)	4,598 (23)
1st dose	11,109,331	82,428 (742)	78,454 (706)	223 (1)	275 (1)	3,476 (17)
2nd dose	9,232,895	23,859 (258)	22,574 (244)	125 (1)	38 (0)	1,122 (12)
Pfizer-BioNTech	44,577,886	163,920 (368)	157,892 (354)	427 (1)	828 (2)	4,773 (11)
1st dose	21,994,707	89,615 (407)	85,915 (391)	228 (1)	660 (3)	2,812 (13)
2nd dose	22,501,177	74,114 (329)	71,788 (319)	199 (1)	168 (1)	1,959 (9)
3rd dose	82,002	191 (233)	189 (230)	0	0	2 (2)
Moderna	12,010,627	74,788 (623)	73,621 (613)	48 (< 1)	211 (2)	908 (8)
1st dose	6,556,837	39,418 (601)	38,550 (588)	30 (< 1)	180 (3)	658 (10)
2nd dose	5,453,736	35,370 (649)	35,071 (643)	18 (< 1)	31 (1)	250 (5)
3rd dose	54	0	0	0	0	0
Janssen	1,486,063	8,540 (575)	8,174 (550)	12 (1)	48 (3)	306 (21)

COVID-19, coronavirus disease 2019.

[a]Data were calculated using information on suspected adverse events after COVID-19 vaccination reported by medical facilities or doctors. The results do not suggest causality between the vaccines and adverse events. [b]Non-serious adverse events include the following: common symptoms such as redness at the site of injection, pain, swelling, muscle pain, fever, headache, chills, and others. [c]Serious adverse events include the following: death, suspected anaphylaxis, and major adverse events (adverse events of special interest, admission in the intensive care unit, life-threatening events, permanent disability/sequelae, and others).

Pfizer-BioNTech COVID-19 vaccine, 14.1 cases per 1,000,000 doses after the Janssen vaccine, and 4.3 cases per 1,000,000 doses after the Moderna COVID-19 vaccine. The median time of anaphylaxis symptom onset was 10 minutes after vaccination, and 83.9% of cases occurred within 30 minutes of vaccination (Tables 2 and 3).

The number of deaths reported after vaccination was 835. The number of reported deaths was slightly higher in men than in women, and deaths were mostly reported in older age groups. In rapid responses to cases of death, the Vaccine Injury Investigation Committee (VIIC) evaluated the causality between vaccination and death based on medical records, death certificates, autopsy results, and epidemiological investigation results. To date, among the death cases, there have been 2 cases of confirmed causality: 1 case of myocarditis after the Pfizer-BioNTech COVID-19 vaccine and 1 case of TTS after the AstraZeneca COVID-19 vaccine.

Discussion

In Korea, 2 types of COVID-19 vaccines (AstraZeneca and Pfizer-BioNTech) were initially administered in priority groups such as residents of long-term care hospitals and facilities, health care workers, and the elderly. After that, Janssen and Moderna COVID-19 vaccines were also rolled out. The type of vaccine was allocated to specific groups in accordance with the recommended conditions of use as follows: the Pfizer-BioNTech COVID-19 vaccine for those 75 years and older with mobility, who were required to visit vaccination centers, and the AstraZeneca vaccine for residents of long-term care facilities who received on-site vaccination. The KACIP then changed the age recommendation for the COVID-19 vaccines due to a possible link between the

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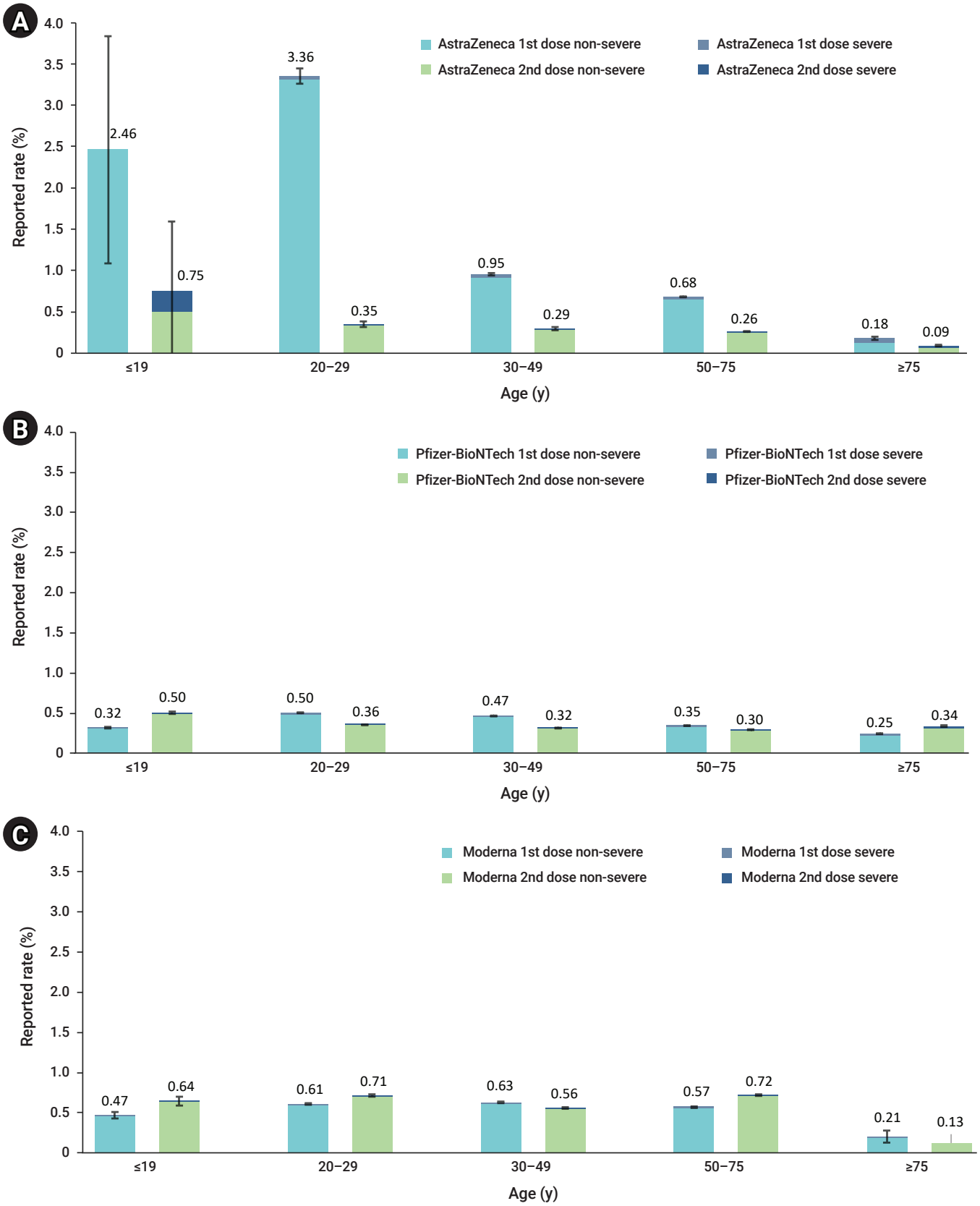

Figure 1. Adverse events reporting rates following coronavirus disease 2019 (COVID-19) vaccination by age group (February 26 to October 31, 2021).
Error bars represent 95% confidence intervals. (A) AstraZeneca, (B) Pfizer-BioNTech, (C) Moderna.

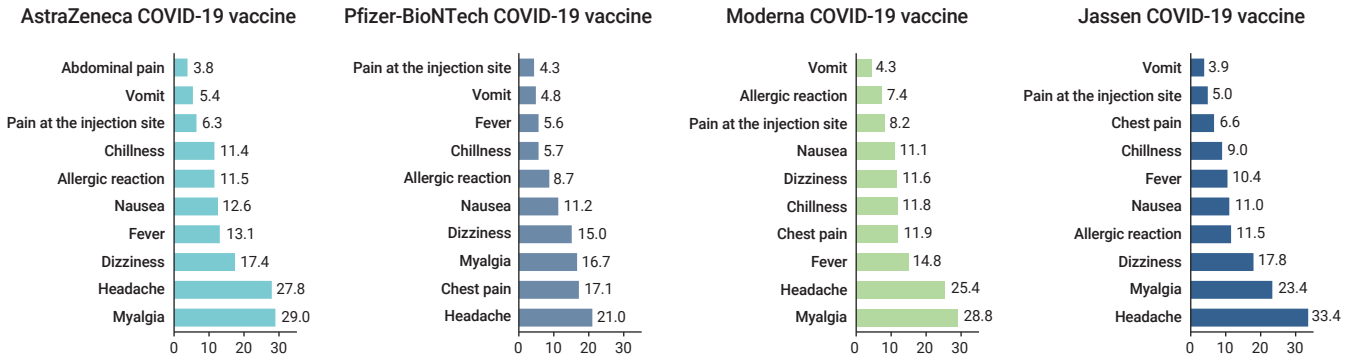

Figure 2. The proportion of symptoms of adverse events following coronavirus disease 2019 (COVID-19) vaccination by vaccine type (February 26 to October 31, 2021).
Values represent percentages and include duplicated reports.

Table 2. Classification of anaphylaxis and anaphylaxis-like acute allergic reactions in recipients of COVID-19 vaccines using the Brighton Collaboration case definition, Republic of Korea, February 26 to October 31, 2021, Republic of Korea Brighton Collaboration case definition level

Vaccine doses	Total (*n* = 78,416,802)	AstraZeneca (*n* = 20,342,226)	Pfizer-BioNTech (*n* = 44,577,886)	Moderna (*n* = 12,010,627)	Janssen (*n* = 1,486,063)
Total	1,278	296	790	144	48
Levels 1–3 (per 1,000,000)	454 (5.8)	85 (4.2)	296 (6.6)	52 (4.3)	21 (14.1)
Level 4	627	131	403	72	21
Level 5	197	80	91	20	6

The Brighton Collaboration case definition uses combinations of symptoms to define levels of diagnostic certainty. Levels 1 to 3 represent the highest level of diagnostic certainty that a reported case represents anaphylaxis (with level 1 > level 2 > level 3); level 4 is a case reported as anaphylaxis with insufficient evidence to meet any of the levels of diagnostic certainty; and level 5 is a case that did not meet the case definition (not a case of anaphylaxis) [1]. This study considered levels 1, 2, and 3 as anaphylaxis cases.
COVID-19, coronavirus disease 2019.

COVID-19 vaccine and adverse events.

As of October 31, 2021, the rate of adverse events was 0.45% out of 78,416,802 doses administered. As has been described in the results from clinical trials and reports from other countries, vaccine recipients can expect non-serious adverse events during the early post-vaccination stage, including myalgia, headache, fever, and pain at the site of injection [5,6]. In addition, the reporting rate decreased from 1.8% in the first week of vaccination to 0.45% in the 35th week [7].

Reviewing the 835 deaths reported after COVID-19 vaccination after October 31, 2021, it was found that most of the individuals who died were older adults or had underlying medical conditions; their deaths were not related to the COVID-19 vaccine. Similar to a previous report from the United States [8], anaphylaxis had a higher incidence among women, with 8.3 cases per million doses (320 out of 38,398,316) compared to 3.3 cases per million doses (134 out of 40,018,486) in men. Furthermore, 68.1% of confirmed anaphylaxis cases occurred within 15 minutes; therefore, the previous recommendation that all recipients should be monitored for 15 to 30 minutes after vaccination in an observation room at vaccination sites should be adjusted.

This study has some limitations. The data for adverse events reported by medical institutions might underestimate the actual incidence because they are reported only for those who visited medical institutions. However, AEFIs for COVID-19 vaccinations are relatively likely to be reported since they relate to newly introduced vaccines. Compared to previous reports of adverse events after mass vaccinations during the 2009 H1N1 influenza epidemic in Korea, far more cases are being reported now. Not all reported symptoms and diagnoses were verified or confirmed by the VIIC. The AEFI cases reported in Korea are similar to those reported in the United Kingdom [5].

According to the World Health Organization, the widespread use of COVID-19 vaccines, including in the elderly and in patients with underlying health conditions, will unfortunately mean that there will be deaths and cases of serious illness that are purely coincidental and unrelated to vaccinations [9]. Since the beginning of COVID-19 vaccination, more than 3.2 billion people have already been vaccinated worldwide.

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Table 3. Characteristics of confirmed cases of anaphylaxis following COVID-19 vaccination, Republic of Korea, February 26 to October 31, 2021

Characteristic	AstraZeneca (*n* = 85)	Pfizer-BioNTech (*n* = 296)	Janssen (*n* = 21)	Moderna (*n* = 52)	Total (*n* = 454)
Age group (y)	51 (21–87)	34.5 (17–91)	37 (30–51)	30.5 (19–51)	37 (17–91)
≤ 19	NR	18 (6.1)	NR	2 (3.9)	20 (4.4)
20–29	12 (14.1)	100 (33.8)	NR	21 (40.4)	133 (29.3)
30–49	27 (31.8)	120 (40.5)	19 (90.5)	28 (53.8)	194 (42.7)
50–74	45 (52.9)	36 (12.2)	2 (9.5)	1 (1.9)	84 (18.5)
≥ 75	1 (1.2)	22 (7.4)	NR	NR	23 (5.1)
Sex					
Female	71 (83.5)	210 (70.9)	6 (28.6)	33 (63.5)	320 (70.5)
Male	14 (16.5)	86 (29.1)	15 (71.4)	19 (36.5)	134 (29.5)
Symptom onset[a)]	10 (1–1,200)	10 (0–900)	5 (1–530)	10.5 (1–210)	10 (0–1,200)
≤ 15 min	58 (68.2)	199 (67.2)	18 (85.7)	34 (65.4)	309 (68.1)
≤ 30 min	66 (77.6)	248 (83.8)	20 (95.2)	47 (90.4)	381 (83.9)
> 30 min	19 (22.4)	48 (16.2)	1 (4.8)	5 (9.6)	73 (16.1)
Prior allergic reaction					
Yes	35 (41.2)	91 (30.7)	3 (14.3)	15 (28.8)	144 (31.7)
No	50 (58.8)	205 (69.3)	18 (85.7)	37 (71.2)	310 (68.3)
Symptom					
Sensation of throat closure	35 (41.2)	114 (38.5)	7 (33.3)	20 (38.5)	176 (38.8)
Upper airway swelling	16 (18.8)	34 (11.5)	1 (4.8)	3 (5.8)	54 (11.9)
Nausea/vomiting	40 (47.1)	114 (38.5)	13 (61.9)	18 (34.6)	185 (40.7)
Tachycardia	32 (37.6)	79 (26.7)	5 (23.8)	17 (32.7)	133 (29.3)
Difficulty breathing without wheeze or stridor	34 (40.0)	58 (19.6)	1 (4.8)	12 (23.1)	105 (23.1)
Angio-edema	20 (23.5)	46 (15.5)	3 (14.2)	5 (9.6)	74 (16.3)
Hypotension	29 (34.1)	133 (44.9)	12 (57.1)	28 (53.8)	202 (44.5)
Decreased level of consciousness	13 (15.3)	40 (13.5)	4 (19.0)	11 (21.2)	68 (15.0)
Other	4 (4.7)	35 (11.8)	2 (9.5)	1 (1.9)	42 (9.3)
Treatments received					
Epinephrine	60 (70.5)	209 (70.6)	19 (90.5)	29 (55.8	317 (69.8)
Anti-histamine	54 (63.5)	143 (48.3)	12 (57.1)	26 (50.0)	235 (51.8)
Steroid	46 (54.1)	132 (44.6)	9 (42.8)	24 (46.2)	211 (46.5)
Other	5 (5.9)	92 (31.1)	1 (4.8)	6 (11.5)	104 (22.9)
Treatment progress					
Hospitalized	13 (15.3)	32 (10.8)	NR	5 (9.6)	50 (11.0)
Outpatient/emergency room	72 (84.7)	264 (89.2)	21 (100)	47 (90.4)	404 (89.0)

Data are presented as median (range) or *n* (%).
COVID-19, coronavirus disease 2019; NR, not reported.
[a)]Multiple responses were possible.

It has been established that the AstraZeneca and Janssen COVID-19 vaccines are associated with TTS, a very rare condition [10]. Considering that COVID-19 vaccines are new, it is necessary to regularly scrutinize the causal relationship between reported adverse events and COVID-19 vaccines and whether the number of observed AEFIs exceeds that of expected cases by chance.

Supplementary Material

Table S1. COVID-19 vaccines administered by age group; **Table S2.** Symptoms after the first and second doses of COVID-19 vaccines by vaccine type (per 100,000 doses). Supplementary data are available at https://doi.org/10.24171/j.phrp.2021.0310.

Notes

Ethics Approval
Since the current activity was conducted and authorized by the public health authorities, and the purpose was to disseminate information to the public, the current study was exempted from ethical board review.

Conflicts of Interest
The authors have no conflicts of interest to declare.

Funding
None.

Availability of Data
The data used in this study is protected under the Personal Information Protection Act.

Authors' Contributions
Conceptualization: YK, YKL; Data curation: IH, KP; Formal analysis: IH, TEK; Investigation: IH, TEK; Methodology: KP, YK; Validation: YK, YKL; Writing–original draft: IH, YK; Writing–review & editing: all authors.

Additional Contributions
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References

1. Korea Disease Control and Prevention Agency (KDCA). Update on COVID-19 and COVID-19 vaccination. Cheongju: KDCA; 2021.
2. European Medicines Agency (EMA). Press briefing on the conclusion of the assessment of the Pharmacovigilance Risk Assessment Committee (PRAC) of Vaxzevria (previously COVID-19 Vaccine AstraZeneca) and thromboembolic events. Amsterdam: EMA; 2021.
3. Korea Disease Control and Prevention Agency (KDCA). Updated action plan for COVID-19 vaccination 2021. Cheongju: KDCA; 2021.
4. Lee E, Lee YK, Kim TE, et al. Reports of anaphylaxis after coronavirus disease 2019 vaccination, South Korea, 26 February to 30 April 2021. Euro Surveill 2021;26:2100694.
5. Medicines and Healthcare Products Regulatory Agency (MHRA). Summary of yellow card reporting [Internet]. MHRA; 2021 [cited 2021 Nov 15]. Available from: https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting.
6. Gee J, Marquez P, Su J, et al. First month of COVID-19 vaccine safety monitoring-United States, December 14, 2020-January 13, 2021. MMWR Morb Mortal Wkly Rep 2021;70:283–8.
7. Oh HK, Kim EK, Hwang I, et al. COVID-19 vaccine safety monitoring in the Republic of Korea: February 26, 2021 to April 30, 2021. Osong Public Health Res Perspect 2021;12:264–8.
8. Shimabukuro TT, Cole M, Su JR. Reports of Anaphylaxis After Receipt of mRNA COVID-19 Vaccines in the US-December 14, 2020-January 18, 2021. JAMA 2021;325:1101–2.
9. World Health Organization (WHO). Statement for healthcare professionals: how COVID-19 vaccines are regulated for safety and effectiveness [Internet]. Geneva: WHO; 2021 Jun 11 [cited 2021 Nov 15]. Available from: https://www.who.int/news/item/11-06-2021-statement-for-healthcare-professionals-how-covid-19-vaccines-are-regulated-for-safety-and-effectiveness.
10. World Health Organization (WHO). Coronavirus disease (COVID-19): vaccine [Internet]. Geneva: WHO [cited 2021 Nov 15]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/covid-19-vaccines.

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MANUSCRIPT PREPARATION

General Requirements

All manuscripts must be in grammatically correct English and should be created using MS Word. The manuscript must be double-spaced and written in an A4 page format. Do not leave a space between paragraphs. Only a single font (preferably Times New Roman) should be used in 11 point with margins of 2.5 cm.

- All pages including the title page should be paginated consecutively. All numbers should be written in Arabic numerals throughout the manuscript except for the first word of the sentence. Texts should be justified on both sides and not hyphenated and headings should be in bold letters, aligned in the center. If possible, avoid using abbreviated words at the beginning of sentences.
- Abbreviations: Where a term/definition is repeatedly referred to (i.e., 3 times in the text), it is written in full when it first appears, followed by the subsequent abbreviation in parentheses (even if it was previously defined in the abstract); thereafter, the abbreviation is used.
- Gene nomenclature: Current standard international nomenclature for genes should be adhered to. Genes should be typed in italic font and include the accession number. For human genes, use the genetic notation and symbols approved by the HUGO Gene Nomenclature Committee (http://www.genenames.org/) or refer to PubMed (http://www.ncbi.nlm.nih.gov/sites/entrez).
- Units: Système International (SI) units must be used, with the exception of blood pressure values, which are to be reported in mmHg. Please use the metric system for expressions of length, area, mass, and volume. There should be a space between the numerals and the unit symbol. When indicating time, the 24-hour system is to be used.
- Math formulae: Present simple formulae in the line of normal text where possible and use the solidus (/) instead of a horizontal line for small fractional terms, e.g., X/Y. In principle, variables are to be presented in italics. Powers of e are often more conveniently denoted by "exp." Number consecutively any equations that have to be displayed separately from the text (if referred to explicitly in the text).

Reporting Guidelines for Specific Study Designs

For specific study designs, such as randomized control studies, studies of diagnostic accuracy, meta-analyses, observational studies, and non-randomized studies, authors are encouraged to consult the reporting guidelines relevant to their specific research design. A good source of reporting guidelines is the EQUATOR Network (https://www.equator-network.org/) and NLM (https://www.nlm.nih.gov/services/research_report_guide.html).

Manuscript Types

PHPR publishes editorials, original articles, review articles, brief reports, short communications, editorials, correspondence, and book reviews.

- **Original articles** are papers containing results of basic and clinical investigations, which are sufficiently well documented to be acceptable to critical readers. These articles should be written in the following format: title page; abstract and keywords; main body (introduction, materials and methods, results, discussion, conclusion [if any]); references; and tables and figure legends. Manuscript limitations are 5,000 words, excluding the abstract, references, and tables and figure legends.
- **Review articles** provide concise reviews of subjects important to medical researchers, and can be written by an invited medical expert. These have the same format as original articles, but the details may be more flexible depending on the content. Manuscript limitations are 6,500 words from introduction to conclusion, 100 references, 10 figures and 10 tables. The abstract should not exceed 200 words, and must be written as one unstructured paragraph.
- **Brief reports** deal with issues of importance to biomedical researchers. The maximum length of the manuscript should be 2,000 words, including tables and figures.
- **Short communications** follow the general rules of the

original article. The maximum length of the manuscript should be 3,000 words, including tables and figures.

- **Editorials** provide invited perspective on an area of PHRP, dealing with very active fields of research, current interests, fresh insights, and debates. An abstract is not required and a brief unstructured text should be prepared. Although editorials are normally invited or written by an editor, unsolicited editorials may be submitted. Manuscript limitations are 1,000 words and 20 references.
- **Correspondence** is a comment from readers regarding a published article with a reply from the authors of the article. Manuscript limitations are 500 words, 2 tables/figures, and 5 references.
- **Book reviews** may be published. Please dispatch a book to the editorial office if you think the book is essential to public health personnel.

Title Page

Title page should include (1) the title of the article (less than 50 words); (2) name of the authors (first name, middle initial, last name in capitals) and institutional affiliation including the name of department(s) and institution(s) of each author; (3) name, full address (including the postal code) of the institutional affiliation, telephone and e-mail address of the corresponding author; (4) a running title of 50 characters or less including blank spaces; and (5) notes (disclaimers). Notes include ethics approval and consent to participate, conflict of interest, funding, availability of data, authors' contributions, additional contributions, and ORCID of all authors. All contributors who do not meet the criteria for authorship as defined above should be listed in an additional contribution section. Examples of those who might be acknowledged include a person who provided purely technical help, writing assistance, or a department chair who provided only general support. Authors should disclose whether they had any writing assistance and identify the entity that paid for this assistance.

Abstract and Keywords

An abstract and 3–6 relevant keywords (in alphabetical order) are required. Abstracts should be no more than 250 words in length. Abstracts should be structured, with the following section headings: Objectives, Methods, Results, Conclusion. For selecting keywords, refer to the MeSH browser (http://www.ncbi.nlm.nih.gov/mesh).

Main Body

- **Introduction** should provide concise yet sufficient background information about the study to provide the readers with a better understanding of the study, avoiding a detailed literature survey or a summary of the results.
- **Materials and methods** should contain detailed procedures of the study or experiment including investigation period, methods of subject selection, and information on subjects such as age, sex or gender, and other significant features, in order to enable the experiment to be repeated. A procedure that has been already published or standardized should be described only briefly using literature citations. Clinical trials or experiments involving laboratory animals or pathogens must elaborate on the animal care and use and experimental protocols, in addition to mentioning approval from the relevant committees. The sources of special equipment and chemicals must be stated with the name and location of the manufacturer (city and country). All statistical procedures used in the study and criteria for determining significance levels must be described. Ensure correct use of the terms "sex" (when reporting biological factors) and "gender" (identity, psychosocial or cultural factors). Unless inappropriate, report the sex and/or gender of study participants, the sex of animals or cells, and describe the methods used to determine sex or gender. If the study involved an exclusive population (only one sex, for example), authors should justify why, except in obvious cases (e.g., prostate cancer). Authors should define how they determined race or ethnicity, and justify its relevance. Institutional Review Board approval and informed consent procedures can be described as follows: The study protocol was approved by the Institutional Review Board of OOO (IRB No: OO-OO-OO). Informed consent was confirmed (or waived) by the IRB.
- **Results** should be presented in logical sequence. Only the most important observations should be emphasized or summarized, and the main or the most important findings should be mentioned first. Tables and figures must be numbered in the order they are cited in the text, kept to a minimum, and should not be repeated. Supplementary materials and other details can be separately presented in an appendix. The authors should state the statistical method used to analyze the results (statistical significance of differences) with the probability values given in parentheses.
- **Discussion** should contain an interpretation and explanation of the results and important aspects of the study, followed by the conclusions drawn from them. Information already mentioned in the Introduction or Results sections should

not be repeated and the main conclusions of the study may be presented in the discussion.

- **Conclusion** (if any) must be linked with the purpose of the study stated in the abstract, and clearly supported by the data produced in the study. New hypotheses may be stated when warranted, but must be clearly labeled.

References

Authors are responsible for the accuracy and completeness of their references and for correct text citations.

- References are presented with [ ] following a surname in the main text, such as Kim [1] and Kim et al. [2]. When a reference is cited within the content, it is shown as [3] or [4,5] at the end. References should be searchable online.
- The last names and initials of all the authors (up to 3) should be included. For articles with more than 3 authors, list the first 3 authors only followed by "et al."
- References cited in tables or figure legends should be included in sequence at the point where the table or figure is first mentioned in the main text.
- Do not cite abstracts unless they are the only available reference to an important concept.
- Uncompleted work or work that has not yet been accepted for publication (i.e., an "unpublished observation" or "personal communication" should not be cited as a reference). In the references list, references should be limited to those cited in the text and listed in the order in which they appear in the text. The journals should be abbreviated according to the style used in the list of journals indexed in the NLM Journal Catalog (http://www.ncbi.nlm.nih.gov/nlmcatalog/journals).
- Use of DOI is highly encouraged. Note that missing data will be highlighted at the proof stage for the author to correct.
- Other types of references not described below should follow the ICMJE Recommendations (https://www.nlm.nih.gov/bsd/uniform_requirements.html).

Please refer to the following examples.

- **Journal articles**
  1. Park AK, Kim IH, Kim J, et al. Genomic surveillance of SARS-CoV-2: distribution of clades in the Republic of Korea in 2020. Osong Public Health Res Perspect 2021; 12:37-43.
  2. Hyun J, Lee JH, Park Y, et al. Interim epidemiological and clinical characteristic of COVID-19 28 cases in South Korea. Public Health Wkly Rep 2020;13:464-74. Korean.
  3. Gultekin V, Allmer J. Novel perspectives for SARS-CoV-2 genome browsing. J Integr Bioinform 2021 Mar 15 [Epub]. https://doi.org/10.1515/jib-2021-0001.
- **Books**
  4. Riffenburgh RH, Gillen DL. Statistics in medicine. 4th ed. London: Academic Press; 2020.
  5. Miller DD. Minerals. In: Damodaran S, Parkin KL, editors. Fennema's food chemistry. 5th ed. Boca Raton, FL: CRC Press; 2017. p. 627-80.
  6. Ministry of Employment and Labor. Statistics on occupational injuries and illnesses, 2008. Gwacheon, KR: Ministry of Employment and Labor; 2009.
- **Websites**
  7. World Health Organization (WHO). COVID-19 vaccines [Internet]. Geneva: WHO; 2021 [cited 2021 Mar 15]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/covid-19-vaccines.
- **Conference papers**
  8. Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, IE. Berlin: Springer; 2002. p. 182-91.
- **Dissertation**
  9. Park HY. The role of the thrombomodulin gene in the development of myocardial infarction [dissertation]. Seoul: Yonsei University; 2000.

Tables and Figures

Tables should be simple, self-explanatory, and supplemental, and should not duplicate the text or figures. Each table must be on a separate page, not exceeding 1 page when printed, and have a concise and informative title. The tables should be numbered with Arabic numerals in consecutive order. Each column should be appropriately headed with units in parentheses if numerical measures are given. All units of measurements and concentrations must be indicated. Footnotes are followed by the source notes, other general notes, abbreviation, notes on specific parts of the table ([a], [b], [c], [d]...), and notes on level of probability (*, **, *** for *p*).

Figures should be numbered with Arabic numerals consecutively in figure legends. The figures must not be interfered and must be clearly seen. The legend for each light microscopic image should include name of the stain and magnification. Electron microscopic images should contain an internal scale marker. All figures may be altered in size by the editor. The legends should briefly describe the data shown, explain abbreviations or reference points, and identify all units, mathematical expressions, abscissas,

ordinates, and symbols.

Figures that are drawn or photographed professionally should be sent as JPG or PPT files. However, if an article receives approval for publication, files must be submitted as .tiff or .pdf. Each figure must have a caption explaining the figure. The preferred size of the images is 8 × 8 cm but 16.5 cm in width × 8 cm in length is also acceptable. It is authors' full responsibility to submit images of sufficient quality for accurate reproduction and to approve the final color galley proof. All images must be correctly exposed, sharply focused, and prepared in files of 500 dpi or more.

When tables and figures are mentioned together in the text, they should be presented in parentheses as follows: (Table 1; Figure 1), (Tables 1, 2; Figures 1–3).

Appendix and Supplemental Data

If any materials are not enough to be included in the main text such as questionnaires, they can be listed in the Appendix. Any supplementary materials that help the understanding of readers or contain too great an amount of data to be included in the main text may be placed as supplementary data. Not only a recording of the abstract, text, audio or video files, but also data files should be added here.

FINAL PREPARATION FOR PUBLICATION

Final Version

After the paper has been accepted for publication, the author(s) should submit the final version of the manuscript. The names and affiliations of the authors should be double-checked, and if the originally submitted image files were of poor resolution, higher-resolution image files should be submitted at this time. Symbols (e.g., circles, triangles, squares), letters (e.g., words, abbreviations), and numbers should be large enough to be legible on reduction to the journal's column widths. All symbols must be defined in the figure caption. If references, tables, or figures are moved, added, or deleted during the revision process, renumber them to reflect such changes so that all tables, references, and figures are cited in numeric order.

Manuscript Corrections

Before publication, the manuscript editor will correct the manuscript such that it meets the standard publication format. The author (s) must respond within 48 hours when the manuscript editor contacts the corresponding author for revisions. If the response is delayed, the manuscript's publication may be postponed to the next issue.

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To correct errors in published articles, the corresponding author should contact the journal's editorial office with a detailed description of the proposed correction. Corrections that profoundly affect the interpretation or conclusions of the article will be reviewed by the editors. Corrections will be published as corrigenda (corrections of the author's errors) or errata (corrections of the publisher's errors) in a later issue of the journal.

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The author does not have pay publication charges for open access. The KDCA will pay to make the article open access.

NOTICE: These recently revised instructions for authors will be applied beginning with the June 2021 issue.

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OSONG PUBLIC HEALTH
AND RESEARCH PERSPECTIVES

Author's checklist

General Requirements

- ▫ The corresponding author (or the representative author of the co-corresponding authors) is the submitter of this manuscript.
- ▫ All manuscripts should be written in English.
- ▫ The main document with manuscript text and tables should be prepared in an MS Word (docx) or RTF file format.
- ▫ Manuscripts should be double-spaced in A4-size pages.
- ▫ Manuscripts should include line numbers.
- ▫ All pages should be numbered consecutively, starting with the abstract.

Title Page

- ▫ The title page and the rest of the manuscript text are prepared separately in two files (not combined together).
- ▫ The title page is arranged in the following order: article title, authors' full name(s), affiliation(s), and corresponding author's information, running title (less than 50 characters), notes.
- ▫ The notes section including (1) ethics approval and consent to participate, (2) conflicts of interest, (3) funding, (4) availability of data, (5) author contributions, (6) additional contributions, and ORCID is in title page, not in the manuscript.

Abstract

- ▫ The abstract does not exceed 250 words (Objectives, Methods, Results, Conclusion) for original articles and 200 words for reviews. Up to 3–6 keywords are listed at the bottom of the abstract.

Main Text

- ▫ The manuscript is organized according to following sequence: Title page, Abstract and keywords, Main text, References, Tables, and Figure legends.

Tables and Figures

- ▫ All tables and figures are numbered in the order of their appearance in a main text.
- ▫ Tables are included at the end of the manuscript as editable text and not as images.
- ▫ Figures are as separate files, in jpg, ppt, tiff, or pdf format.

References

- ▫ References are listed in proper format.
- ▫ All references listed in the reference section are cited in the text and vice versa.

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The authors hereby transfer all copyrights in and to the manuscript named above in all forms and media, now or hereafter known, to the Korea Disease Control and Prevention Agency effective if and when the paper is accepted for publication in the *Osong Public Health and Research Perspectives*. The authors reserve all proprietary right other than copyright, such as patent rights.
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All authors are responsible for recognizing any conflict of interest that could bias their work in the acknowledgments, disclosing all financial support and any other personal connections. Please check the appropriate box below:

- ☐ No author of this paper has a conflict of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included in this manuscript.

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