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Pediatric preventable diseases

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Pediatric preventable diseases

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Editorial: Pediatric preventable diseases

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Preventable diseases are a leading cause of disability and death worldwide and prevention remains the most efficacious medical intervention, even though its effect may not be immediately apparent. The advancement of research and technology plays a crucial role in reducing child mortality from preventable diseases, leading also to improved neurophysiological development for children and adolescents.

The World Health Organization advocates for national strategies to strengthen ongoing control of infectious diseases and reduce associated transmission, mortality, and morbidity. To develop appropriate immunization recommendations and implement public health policies, timely epidemiologic evaluations are crucial in understanding the circulation of infectious diseases and identifying high-risk populations in the pediatric age group. For instance, orphans and vulnerable children in African areas are a high-risk group for infectious diseases, including human immunodeficiency virus infection, as shown by socioeconomic analyses. Education of families also plays a major role: education of mothers on diarrhea management has been linked to reduced death rates (Shah et al.; Gessesse and Tarekegn).

Immunization is an effective approach to prevent the substantial impact of preventable infectious diseases. Through vaccination, smallpox has been eradicated, and the prevalence of preventable infectious diseases, such as measles, diphtheria, and whooping cough, has been significantly reduced worldwide. The implementation of immunization programs has also led to a decrease in hospitalization costs and socio-economic burden. Currently, new vaccines and immunization strategies are being developed and adapted to the epidemiological burden of preventable infectious diseases. For example, different immunization options have being developed to prevent respiratory syncytial virus (RSV) infections in children. Of note, evidence indicates that RSV is responsible for almost 13 million cases of lower respiratory tract infections, 2.2 million hospitalizations, and 66,300 deaths globally each year Bont et al.

Effective health messages, immunization strategies, and risk factor awareness require robust communication strategies. It is crucial to communicate the benefits of immunization strategies to parents using simple and appropriate language. Using communication methods such as social media can enhance the dissemination of health information, facilitate interactions, boost family confidence and compliance, and positively influence parental vaccination acceptance. These strategies can help reassure parents about the safety and efficacy of immunization strategies and counteract infodemics Di Mauro et al.

To enhance the quality of life of children and prevent disabilities in later life, high-quality research should focus on major modifiable risk factors for non-infectious preventable pediatric diseases such as tobacco use, unhealthy diets, and physical inactivity. Early detection of high-risk behaviors is essential to achieving this goal. For instance, identifying predictors of childhood obesity can prevent long-term consequences such as metabolic syndrome and diabetes Byeon.

Similarly, reducing pollution can decrease respiratory infections in children, preventing long-term sequelae such as asthma. Evidence indicates that short and long-term exposure to air pollutants, including PM2.5, may lead to respiratory diseases in children, regardless of country development status. Fine particulate's small size enables easy penetration of human barriers, causing tissue damage and lung inflammation Liu et al.

Screening guidelines should also be widely implemented to prevent diseases, such as amblyopia, a common neurodevelopment disorder among children Yan et al.

Secondary prevention is also essential to reduce the burden and prevent long-term consequences. For instance, the rising number of myopia cases in adolescents emphasizes the need for developing strategies to slow the progression of visual impairment and its consequences. Multifocal lenses have been proven an effective approach to controlling myopia progression, thereby avoiding complications such as macular degeneration, retinal detachment, glaucoma, and premature cataracts Chen et al.

Creating a safe environment through preventive measures is crucial in avoiding pediatric diseases and disabilities caused by unintentional injuries. The ingestion of foreign bodies is a common clinical problem, particularly in the youngest age group, aged 6 months to 3 years. These children may be unaware of the risks associated with pediatric foreign body ingestion, particularly in cases of accidental ingestion of magnets or chemicals Ding et al.

Author contributions

EB and AET contributed equally to the plan and the writing of the editorial.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Association Between Air Pollutants and Pediatric Respiratory Outpatient Visits in Zhoushan, China

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Objective: This study aimed to explore the time-series relationship between air pollutants and the number of children's respiratory outpatient visits in coastal cities.

Methods: We used time series analysis to investigate the association between air pollution levels and pediatric respiratory outpatient visits in Zhoushan city, China. The population was selected from children aged 0–18 who had been in pediatric respiratory clinics for eight consecutive years from 2014 to 2020. After describing the population and weather characteristics, a lag model was used to explore the relationship between outpatient visits and air pollution.

Results: We recorded annual outpatient visits for different respiratory diseases in children. The best synergy lag model found a 10 $\mu g/m^3$ increase in $PM_{2.5}$ for every 4–10% increase in the number of pediatric respiratory outpatient visits ($P < 0.05$). The cumulative effect of an increase in the number of daily pediatric respiratory clinics with a lag of 1–7 days was the best model.

Conclusions: $PM_{2.5}$ is significantly related to the number of respiratory outpatient visits of children, which can aid in formulating policies for health resource allocation and health risk assessment strategies.

Keywords: children, air pollutant, respiratory diseases, outpatients, lag pattern

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HIGHLIGHTS

- Instruct policies of health allocation and health risk assessment regarding childhood respiratory diseases.
- Help verify the relationship between childhood respiratory problems and air pollutants.
- Indicate for every 10 $\mu g/m^3$ increase in $PM_{2.5}$, the number of childhood respiratory outpatient visits increase by 4–10%.
- Significantly contribute to the existing literature by adding developing country data.
- Fill the research gap of establishing the relationship between air pollutants and respiratory diseases in coastal cities.

INTRODUCTION

In China, the unprecedented economic growth and increased population density have led to the increased severity of environmental problems, especially air pollution (1). Since January 2013, severe haze events have affected 800 million people in 75% of China's cities, restricting sustainable societal and economic growth and threatening public health (2, 3).

Air pollution increases economic loss and respiratory disease morbidity and mortality (4–6). Children are at high risk of environmental stress; additionally, a relationship has been observed between childhood respiratory disease severity and air pollutant concentration (7). Respiratory diseases, such as pneumonia, bronchitis, and asthma, are the most common causes of mortality and morbidity in children worldwide (8). Environmental exposure may lead to low pulmonary function in children, increasing the risk of short-term clinical symptoms and adversely affecting pulmonary function. This subsequently increases the risk of adult chronic respiratory diseases resulting in a significant social burden (9–12).

The relationship between air pollution and children's respiratory health is predominantly established in developed countries. In China, previous studies were mostly conducted in northern cities where air pollution was relatively severe and found a relationship between air pollution exposure and increased outpatient visits in children with respiratory problems (13, 14). Only one study in Shanghai used data from a limited range of air pollutants tested before 2013 (15). Recent studies have found a strong link between air pollution and childhood respiratory problems (16–18).

The Chinese government developed several strategies to address regional air pollution. Since 2013, China has constructed air quality monitoring stations across the country and has gradually released real-time monitoring data of air pollutants such as $PM_{2.5}$ and ozone (O_3). In 2016, the Central Committee of the Communist Party of China and the State Council released the Health China 2030 Plan, which emphasizes the strengthening of the management of health-related environmental issues (19). This study investigated the relationship between short-term air pollution exposure and daily hospital admissions in children with respiratory diseases to understand the pertinence and refinement of air quality management policies.

METHODS

Air Pollution and Meteorological Data

Zhoushan City is one of the 27 cities in the central area of the Yangtze River Delta in the northeast of Zhejiang Province. It is a coastal city with a subtropical monsoon climate, a warm winter, cool summer, mild and humid, with sufficient sunlight. By the end of 2018, the annual average $PM_{2.5}$ concentration in Zhoushan was 22 $\mu g/m^3$; additionally, the proportion of days with good daily air quality (AQI) was 94.8%. We collected the average daily records of environmental pollutants ($\mu g/m^3$) from the Zhoushan Environmental Monitoring Center from January 2014 to December 2020, including the average daily levels of $PM_{2.5}$, sulfur dioxide (SO_2), nitrogen dioxide (NO_2), carbon monoxide (CO), and O_3. Additionally, the daily average temperature, relative humidity, and atmospheric pressure of Zhoushan during the same period were obtained from the China Meteorological Data Sharing Service System (http://zshbj.zhoushan.gov.cn/index.html). Finally, the overall air quality data of Zhoushan City was obtained from the comprehensive correction of data collected from Putuo East Port, Dinghai Tain, Feng, and Lincheng New Area.

Study Population

The population of Zhoushan has stably increased from 1.145 million to 1.176 million between 2014 and 2020 (19). This study selected the Zhoushan Hospital as the research site since it is the only tertiary, first-class general hospital in Zhoushan City and is preferred by residents due to its technology, professionalism, service, and advanced facilities and equipment.

Daily pediatric outpatient records from January 2014 to December 2020 were obtained from the Zhoushan Center for Disease Control and Prevention. Outpatient records for respiratory events were coded using J00–J99 and R04–R09 of the International Classification of Diseases, 10th edition. This study included children aged 0–18 years, regardless of history of hospitalization. All data were anonymized to protect participants' privacy. This observational study was approved by the Institutional Review Board of the Shanghai International Medical Center (SIMC-IRB No: 20210513).

Statistical Analysis

A generalized additive model with natural splines was constructed to link data by date to explore the association between ambient air pollutants and daily pediatric respiratory outpatients. Additionally, the associations between daily pediatric respiratory outpatients, daily concentrations of ambient air pollutants ($PM_{2.5}$, PM_{10}, SO_2, O_3, NO_2, and CO), and meteorological factors (temperature, humidity, and atmospheric pressure) were analyzed. A basic model was constructed without air pollutants. Natural spline functions of time and meteorological parameters were incorporated into the model to adjust for confounding effects, with the day of the week (DOW) as a dummy variable. To prevent model multilinearity, we used Spearman's test to examine the correlation between daily concentrations of ambient air pollutants (20).

The model was examined using Akaike's information criterion (AIC). Additionally, partial autocorrelation functions were used to examine the autocorrelations of the residuals. Synthesizing the results from AIC, PACF, 3 df for the relative humidity, and 6 df for the mean temperature were added in our work as indicator variables. The model is described as follows.

$$\log[E(Y_t)] = intercept + ns(time, 6) + ns(temperature, 6) + ns(humidity, 3) + DOW + \sum_{i=1}^{q} \beta_i(X_i)$$

Where: $E(Y_t)$ is the number of expected pediatric outpatients at day t; β_i, the association between the log-relative rate of outpatient visits and air pollutant unit increase; X_i, the

TABLE 1 | Descriptive statistics for daily outpatient visits, concentrations of air pollutants, and weather conditions.

	2014	2015	2016	2017	2018	2019	2020	*P* value
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Pressure (Pa)	1,012.05 (8.36)	1,012.18 (8.74)	1,011.98 (8.62)	1,012.57 (8.17)	1,011.78 (8.68)	1,011.84 (8.70)	1,012.45 (8.46)	0.847
Temperature (°C)	17.04 (7.59)	17.17 (7.40)	17.85 (8.13)	17.83 (8.11)	17.69 (8.11)	17.51 (7.36)	18.02 (7.38)	0.552
Humidity	80.14 (11.66)	80.77 (11.40)	82.30 (11.59)	79.01 (12.04)	81.92 (11.81)	81.34 (11.62)	77.76 (11.79)	<0.001
SO_2 (μg/m^3)	5.83 (4.56)	6.39 (3.74)	8.98 (2.88)	10.21 (2.86)	6.73 (3.28)	4.65 (1.52)	4.87 (1.70)	<0.001
NO_2 (μg/m^3)	22.19 (12.79)	23.42 (13.61)	19.93 (10.85)	18.03 (10.48)	17.55 (10.78)	18.28 (9.55)	17.51 (9.32)	<0.001
CO (mg/m^3)	0.66 (0.24)	0.59 (0.25)	0.66 (0.21)	0.70 (0.20)	0.73 (0.23)	0.57 (0.15)	0.58 (0.18)	<0.001
O_3 (μg/m^3)	89.90 (32.09)	93.90 (32.41)	95.59 (35.15)	101.91 (34.55)	86.41 (32.77)	96.28 (31.31)	97.91 (32.35)	<0.001
PM_{10} (μg/m^3)	57.01 (35.91)	49.43 (31.82)	44.35 (25.49)	46.03 (26.83)	39.58 (23.42)	37.12 (24.60)	29.83 (17.37)	<0.001
$PM_{2.5}$ (μg/m^3)	31.18 (20.67)	31.28 (22.95)	26.76 (17.62)	26.04 (16.80)	23.31 (16.61)	19.82 (14.54)	15.98 (10.97)	<0.001
J00–J06	23.73 (14.83)	29.15 (9.84)	30.51 (9.94)	29.48 (14.09)	30.37 (14.17)	34.89 (12.58)	18.44 (17.04)	<0.001
J09–J18	3.31 (3.06)	1.90 (1.90)	2.68 (2.47)	1.60 (1.81)	2.06 (2.64)	4.57 (3.41)	2.14 (4.15)	<0.001
J20–J22	5.99 (5.64)	9.68 (6.25)	11.14 (7.74)	13.84 (8.58)	18.86 (8.34)	24.21 (10.36)	8.81 (13.06)	<0.001
J30–J39	1.39 (3.07)	0.13 (0.36)	0.04 (0.19)	0.04 (0.19)	0.52 (1.57)	1.45 (3.58)	1.17 (2.58)	<0.001
J40–J47	13.30 (8.26)	10.65 (6.76)	10.32 (6.71)	7.21 (5.52)	6.98 (6.17)	5.67 (4.92)	7.31 (11.95)	<0.001
J60–J70	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.04 (0.19)	<0.001
J80–J84	0.02 (0.14)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.31 (0.96)	<0.001
J85–J86	0.01 (0.09)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.02 (0.17)	<0.001
J90–J94	0.09 (0.34)	0.00 (0.00)	0.00 (0.05)	0.00 (0.00)	0.00 (0.00)	0.00 (0.05)	0.10 (0.36)	<0.001
J95–J99	0.62 (1.72)	0.00 (0.00)	0.00 (0.05)	0.00 (0.00)	0.02 (0.13)	0.00 (0.05)	0.64 (1.88)	<0.001
R04	0.12 (0.39)	0.10 (0.33)	0.10 (0.32)	0.10 (0.35)	0.12 (0.34)	0.10 (0.33)	0.22 (0.53)	<0.001
R05	1.95 (4.72)	0.51 (1.44)	0.28 (0.62)	0.51 (0.83)	1.10 (1.34)	2.26 (2.49)	2.89 (4.88)	<0.001
R06	0.37 (0.67)	0.34 (0.71)	0.20 (0.49)	0.00 (0.05)	0.01 (0.12)	0.01 (0.10)	0.14 (0.55)	<0.001
R07	2.45 (5.69)	0.07 (0.29)	0.10 (0.32)	0.07 (0.26)	0.13 (0.36)	0.16 (0.41)	1.29 (2.81)	<0.001
R09.0–R09.3	0.02 (0.14)	0.00 (0.00)	0.00 (0.05)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.07 (0.32)	<0.001
Respiratory	53.35 (24.79)	52.53 (16.07)	55.38 (18.97)	52.84 (22.45)	60.16 (21.95)	73.32 (22.47)	43.58 (40.88)	<0.001

Coding from the International Classification of Diseases, 10th edition: J00–J99, respiratory diseases; J00–J06, acute upper respiratory tract infection; J09–J18, influenza and pneumonia; J20–J22, other acute lower respiratory infections; J30–J39, other diseases of the upper respiratory tract; J40–J47, chronic lower respiratory disease; J60–J70, pulmonary diseases caused by external substances; J80–J84, other respiratory diseases mainly affecting stroma; J85–J86, suppurative and necrotic condition of lower respiratory tract; J90–J94, other diseases of the pleura; J95–J99, other diseases of the respiratory system; R04, respiratory tract bleeding; R05, cough; R06, abnormal breathing; R07, sore throat and chest pain; R09, other symptoms and signs involving the circulatory and respiratory systems; R09.0, asphyxia; R09.1, pleurisy; R09.2, breathing stops; R09.3, abnormal sputum.

concentration of air pollutants on day t; DOW, the dummy variable; ns (time/temperature/humidity, 6/6/3) is the natural spline function for time, temperature, and humidity with 6/6/3 df.

Relative risks and their confidence intervals (CIs) were estimated to quantify the influence of each air pollutant on pediatric outpatients. All results are presented as relative risk (RR) and 95% CI of daily pediatric respiratory outpatients, which were associated with every unit increase in ambient air pollutant concentration.

Data were stratified according to seasonal patterns, namely, the cool season (November to March), the hot season (June to August), and the transition season (April, May, September, and October). In addition, we built two-pollutant models to evaluate the stability of $PM_{2.5}$ effects after adjustment for co-pollutants. Lag analysis was conducted to observe the aspect of time in revealing some delayed effects of air pollutants on pediatric respiratory outpatients. The following lag structures were used: single-day lag (0–5) and multi-day lag (01,03,05). Considering the lagged and usually non-linear relationship, we applied a distributed lag non-linear model (DLNM) to explore the influence of $PM_{2.5}$ on pediatric respiratory outpatients (21).

All statistical tests were performed using R software (version 4.0.4) with "mgcv" (https://github.com/cran/mgcv) and "DLNM" (https://github.com/gasparrini/dlnm) packages. Statistical significance was set at $P < 0.05$. The results are presented as the percentage change of pediatric respiratory outpatient visits per μg/m^3 increase in $PM_{2.5}$/day.

RESULTS

This study extracted data from 142,825 pediatric patients from the respiratory department between January 1, 2014, to December 31, 2020. The daily average temperature and humidity were 17.58°C and 80.46%, respectively. The mean daily air pollutant concentration of CO was 0.64 mg/m^3, the mean concentrations of other pollutants were 6.8 μg/m^3 for SO_2, 19.55 μg/m^3 for NO_2, 94.55 μg/m^3 for O_3, 24.89 μg/m^3 for $PM_{2.5}$, and 43.32 μg/m^3 for PM_{10}. The average concentrations of air pollutants and weather conditions per year were showed in

Table 1. Children were affected most by the J00–J06 respiratory disease category. Significant differences were observed among disease categories between different years ($P < 0.001$).

Figure 1 shows the correlation between ambient air pollutants. A strong correlation was observed between $PM_{2.5}$ and PM_{10} with a Pearson's correlation coefficient of 0.885. Additionally, $PM_{2.5}$ was correlated with CO, and SO_2 was positively correlated with $PM_{2.5}$, PM10, NO_2, and CO, which suggest collinearity of these variables.

The lag model was used to explore the relationship between air pollution and outpatient volume since they exhibited a hysteresis effect. **Table 2** shows the correlations between air pollutants and daily pediatric outpatients on single-lag (lag0–lag5) and multi-lag days (lag01–lag03). $PM_{2.5}$ was significantly associated with daily pediatric outpatients in the single and multi-pollutant models, either from single-lag or multi-lag models. The correlation coefficient fluctuated between 0.999 and 1.007.

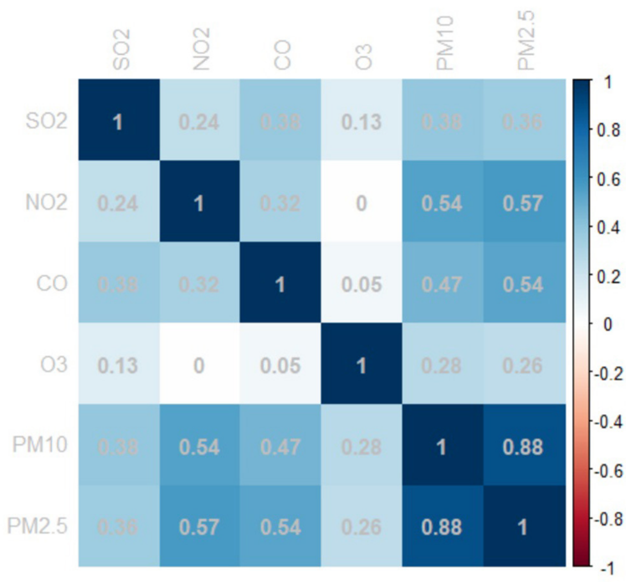

FIGURE 1 | Heatmap of spearman correlation coefficients between daily ambient air pollutants.

The temperature in different seasons affected the number of pediatric outpatient visits. The seasons and effects estimates of different seasons were stratified into three categories according to the mean and 95% CI of daily visits per unit increase in $PM_{2.5}$, PM_{10}, SO_2, O_3, and NO_2 (**Figure 2**). In all seasons, daily pediatric outpatients were significantly correlated with increased $PM_{2.5}$, PM_{10}, SO_2, O_3, and NO_2. In the cold environment, CO was similar to the number of pediatric respiratory outpatients and the other pollutants; on the other hand, CO was negatively correlated with pediatric respiratory outpatients during the hot season. In transition season, CO was highly positively correlated with pediatric respiratory outpatients while other air pollutants effects were unconspicuous.

We explored the daily change in the RR of pediatric respiratory outpatients for an increase in the average $PM_{2.5}$ by one microgram/m^3 for 3, 7, and 30 days. A direct relationship was observed between the RR of pediatric respiratory outcomes and $PM_{2.5}$ average accumulative amount and rate (**Figure 3**). For all cumulative lag days, $PM_{2.5}$ greater than 25 $\mu g/m^3$ was a consistent risk factor (22); particularly, a direct relationship was observed between $PM_{2.5}$ concentration and respiratory risk in children. **Figure 4** shows the RR increase of $PM_{2.5}$ per unit in pediatric respiratory outpatients on different cumulative lag days. In lag days $<$15 days, a direct relationship was observed between $PM_{2.5}$ concentration and RR. When the lag days exceeded 15 days, the lag effect of $PM_{2.5}$ began to weaken.

DISCUSSION

Clinical Implications

This is one of the few studies exploring the relationship between the number of pediatric respiratory outpatient visits and air pollution in developing country. Previous studies, most in developed country, have discussed the impact of air pollutants, such as NO_2 and $PM_{2.5}$, on the development of asthma in children (23–25). Other studies have found that changes in air quality affect the development of respiratory diseases in children, with an incidence rate ratio of ~0.8 for NO_2 and

TABLE 2 | Relative risk (RR) for significant associations between air pollutions and daily respiratory outpatient visits due to lag effects.

	$PM_{2.5}$	$PM_{2.5}$+SO_2	$PM_{2.5}$+CO	$PM_{2.5}$+NO_2	$PM_{2.5}$+O_3
	RR (95%CI)	**RR (95%CI)**	**RR (95%CI)**	**RR (95%CI)**	**RR (95%CI)**
lag0	1.003 (1.003–1.003)	1.002 (1.002–1.002)	1.003 (1.003–1.003)	1.000 (1.000–1.000)	1.004 (1.004–1.004)
lag1	1.003 (1.002–1.003)	1.002 (1.001–1.002)	1.003 (1.003–1.003)	0.999 (0.999–1.000)	1.003 (1.003–1.004)
lag2	1.002 (1.002–1.003)	1.002 (1.001–1.002)	1.003 (1.003–1.003)	1.000 (0.999–1.000)	1.003 (1.003–1.004)
lag3	1.002 (1.002–1.003)	1.002 (1.001–1.002)	1.003 (1.002–1.003)	0.999 (0.999–1.000)	1.003 (1.003–1.004)
lag4	1.002 (1.002–1.003)	1.002 (1.001–1.002)	1.002 (1.002–1.003)	0.999 (0.999–1.000)	1.003 (1.003–1.004)
lag5	1.002 (1.002–1.002)	1.001 (1.001–1.001)	1.002 (1.002–1.002)	0.999 (0.998–0.999)	1.003 (1.003–1.003)
lag01	1.004 (1.003–1.004)	1.003 (1.002–1.003)	1.004 (1.004–1.004)	1.000 (0.999–1.000)	1.005 (1.005–1.005)
lag03	1.005 (1.005–1.006)	1.004 (1.003–1.004)	1.005 (1.005–1.006)	0.999 (0.999–1.000)	1.007 (1.007–1.008)
lag05	1.003 (1.003–1.003)	1.002 (1.002–1.002)	1.003 (1.003–1.003)	1.000 (1.000–1.000)	1.004 (1.004–1.004)

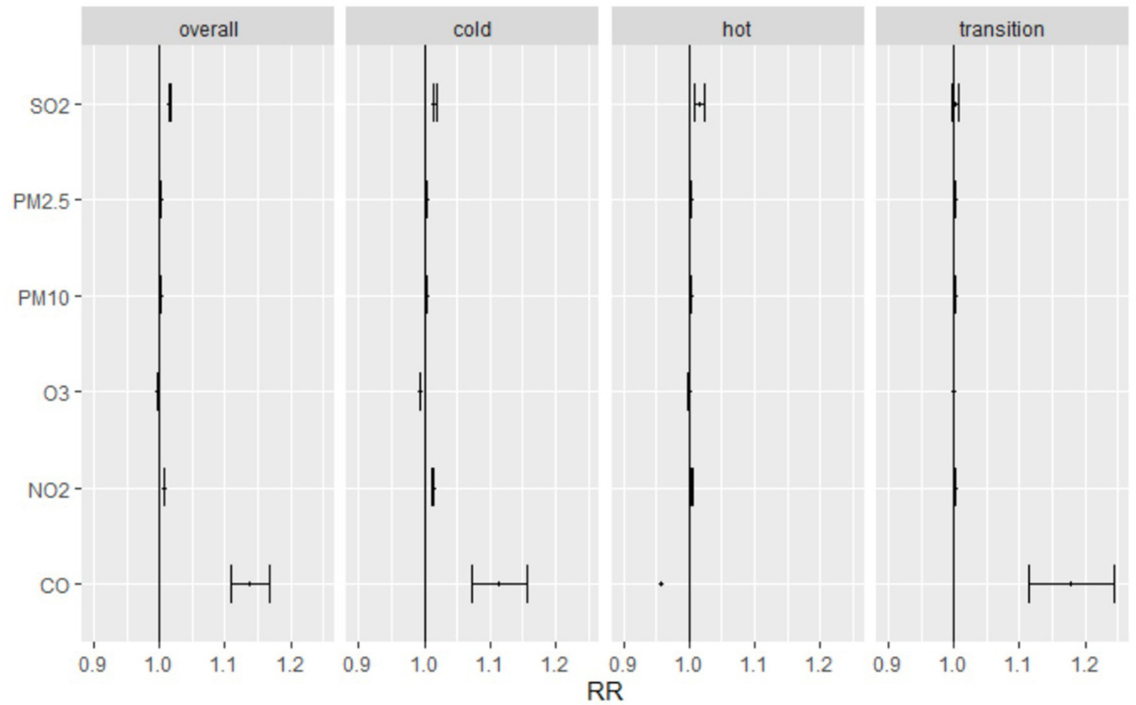

FIGURE 2 | Relative risk and 95% confidence intervals for daily pediatric respiratory outpatients with per unit increase of $PM_{2.5}$, PM_{10}, SO_2, O_3, NO_2 and CO in hot, cold, transition seasons. Cold Season: November to March; Hot Season: June to August; Transition Season: April, May, September, and October.

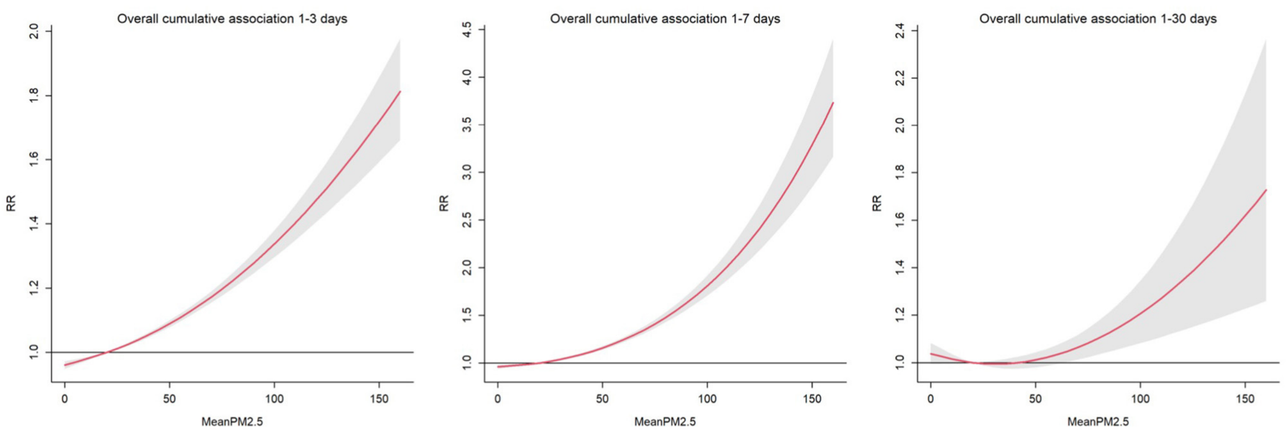

FIGURE 3 | Relative risk and 95% confidence intervals for daily pediatric respiratory outpatients with per unit increase of $PM_{2.5}$ at different cumulation lag days.

$PM_{2.5}$ (26), consistent with other studies in north China (13, 14, 27, 28). However, the ocean currents, climate, and economic development in south coastal cities have led to variations in the type and components of pollutants in different places (29). Another US study found a difference in $PM_{2.5}$ levels between indoors and outdoors (29); however, we found that $PM_{2.5}$ levels were five times elevated. Therefore, three important points are emphasized in this study. First, this study fills the gap of studies focus on the relationship between air pollution and children respiratory diseases in southern Chinese cities. Second, this study emphasized the impact of air pollutants in coastal cities, represented by Zhoushan, and the children with respiratory diseases. Third, the outpatient data of children with respiratory diseases were used. This was a comprehensive overview of all possible variations in childhood respiratory diseases. We used ICD codes to classify diseases to avoid missing relevant diagnoses.

Long-term and short-term exposure to fine particulate matter, such as $PM_{2.5}$ and PM_{10}, may indirectly affect the central nervous system and gastrointestinal tract (30). The small size of the particles allows easy penetration of the body's immune barriers,

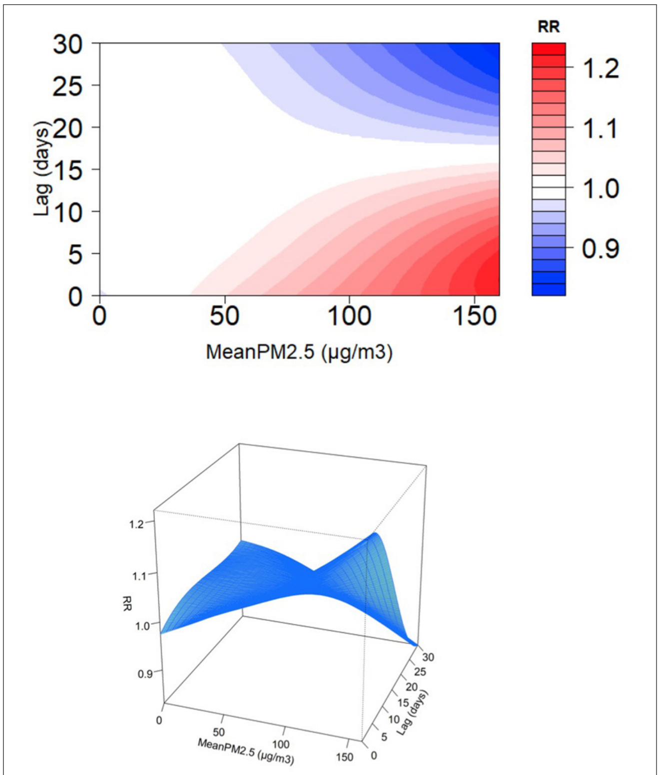

FIGURE 4 | Relative risk for daily pediatric respiratory outpatients with per unit increase of $PM_{2.5}$ at different cumulation lag days.

causing acute and chronic diseases and even premature death (31–33). A synergy exists between these major air pollutants, which travel from the nasal cavity to the trachea or the lungs, where they interact with each other. The mucosal layer, epithelial tissue, or respiratory tract cells coordinate with immune cells such as dendritic cells, macrophages, and monocytes to protect the body from pollutants. However, air pollutants can interrupt the body's homeostasis and release cytokines, which can damage respiratory health (34, 35). The air pollutant-induced excessive release of cellular inflammatory factors and immune cells may cause tissue damage and lung inflammation. Additionally, the immune system may be targeted, leading to immune dysfunction due to damage to immune cells such as natural killer cells (36–38). In addition, organic compounds in air pollutants can release electrons to form superoxides, damaging the body's antioxidants and causing inflammation (39, 40). Other studies have shown that prolonged exposure to low doses of $PM_{2.5}$ causes mast cell overexpression, which leads to increased inflammatory cytokine and histamine production (41, 42). Overall, the number of outpatient visits was the most sensitive indicator of impaired respiratory function. In Yangcheng, China, a time-series analysis found a 1.69% increase in the number of outpatient visits for respiratory diseases caused for every 10 $\mu g/m^3$ increase in $PM_{2.5-10}$ (43), which was consistent with that of eastern and western cities in China (44, 45). These findings prove the relationship between air pollutants and the number of outpatient visits.

Additionally, air pollution and temperature exhibit a synergistic effect. Studies have found that air pollutants in drought conditions can exacerbate chronic respiratory diseases and cause acute reactions (46, 47). Our study found differences in pollutant concentrations at different temperatures. Notably, carbon monoxide concentration was highest in the cold season but lowest in the hot season. This may be attributed to the status of Zhoushan city as a coastal city, where residents burn coal for outdoor heating in the cold season. There was no relationship observed between the mean annual air temperature and the annual trend of pollutant concentration, suggesting the presence of many unknown confounding factors between temperature change and pollutant concentration.

In this study, we found that short-term exposure (within 1 month) to $PM_{2.5}$ was significantly associated with increased pediatric respiratory outpatient visits, especially in the lag mode of 1–7 days. In addition, the lag patterns of 1–3 and 1–30 days showed significantly rising levels. Jiang et al. found a significant association between coarse particulate matter and a 5-day lag in respiratory and cardiovascular outpatient visits (43), Other studies have shown similar results, such as $PM_{2.5}$ being associated with a a-day lag in asthma visits and $PM_{2.5-10}$ being associated with 1-day lag mortality (48, 49). We observed that an increase in $PM_{2.5}$ concentration by 10 $\mu m/m^3$ resulted in ∼4 and 10% in pediatric respiratory clinic visits for a lag of 1–3 days and 1–7 days, respectively. This is much higher than the 1% to 3% observed in previous studies and may be attributed to the growth and development period of the children's respiratory system. During this period, children's lungs are more vulnerable to air pollutants compared to adults. The lag time we observed was between 1 and 7 days, which is similar to previous studies. Additionally, the lag model of pollutant synergy revealed that the combination of $PM_{2.5}$ and O_3 reached a maximum value of 0.7% at lag03, which reached 1.6% in the Yancheng study. This may be attributed to the relatively low level of O_3 and the weak coordination effect of $PM_{2.5}$ caused by Zhoushan city being a coastal city with a lower industrial level and vehicle number than Yancheng.

Lower concentrations of $PM_{2.5}$ caused a gentle decrease in slope (**Figure 3**); in contrast, an increasing slope was observed with increased $PM_{2.5}$ concentration. This finding may be due to the small size of $PM_{2.5}$; furthermore, it is mainly deposited in the lower respiratory tract, and a high concentration is required to reach the lungs. However, further randomized clinical trials are needed to validate these results.

The reason we choosed DLNM, which is a non-parametric model, based on following two points. Firstly, we discovered that the distribution of scatter plot is a non-linear wavy curve; Secondly, the DLNM takes account of both lag effects and the exposure-reaction non-linear relationship, and initially applied in epidemiological studies in 2006 (50). Multiple studies have suggested that the effects of air pollution and meteorological factors on outcomes have lag effects, while traditional linear models, which only study effects on certain time points without considering lag effects, are likely to produce high linearity, biasing the results (51, 52). Therefore, DLNM is a better choice to study the lag effects of exposure, especially in the analysis of air pollution. This study also use GAM with smooth spline function to fit variables in order to reduce the model risk caused by linear settings. Which means predictor variable in the model will be divided into multiple parts, and then fits each part separately through a polynomial function.

Limitations

This study has several limitations. First, exposure error bias greatly affects time series analysis, limiting the extrapolation of this study's inferences. Second, we used outpatient data; therefore, misclassification bias was inevitable. Third, the cities included were located in a specific region, which may affect the generalizability of the results. Future studies using larger sample sizes over a wider range of regions are needed to validate the findings of this study.

CONCLUSIONS

This study provides evidence regarding the effect of air pollutants on children's respiratory function in coastal cities. Particularly, an increase in $PM_{2.5}$ increased the number of outpatient children in respiratory clinics. Furthermore, different lag effects were correlated with different exposure levels. These findings can improve Zhoushan's medical service and health risk assessment policies, providing implications for other similar places or countries.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of the Shanghai International Medical Center (Approval Number: S20210513). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

W-YL, J-PY, LS, and T-HT conducted the study and drafted the manuscript. W-YL and J-PY participated in the design of the study and performed data synthesis. LS and T-HT conceived the study and participated in its design and coordination. All authors read and approved the final manuscript.

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Social Media Interventions Strengthened COVID-19 Immunization Campaign

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Background: Since The Italian Medicines Agency (AIFA) has recommended the COVID-19 vaccine Comirnaty in children aged 5–11, the immunization campaign faced vaccine hesitancy in parents. Social media are emerging as leading information source that could play a significant role to counteract vaccine hesitancy, influencing parents' opinions and perceptions. Our aim was to evaluate the coverage of the COVID-19 vaccine Comirnaty in a cohort of children aged 5–11 whose families have been counseled to use Social Media to counteract vaccine hesitancy.

Methods: All parents of children aged 5–11 in a primary care setting were instructed by their pediatrician to get accurate information about the COVID-19 vaccine from a *Facebook* page. Active calls to vaccinate children were also scheduled through messaging services *Pediatotem* and *Whatsapp*. Vaccination rates of children in the study were assessed with an electronic database and compared to both regional and national child vaccination rates.

Results: Coverage of 277 children aged 5–11 was analyzed from 16 December 2021 to 31 January 2022. A total of 62.4% (173/277) of enrolled children received the 1st dose of COVID-19 vaccine Comirnaty and 39.7% (110/277) the 2nd dose. Coverage rates were higher compared both to the regional population (1st dose: 48.8%, 2nd dose: 24.6%; $p = 0.001$) and national population (1st dose: 32.1%, 2nd dose: 13.8%; $p < 0.001$).

Conclusion: Increasing vaccine confidence using Social Media interventions have a positive impact on vaccination acceptance of parents.

Keywords: social media, vaccine hesitancy, COVID-19 vaccine acceptance, COVID-19 pandemic, primary care pediatrician

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INTRODUCTION

Since the beginning of the COVID-19 pandemic in Italy, more than two million children and adolescents aged 0–19 years have been infected by the Sars-Cov-2 virus. Of these cases, more than 12,000 children needed hospitalization, around 300 required intensive care, and 39 have died. Pediatric cases represent 20% of the Italian Sars-Cov-2 infections, with an estimated lethality rate of <0.1% (1).

Despite most pediatric cases being milder forms compared to adult ones, growing evidence has shown that a minority might experience a severe multisystem inflammatory syndrome temporally associated with COVID-19 (MIS-C) (2).

Furthermore, there is now mounting evidence of persisting symptoms in children following acute Sars-Cov-2 infection, which has been named Long COVID, and studies that highlight how lifestyle changes during the COVID-19 pandemic have had a significant psychological impact on the pediatric population (3, 4).

For all these reasons, since a vaccination regimen of two doses of the Comirnaty vaccine was found to be safe, immunogenic, and efficacious in children 5–11 years of age (5), the Italian Medicines Agency has recommended an extension of Comirnaty vaccination to this pediatric population.[1]

Parents' attitude toward vaccine use is a key factor affecting children's immunization programs and vaccine hesitancy is a known threat to global health (6–8). In this scenario, social media are emerging as a leading information source that could play a significant role in increasing or mitigating vaccine hesitancy, influencing the opinion and perceptions of parents (9–11).

The primary aim of this study is to evaluate coverage of COVID-19 vaccination in a cohort of children 5 to 11 years of age, whose families have been counseled to use Social Media to counteract vaccine hesitancy.

The secondary aim is to compare vaccination rates of the interventional cohort with those of regional and national pediatric populations of the same age range.

METHODS

Population and Setting

We performed a prospective study in a primary care setting to evaluate coverage of COVID-19 vaccination in a cohort of children aged 5–11 years from 16 December 2021 to 31 January 31 2022.

Children of the study cohort were followed at Pediatric Primary Care Office (PPCO) in Margherita di Savoia (BAT, Apulia, Italy) which offers primary pediatric care to 651 children from birth through adolescence.

According to the national guidelines, the regional Apulian government offered two 10-μg doses of the Cominraty vaccine administered 21 days apart, free of charge, to children aged 5–11 years.

Furthermore, the Regional Apulian Covid-19 Immunization Campaign started an active collaboration between the Primary Care Pediatricians, the Local Health Organizations (Public Health Departments), and the Regional School Offices, focused on collective vaccination process management. In fact, the Local Health Authority set up a COVID-19 Vaccine Pediatric Hub in a school gym in Margherita di Savoia, driven by five local primary care pediatricians.

Abbreviations: PPCO, Pediatric Primary Care Office.

[1]https://www.aifa.gov.it/documents/20142/1123276/Parere_CTS_Comirnaty_5-11_01.12.2021.pdf

Interventions

The primary care pediatrician of Margherita di Savoia has managed a Social Media-based strategy to counteract COVID-19 vaccine hesitancy in parents.

Through a professional *Facebook page* (https://www.facebook.com/antoniodimauropediatra) with a fanbase of over 50,000 users, he posted, on a regular basis, official and certified messages on health, vaccine-related scientific data, info-graphics, useful information, and videos from institutional pages, such as that of the *Italian Society of Pediatrics* (https://www.facebook.com/societaitalianadipediatria).

Other Facebook posts were arranged into short, easy-to-read paragraphs, discussing risks and benefits of vaccines, and news on pediatric COVID-19 and its management. The pediatrician certified the validity and trustworthiness of the material posted. Posts used in the study are easily accessible and manageable to allow replication studies in previously cited Facebook Pages.

All parents were allowed to post comments and questions and to get answers from the pediatrician in a public dashboard, thus overcoming the obsolete one-way communication typical of traditional media.

In the study period, 84 posts were published with a total of 462,883 interactive visualizations, 34,398 likes, 5.450 shares, and 5,707 comments. The total estimated coverage of the Social Network activity was of 1,811,560 Facebook users reached. All these data were extracted by Facebook Insight.

Furthermore, four active calls to vaccinate children, on dedicated open days, was also scheduled through messaging services *Pediatotem* and *Whatsapp*.

Statistical Data

The list of children aged 5–11 followed in the Margherita di Savoia PPCO was obtained by a regional database (EDOTTO). For each children doses were registered in a standardized form, obtained through the Apulian Regional Vaccination Register (GIAVA).

Coverages of Margherita di Savoia PPCO were compared with that of the Apulian and Italian pediatric population of 5–11 years of age. All data were extracted on 31 January 2022 and analyzed by STATA MP12 software. Categorical variables were expressed as proportions. The Chi-square test was used to compare proportions. A $p < 0.05$ was considered as significant.

RESULTS

Of the 651 children followed at Margherita di Savoia PPCO, 277 were aged 5–11 years (42.5%).

From 16 December 2021 to 31 January 2022, 173 (62.4%) of enrolled children received the 1st dose of Comirnaty and 110 (39.7%) the 2nd dose.

On the same day, the regional child population of 5–11 years exhibited an immunization rate of 51 and 25.1% for the 1st and 2nd dose of the Comirnaty vaccine, respectively. COVID-19 vaccine coverage decreased to 32.1 and 13.8% for the 1st and 2nd dose respectively of the Comirnaty vaccine when the entire Italian child population aged 5–11 was analyzed (**Figure 1**).

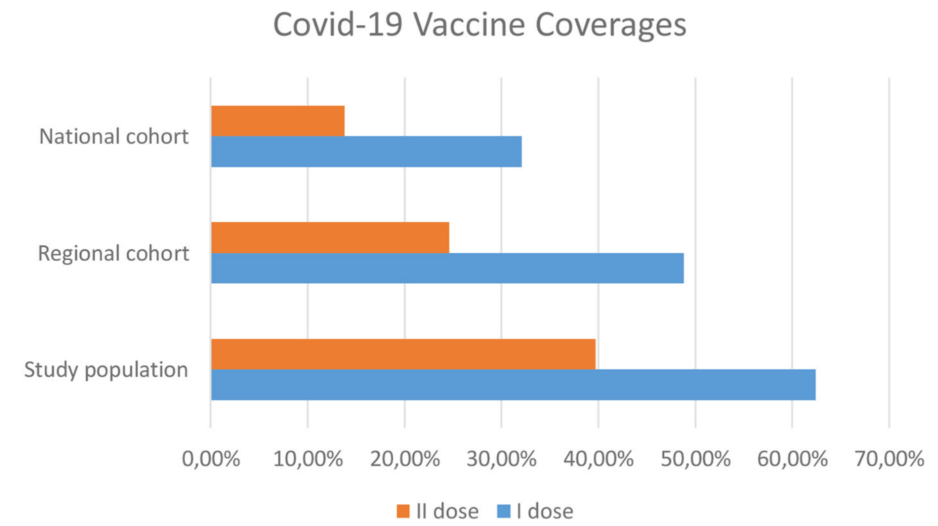

FIGURE 1 | A significantly higher coverages were observed in the study population compared to both regional (**Table 1**) and national ones (**Table 2**).

TABLE 1 | Differences in vaccine coverages between study cohort and regional population.

	Study population	Regional population	*P*
I dose	62.4% (173/277)	48.8% (117.366/240.444)	0.001
II dose	39.7% (110/277)	24.6% (59.289/240.444)	0.001

TABLE 2 | Differences in vaccine coverages between study cohort and national population.

	Study population	National population	*P*
I dose	62.4% (173/277)	32,1% (1.175.365/3.656.069)	<0.0001
II dose	39.7% (110/277)	13.8% (505.931/3.656.069)	<0.0001

DISCUSSION

Our study shows that COVID-19 vaccination coverage in pediatric patients is higher when parents have been subjected to social media-based interventions, compared to the general pediatric population (**Tables 1**, **2**).

It is of note that Apulian coverages are higher compared to the Italian pediatric 5–11 years population as an effect of efficacious vaccination strategy adopted at a regional level. Apulia scores first in the national ranking for vaccination in the 5–11 age group, with 48.8%, 16.7% points above the national average. These data confirm the fundamental active collaboration between Primary Care Pediatricians, Local Health Organizations (Public Health Departments), and Regional School Offices.

We believe that the Social Media-based vaccination strategy enforced the regional campaign, overcoming parental COVID-19 vaccine hesitancy, with well-structured and continuous counseling activity on Social Media that supports the final parental vaccination decisions.

Our results are different, but very promising, from the growing literature on parental COVID-19 vaccine hesitancy (12–14). On the other hand, another study suggested how an actively and directly neonatologists' interaction on Social Media can improve vaccine acceptance in preterm infants' parents after hospitalization (15).

With the increasing use of the internet in the last decades, social media became an attractive platform to promote a healthy lifestyle (16). In this scenario, a new form of social media celebrity, defined as "influencers", has emerged as credible in specific topic areas and so are followed by a fanbase, with the real possibility to promote healthy lifestyle behaviors.

The Italian Paediatric Society has previously promoted healthy lifestyle campaigns, engaging pediatricians as "influencers", demonstrating how social media increased families' interaction with correct information, thus contrasting the spreading of fake news (17). However, in this previous pilot study, they did not analyze the effects of influencers' social media interventions on the health of children and adolescents.

To the best of our experience, this is the first study that analyses the effects of social media interventions directly on an Italian pediatric cohort. Our high vaccination coverage demonstrated how social media could be a very useful partner for vaccination campaigns, especially in a pediatric primary care setting.

Primary Care Pediatricians' counseling, online contributions, opinions, and posts could be essential to recovering hesitant parents, considering both the relationship of trust with the families and their credible reputation, known in local setting due to the capillary network of Italian PCCO (18).

For such reasons, according to others, we encourage Primary Care Pediatricians' active participation in social media communication (19).

The strengths of our study were the social media strategy organized by a trained pediatric influencer and the accuracy of data extracted from a computerized surveillance system (GIAVA). There are also some limitations. First, we are aware that further RCT trials are needed to confirm our data because we compared our cohort to general regional and national populations, with no randomized intervention and a short enrolment period. Secondly, participants had unlimited access to social networks, but we cannot know how they spent time, participate and have effective dialogic communication with posts we published on the Facebook page. RCT trials with specific surveys among parents may better clarify the role of social media interventions. Finally, the trial was conducted in a single PPCO, and in a specific region with a very effective protocol for vaccination and our results could not be applied to other Local Health Systems without the same availability of vaccine services.

CONCLUSIONS

A scientific-based use of social media, with effective dialogic communication and interpersonal influence, could be considered as useful partners in vaccination campaigns to positively influence parental vaccine acceptance. In our experience, the trusting Pediatrician-Family-Patient relationships built *via* the social web strengthened the effective collaboration between Primary Care Pediatricians and the Local Health Authorities.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

AD planned the study, coordinated the study, and wrote the first draft of the manuscript. FD, LR, and SD examined the data from national and regional dataset. CG and PS explored the literature and performed statistical analysis of data. NL, MB, and ST revised the final manuscript. All authors have read and approved the final manuscript.

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BRIEF RESEARCH REPORT
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Pediatric Multiple High-Powered Magnetic Buckyballs Ingestion—Experience From Six Tertiary Medical Centers

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Multiple high-powered magnetic Buckyball ingestions may lead to a high risk of severe complications. Great concerns have been raised by public health workers, and it remains challenging for clinicians to solve this troublesome problem. We report a large case series of children with Buckyball ingestion from six tertiary medical centers. The clinical data, including demographics, medical history, diagnosis tools, management options, intraoperative or endoscopic findings, and outcomes, were retrospectively analyzed. Seventy-one children aged 1–13 years ingested 2–41 Buckyballs. Among them, Buckyballs passed spontaneously on 2–10 days post-ingestion in seven cases; gastroscopic removal was performed in 14 cases; laparoscopic removal in 13 cases; laparoscopic-assisted surgical removal in 6 cases; and open surgical removal in 31 cases. Surgical indications included small bowel obstruction, perforation, peritonitis, acute abdominal pain, or along with ingestion of other metallic foreign bodies. Among those who underwent a surgical procedure, primary intestinal repair was performed in 44 cases, enterectomy with primary anastomosis in 6 cases. The postoperative hospital stay ranged from 5 to 28 days. No major complications occurred. In unwitnessed cases, a vague medical history and nonspecific symptoms usually make the diagnosis difficult. The treatment options should include the watch-and-wait approach, endoscopic, laparoscopic-assisted, or open surgical removal of Buckyballs, with primary intestinal repair or anastomosis. Preventive measures, including children's not having access to Buckyballs, are essential to protect children from this kind of unintentional injury.

Keywords: foreign body ingestion, high-powered magnet, Buckyballs, acute abdomen, children

INTRODUCTION

Ingestion of foreign bodies, including coins, button batteries, bones, needles, and magnets, is one of the common unintentional injuries in children worldwide (1). Buckyball, approximately 5 mm in diameter, with high powered magnet, can steadily attract one another, even though six layers of the bowel wall apart (2, 3). Infants and toddlers usually explore objects they can touch *via* their mouth (4, 5). Ingestion of two or more Buckyballs poses a high risk of catastrophic sequelae (5). Severe alimentary tract injuries related to Buckyball ingestion, including perforation, small bowel obstruction, fistulae, peritonitis, and even life-threatening events, are increasingly reported in the past decade (6–16). Although great concerns for this preventable disease have been raised by clinicians, public health workers, and child caregivers, Buckyball ingestions in children are not uncommon in clinical practice, and this remains challenging for clinicians to solve this troublesome problem (1, 17). Herein, we present a large case series of Buckyball ingestion in pediatric patients from six tertiary medical centers, aiming to provide clinical experience in early diagnosis, rational management options, and preventive measures.

MATERIALS AND METHODS

From June 2018 to June 2021, there were 71 cases with ingestion of multiple high-powered magnetic Buckyballs at 6 tertiary medical centers. Patients' medical records, including age, gender, medical history, time since ingestion, diagnostic imaging, management options, endoscopic or intraoperative findings, and outcomes, were retrospectively analyzed. A 6-month follow-up was conducted after discharge.

ETHICAL CONSIDERATIONS

Informed consent was obtained from the parents/legal guardian(s) of all children involved in the study.

RESULTS

Seventy-one children who accidentally ingested two or more Buckyballs were enrolled in this study. Of the 71 cases, there were 48 boys (69.01%). The age ranged from 1 to 13 years (the median age was 2), $<$ 3 years in 40 cases (56.31%), 3–5 years in 21 cases (29.58%), and $>$5 years in 10 cases (14.08%). Among females, 21/23 cases were aged 3 years or younger. The ratio was equal for both genders, with children being $\leq$ 3years of age (19 males, 21 females).

The number of ingestions of Buckyballs ranged from 2 to 41; the median number was 5. Seventy cases were witnessed, and one was unwitnessed. The time since ingestion of Buckyballs in the outpatient or emergency department ranged from 3 h to 1 year, including 3 h-9 days in 60 cases, $\geq$ 10 days in 10, $>$1 year in one.

All cases received plain abdominal radiography, and ingestion of 2 or more Buckyballs was confirmed. For cases planned with conservative observation, the progression of the Buckyballs was tracked by plain abdominal and pelvic radiography (**Figure 1**). Ultrasonographys were assessed in 45 cases. The ultrasonography revealed dilated bowel loops with bowel wall thickening, ascites, and sphere metal foreign bodies, which are located in the stomach (14), duodenum (3), small bowel (18), or colon (1), undefined localization (2). The ultrasonographic findings were consistent with the intraoperative or gastroscopic findings in 43 cases (93.33%).

In all cases, ingestion of 2–4 Buckyballs passed spontaneously on the 2 to 10 post-ingestion days in seven cases (2 days in four, 3 days in two, 10 days in one). Fourteen cases received gastroscopic removal of the Buckyballs. A child with a 10-day history of ingestion of ten Buckyballs received gastroscopic removal of

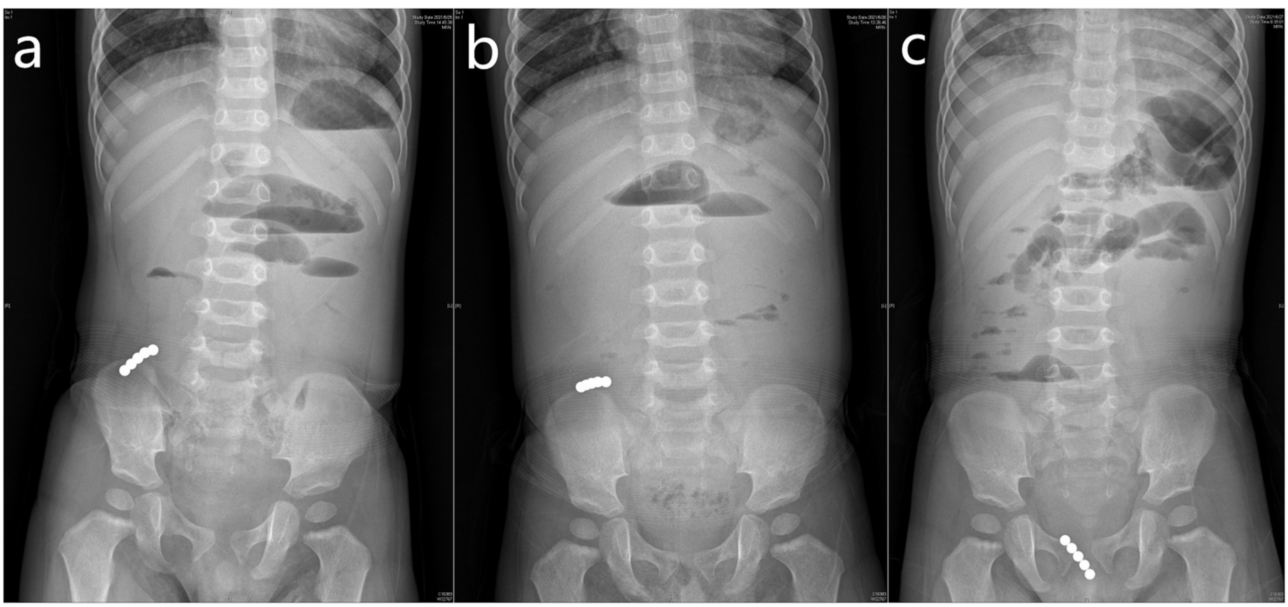

FIGURE 1 | Plain abdominal and pelvic radiographic imaging revealed the progression of the Buckyballs. The Buckyballs passed spontaneously on 5 post-ingestion days and partial small bowel obstruction relieved.

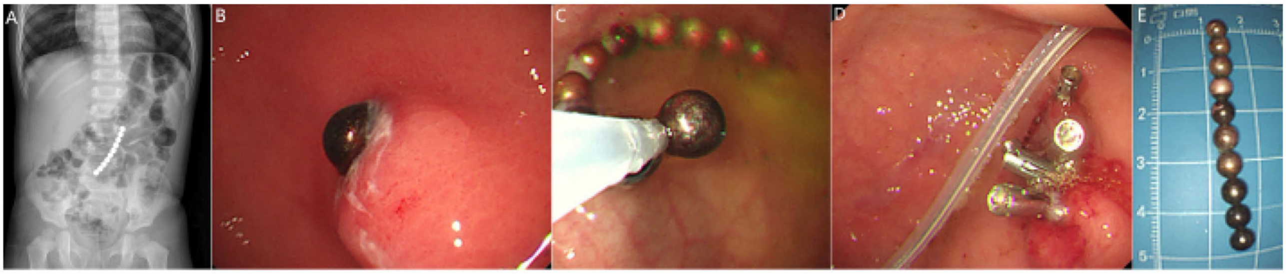

FIGURE 2 | Plain abdominal radiograph showed ingestion of ten Buckyballs **(A)**. Gastroscopy revealed that only one Buckyball lodged in the stomach cavity **(B)**. Gastroscopic removal of the Buckyballs **(C,E)** and primary repair of the gastric fistula using metal closure technique **(D)** were performed, and a nasojejunal tube was inserted for early enteral nutrition **(D)**.

the Buckyballs, with primary repair of the gastric fistula *via* an endoscopic metal closure technique. A nasojejunal tube was also inserted for early enteral nutrition (**Figure 2**). The child recovered uneventfully without evidence of abdominal free air to suggest perforation on abdominal radiography. The remaining 50 cases underwent a surgical procedure, including laparoscopic, laparoscopic-assisted, or open surgical procedure.

Surgical indications included signs of peritonitis; bowel obstruction due to adhesion, internal hernia, or volvulus; acute abdominal pain; ring-like form, along with other metallic foreign body ingestion (button battery, screw, or iron wire, etc). The approach to the removal of Buckyballs included laparoscopic in 13 cases, laparoscopic-assisted surgical in 6 cases, and open surgical procedure in 31 cases, following primary intestinal repair in 44 cases and enterectomy, with primary intestinal anastomosis in 6 cases. The location of Buckyballs and the number and location of the perforations or fistulae were summarized in **Table 1**.

The postoperative hospital stay ranged from 5 days to 28 days (median, 12 days). All cases recovered uneventfully and discharged home. No major complications occurred in a 6-month follow-up period.

TABLE 1 | A summary of the location of Buckyballs and perforations or fistulae.

Buckyballs' location	
gastro-intestine	7
gastro-intestinal-colon	3
gastro-duodenum	2
intestinal-intestine	21
intestinal-colon	8
duodenal-intestine	3
duodenum	1
duodenal-intestinal-colon	1
pelvis	1
not available	3
Location of perforation or fistula	
stomach	11
duodenum	4
small intestine	35
colon	14
Number of perforation or fistula	
2	10
3	4
4	8
5	1
6	4
9	1

DISCUSSION

Ingestion of a foreign body is an increasingly common clinical problem, especially in the pediatric population (1). Ingestion of two or more high-powered magnetic Buckyballs with unintentionally severe injury has been reported worldwide in the last decade (2, 5, 10, 16). It occurs most frequently in children aged 1–5 years old (19), and there is male-to-female predominance of 1.3–3.9: 1 (15, 16, 20). In the present case series, the ratio of male to female is about 2:1. However, our results showed that the ratio was equal for both genders in those aged 3 years or younger, which may provide evidence for gender differences in the prevalence in this age group.

Symptoms of ingestion of two or more Buckyballs usually emerge within 1–40 days (19, 21–23), and most cases present symptoms and signs of acute abdomen, which include onset of abdominal pain, refusal to eat, bilious vomiting, abdominal distension, dehydration, and fever.

For a prompt and precise diagnosis, investigations are needed in patients with witnessed or suspected multiple magnet ingestion (7, 12). Plain abdominal radiography may reveal the cause of small bowel obstruction of unknown origin, as our unwitnessed case. Biplane radiography, including neck, chest, abdomen, and pelvis, is essential to assess the number of Buckyballs (24) and to observe the movement of the Buckyballs and signs of potential complications, including evidence of free air or air-fluid levels in the abdomen. The ultrasonography for identification of Buckyballs is reliable and safe (25). The higher accurate rate of preoperative localization may depend on physicians' experience (as in our case series). CT scan can assess potential complications, such as a thickened bowel segment or localized pneumoperitoneum, suggesting inflammation or perforation (18, 25). Magnetic resonance imaging is strongly contraindicated due to a high risk of bowel perforation (18, 26).

The management options of ingestion of multiple Buckyball are crucial to improve patients' outcomes. Patients who present with multiple Buckyball ingestion-related complications usually require emergent surgical interventions, including laparoscopic, laparoscopic-assisted, or open surgical procedures (7, 10, 17). However, in some cases, the Buckyballs may pass through the gastrointestinal tract spontaneously under close observation (13). Watch-and-wait, close observation, and endoscopic removal may reduce the need for surgical intervention in individual patients; a well-structured management protocol needs to be elucidated (15).

As for asymptomatic patients, radiography every 12–24 h was recommended (27). Early (≤12 h) upper gastrointestinal endoscopy is recommended to retrieve Buckyballs from the stomach prior to their passage through the duodenum. Delicate manipulation is essential, while excessive force may lead to a risk of gut perforation and leak (28, 29). If the time since ingestion

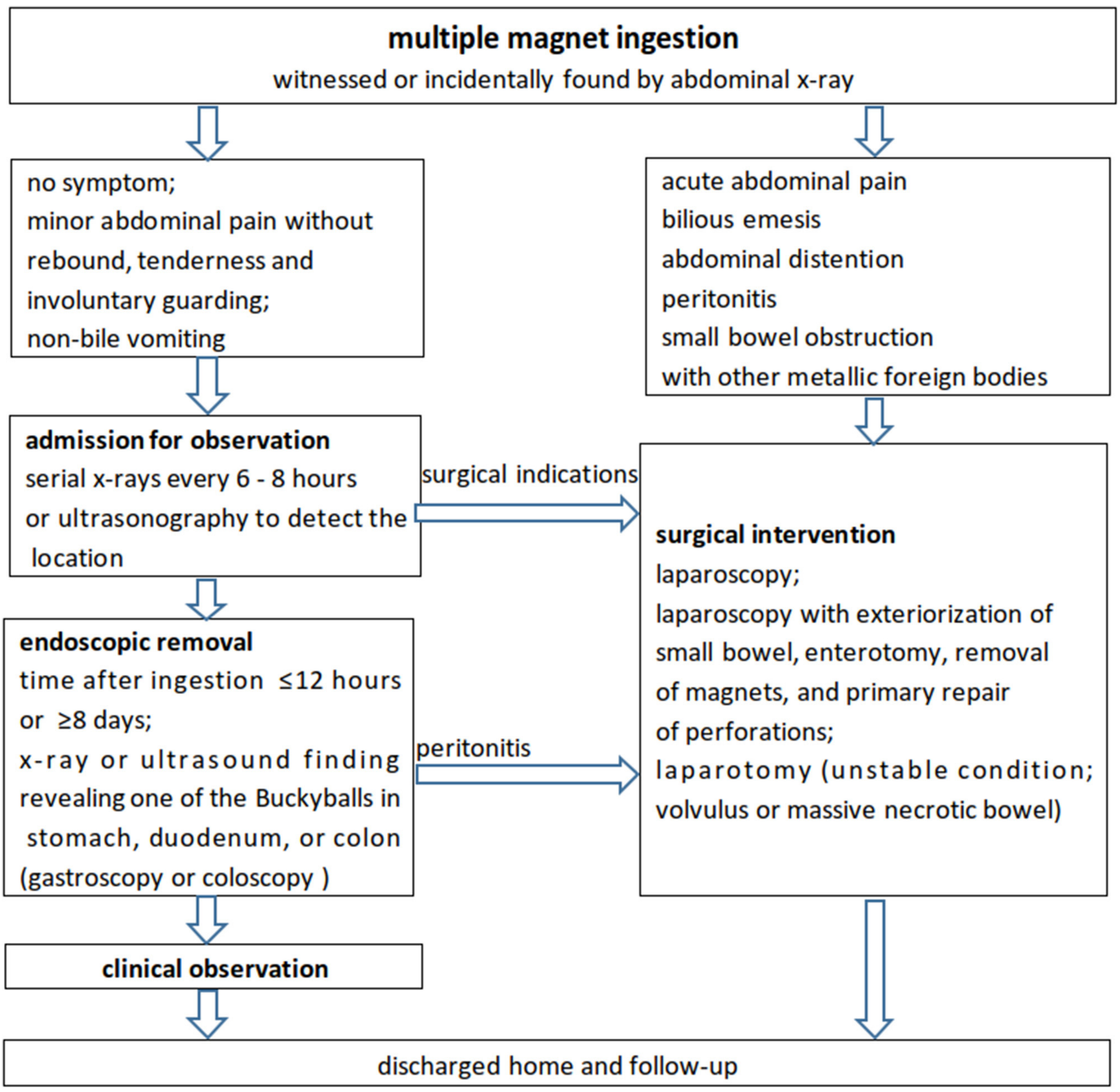

FIGURE 3 | A recommended flowchart for the management of multiple high-powered magnet ingestions in the pediatric population according to the literature and our experience.

is >12 h and Buckyballs are suspected to have passed through the pylorus into the small bowel, a series of abdominal radiography is needed (30, 31), and surgical intervention should be considered in those who present symptoms and signs of acute abdomen. Laparoscopic surgery is an ideal approach depending on an experienced surgeon team and available facilities. The metallic tips of laparoscopic instruments may help to identify and remove the Buckyballs (8). However, in many cases, enterotomy with primary repair or bowel resection, along with primary bowel anastomosis, is needed, owing to intestinal perforation, fistulae, or bowel necrosis; a laparoscopic-assisted surgical procedure may be the choice (11). In addition, Wang et al. (2) mentioned coloscopic removal of Buckyballs. This technque may be another approach in selected cases.

Based on the literature (1–4, 11, 14, 17, 27–29) and our multicenter experience, a flow chart (**Figure 3**) was introduced for the management of multiple high-powered magnetic ingestion in the pediatric population.

CONCLUSION

Ingestion of multiple high-powered Buckyballs in children may lead to a high risk of severe gastrointestinal injuries, which need prompt decision-making and surgical intervention (30). In unwitnessed cases, a vague medical history and presentation of nonspecific symptoms often make the diagnosis difficult. The management options should include conservative observation, removal of the Buckyballs with primary gastrointestinal repair *via* endoscopic, laparoscopic, laparoscopy-assisted, or open surgical procedure. Minimally invasive approaches might be one of the choices (31). Taking preventive measures, such as restrictions on Buckyball manufacture and sales, health education *via* media and newspapers, and children's not having access to Buckyballs, are essential to prevent this kind of injury.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

GD, LG, ZB, and TF contributed to the conception and designed the study. GD, HL, PZ, QN, WW, ZF, SZ, and ZZ organized the clinical data. GD, ZB, LG, and TF wrote the manuscript. SZ, ZZ, LG, and ZB reviewed the manuscript. All the authors contributed to revising the manuscript and approved the submitted version.

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Myopia Control With Multifocal Lens in School-Aged Children: A Meta-Analysis

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Background: Myopia is one of the most common eye diseases in school-aged children. Multifocal lens (MFL) is one of the interventions that has being widely applied to control the progress of myopia. However, the treatment effects of MFLs in school-aged children require to be systematically evaluated.

Methods: A systematic analysis on qualified randomized controlled trials (RCTs) in which MFLs were prescribed as the intervention and single-vision lenses (SVLs) as the control was conducted. The treatment effects referring to the mean differences in spherical equivalent refraction (SER) and axial length (AL) between MFLs and SVLs groups were analyzed.

Results: With annual visit (3-years follow-up), the weighted mean differences (WMDs) in SER between MFLs and SVLs were 0.29 D (95% CI, 0.21 ∼ 0.37, $p < 0.00001$), 0.46 D (95% CI, 0.32 ∼ 0.60, $p < 0.00001$), and 0.64 D (95% CI, 0.40 ∼ 0.88, $p < 0.00001$) at the first, second, and third year; in AL were −0.12 mm (95% CI, −0.14 ∼ −0.11, $p < 0.00001$), −0.19 mm (95% CI, −0.22 ∼ −0.16, $p < 0.00001$), and −0.26 mm (95% CI, −0.31 ∼ −0.21, $p < 0.00001$) at the first, second, and third year. With 6-months interval trials (2-years follow-up), the WMDs in SER from MFLs were 0.14 D (95% CI, 0.08 ∼ 0.20, $p < 0.0001$), 0.19 D (95% CI, 0.11 ∼ 0.28, $p < 0.0001$), 0.24 D (95% CI, 0.16 ∼ 0.33, $p < 0.0001$), 0.31 D (95% CI, 0.18 ∼ 0.44, $p < 0.0001$) and in AL from MFLs were −0.08 mm (95% CI, −0.09 ∼ −0.07, $p < 0.00001$), −0.10 mm (95% CI, −0.12 ∼ −0.09, $p < 0.00001$), −0.14 mm (95% CI, −0.17 ∼ −0.11, $p < 0.00001$), and −0.18 mm (95% CI, −0.22 ∼ −0.14, $p < 0.00001$) slower comparing with SVLs at follow up of 6, 12, 18, and 24 months, respectively.

Conclusion: The treatment effects of MFLs to slow down the myopic progress are positive in both 6-months and annual-visit trials and which could be sustained till 36 months. While a slight weaker treatment effect was observed after the first visit in 6-months visit, a slight rebound was observed at the following visit points. Furthermore, the treatment effects in annual visit are more profound than 6-months visit at almost all stages especially in SER. Our analysis encourages the MFLs users to maintain a long-term treatment with annual visit.

Keywords: multifocal lens, bifocal lens, peripheral additional lens, myopia control, meta-analysis, children

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INTRODUCTION

High myopia (spherical equivalent, >−6.00 D) leads to the irreversible retinal atrophy and will cause a lot of complications such as macular degeneration, retinal detachment, glaucoma, and premature cataracts (1–3). The risk of suffering from a retinal detachment is 20 times more in a person with high myopia than an emmetropic one (4). Recently, the high prevalence of myopia worldwide among children and teenagers is a serious threat of public health especially in Asia (5–7). In China, the myopia incidence rate in primary school is approximately 40%, in middle and high school students is even higher and could be even severer in near future (8–10). The increasing number of myopias in teenagers whose myopia progress even faster attracts more attention to develop novel strategies to slow down the progress of myopia (11).

To slow down the progress of myopia, it is the prerequisite to understand the risk factors and mechanisms of myopia. The previous studies suggested that the genetic factors play substantial roles than the environmental ones (12, 13). Thus, the children whose parents are myopia trend to be easier to suffer from myopia than those children who have only one or no myopic parent. However, there are solid evidences also clearly showed that the environmental factors could not be ignored for developing myopia especially at current age when it requires school-aged children to take longer time reading, sustainable homework and spend fewer hours for outdoor activities (14–16).

According to animal studies, it was demonstrated that hyperopic defocus in retina causes refractive development and eye axial excessive growth, which promotes myopia progression. Conversely, myopic defocus in retina could retard the eye axial growth, which slows myopia progression (17–20). On the basis of these observations, a novel lens, namely, multifocal lens (MFL) was developed with peripheral focus technology that provides a central zone containing the distance correction and periphery zone having a myopic defocus by adding an extra positive power, resulting in myopic defocus in retina to slow down the eye axial elongation. Currently, there are two main types of MFLs designs including concentric rings/bifocals (BF) and progressive power/peripheral add lens (PAL), which principally provide both near- and distance-vision spectrum (21). With BF, it has two zones of myopia correction for all gaze positions and two neighboring concentric treatment zones with plus power addition to simultaneously deliver peripheral myopic defocus (22, 23). However, PAL simultaneously produces constantly peripheral myopization defocus that increases gradually from the central optic axis toward the periphery (21, 23).

Although it is in theory that MFLs could slow down the myopia progression, the outcomes from clinic practice are controversy. Thus, the several earlier meta-analyses also could not achieve consistent conclusion due to multiple reasons. Li et al. (24) collected nine randomized controlled trials (RCTs) from 1989–2010 to compare effects of MLCs with single vision lenses (SVLs) in children. The data suggested that MLCs with powers ranging from + 1.50 to + 2.00 D were associated with a statistically significantly decrease in myopia progression in school-aged children compared with SVLs. In 2017, the other group (24) evaluated the possible difference between BFs and PALs. They found that both BFs and PALs are clinically effective to control myopia in school-aged children. However, it seems that BFs seem to have greater effect than PALs. Recently, Kaphle et al. (25) performed a meta-analysis to compare the absolute progression rates over the successive 6-months or 1-year periods to gauge how long the efficacy of the intervention lasts. They found that the treatment effect of MFLs is maximum in the first 6- and 12-months intervals and is reduced in subsequent intervals. A latest study (26) also suggested a similar tendency when comparing the relative increases rather than absolute increases in measures of myopia progression for PALs and SVLs that the relative efficacy of PALs tends to be weaker after the first 12 months. Overall, these studies indicate that MFL is effective to slow down the progress of myopia in children, but how long the treatment effects could be sustained and whether treatment interval affects the effects remain to be intensively reviewed.

In this study, we conducted a systematic meta-analysis focusing on currently available evidences from 15 high quality RCTs involving 1,840 children aged 6–18 years to assess the effects of MFLs vs. SVLs on slowing myopic progress. We extended our analyzed treatment period up to 36 months and subdivide into 6- and 12-months (annual) visit intervals. To more precisely evaluate the treatment effects, both spherical equivalent refraction (SER) and axial length (AL) are analyzed.

MATERIALS AND METHODS

Search Strategy

A search was performed in PubMed, MEDLINE, Embase, Web of Science, and Cochrane Library (up to July 2021) using the following keywords: Myopias (MeSH Terms), Near sighted*, short sight*; eyeglasses (MeSH Terms), spectacles, single vision lenses; multifocal (MeSH Terms), bifocal, progressive addition lenses; RCT (MeSH Terms), controlled clinical trials, randomized, clinical trials, randomized, trials, randomized clinical, clinical trial. We used the Boolean operator "AND" to combine all search sets as the final step. The articles performed in "humans" and published in "English" language were used as filters.

Studies Selection

Relevant clinical trials were selected according to the following criteria: (1) Study type: RCTs, (2) Participants: 6–18-year-old school-aged children with myopia, (3) Interventions: MFL or bifocal lens or progressive additional lens as the experimental group, and single vision soft contact lenses or spectacles as the control group, and (4) Primary outcomes: the change in refractive errors (cycloplegic SER), that is, myopia progression, with 95% confidence interval (CI) or standard deviation and the change in axial elongation (AL) compared with the baseline at different visits. The exclusion criteria were as follows: (1) Duplicates; (2) Studies with missing information; (3) Studies that were published earlier than 2000; (4) Corresponding authors could not be contacted for missing information; (5) Articles that were not published in English; (6) Myopia progression measured in participants who wore contact lenses or orthokeratology or were using eye drops; and (7) Review articles, case studies, and cross-sectional studies.

Data Extraction and Quality Assessment

The data were independently extracted including the following information: Authors, publication year, country or area, type of multifocal lenses, age and sex of the study population, sample size, proportion lost to follow-up, length of follow-up, myopia progression with standard deviation at 6- or 12-months intervals, and information on methodology. For the studies with missing information, an email was sent to the corresponding authors who supplied additional data, if needed, used GetData Graph Digitizer 2.24[1] to read data of different follow-up periods, which were only illustrated in figures. For studies that provided baseline and final SER and standard deviation, but not the standard deviation of the change, an equation suggested by Cochrane collaboration (27) was used to calculate the standard deviation of the change.

Quality assessment of the included studies was performed by the Newcastle–Ottawa Quality Assessment Scale items. This includes 16 items with the following three domains: Selection (representativeness), comparability (because of design or analysis), and outcomes (assessment and follow-up). One study can be awarded a maximum of one star for each numbered item within the selection and outcome categories. A maximum of two stars can be given for comparability. Any discrepancy between the two reviewers about the above issues was resolved by discussion or a third reviewer.

Statistical Analysis

All statistical analyses were conducted by Review Manager, version 5.3.[2] The differences in refraction and AL between the two groups were assessed as mean differences (experimental group minus control group, Cochrane Handbook 5.1.0, 9.2.3.1) and 95% CI. The random effects analysis method was used for meta-analysis when there was significant heterogeneity between studies. Statistical heterogeneity in articles was assessed with the I^2 statistic, with $I^2 > 50\%$, and $p < 0.1$ considered to indicate high heterogeneity. The sensitivity analyses were performed by sequentially removing the individual studies to determine whether each resulted in a substantial change in the magnitude or direction of the pooled estimates and heterogeneity. When the excluded study substantially changed the mean difference in SER and I^2 value, it is reported in the results. Statistical significance was declared as $p < 0.05$.

RESULTS

Characteristics of Studies Included in the Meta-Analysis

A flowchart of study selection is presented in **Figure 1**. Totally 1,179 studies were identified from the search using PubMed, Cochrane, EMBASE, MEDLINE and Web of Science. After removing the duplicates, there were 699 studies remained. By reviewing the title and abstract, 642 studies were excluded and 57 studies were remained. After a full-text review, 29 studies were included. Among these 29 remaining trails, 13 studies were excluded for the following reasons: Five studies had missing information (28–32), authors of two studies could not be contacted for missing information (33, 34), one study was a part of a longer study (35). Two studies was not randomized control trial (36, 37), one trail was recorded with 5-months interval (38), one trial was crossover trial (39), one trial recorded only one outcome (40), and in one study, the control group switched to MFLs at the second year (41).

The characters of 15 included studies are showed in **Tables 1**, **2**. It was conducted on 1,840 children aged between 6 and 18 years. The time length of the follow-ups varied from 12–36 months as follows: Four studies were of 12-months duration (42–45), seven studies were of 24-months duration (22, 46–51), and four studies were of 36-months duration (33, 52–54). Four studies were conducted in the United States America (48, 51, 52, 54). Two studies were multi-country studies as follows: The trial from Chamberlain et al. was conducted in (Portugal, United Kingdom, Singapore, Canada) and the study of Hasebe et al. was carried in China, Japan, and South Korea (50, 53). Two studies were carried out in Spain (22, 42), five studies were carried out in China (44–47, 49) and the rest of the studies were conducted in the following countries: Australia (43) and Canada (55). Eight studies used bifocals (BFs), one used novel lens designs that corrected hyperopic defocus partly or fully in the periphery, and the other six used PALs as the intervention. For the relative peripheral positive powers, + 3.50 D was used in one study (46), + 2.5 D was used in four studies (42, 47, 49, 52), + 2.00 D was used in six

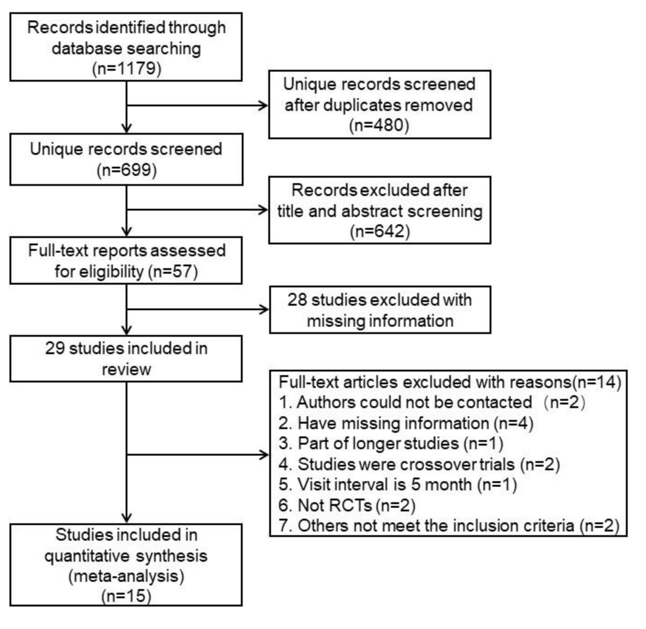

FIGURE 1 | A flowchart of study selection.

[1]http://getdata-graph-digitizer.com

[2]http://tech.cochrane.org/revman

TABLE 1 | Characteristics of included annual-visit studies in meta-analysis.

Study	Location	Intervention/ Control	Age of participants (years)	No. of participants	Female (%) MSLs SVLs	Drop-out N (%) MSFs SVLs	Follow-up, months	Baseline SER
Walline et al. (52)	United States	BF a: H:add + 2.5 Day SVL	(7–11 years) 10.2 ± 1.2 10.5 ± 0.96	196 (98 + 98)	64 (65.3) 64 (65.3)	12 (4.1)	36	−0.75 ∼ −5.0 Day −2.28 ± 0.9 Day −2.46 ± 0.97
Chamberlain et al. (53)	Portugal + United Kingdom + Singapore + Canada	Misight, BF add + 2.0 Day SVL	(8–12 years) 10.1 ± 1.3 10.1 ± 1.4	144 (70 + 74)	32 (46) 37 (50)	12 (24.2) 18 (24.3)	36	−0.75 ∼ −4.0 Day −2.02 ± 0.77 −2.19 ± 0.81
Ruiz-Pomeda et al. (22)	Spain	Misight, BF add + 2.0 Day SVL	(8–12 years) 11.01 ± 1.23 10.12 ± 1.38	79 (46 + 33)	NA	5 (10.9) 0 (0)	24	−0.75 ∼ −4.0 Day −2.16 ± 0.94 −1.75 ± 0.94
Cheng et al. (55)	Canada	BF a: add + 1.5 Day, b: Prismatic, add+1.5 Day + $3^{-\blacktriangle}$ SVL	(8–13 years) 10.1 ± 0.2 10.4 ± 0.3 10.3 ± 0.3	150 (50 + 50 + 50)	24 (48) 25 (50) 24 (48)	2 (4) 4 (8) 0 (0)	36	>1.0 Day −3.08 ± 0.1 Day
Walline et al. (51)	United States	BF, add + 2.0 Day SVL	(8–11 years) 10.8 ± 0.7 10.8 ± 1.0	80 (40 + 40)	18 (56.3) 18 (56.3)	13 (26) 13 (26)	24	−1.0 ∼ −6.0 Day −2.35 ± 1.05 −2.24 ± 1.02
COMET (54)	United States	PAL add + 2.0 Day SVL	(8–12 years) 10.2 ± 1.1 10.0 ± 1.1	118 (59 + 59)	33 (63.5) 27 (47)	7 (11.86) 1 (1.69)	36	−0.75 ∼ −2.5 Day −1.45 ± 0.47 −1.5 ± 0.45

BF, bifocal; PAL, progressive addition lens; SVLs, single-vision lenses; NA, not available.

studies (22, 36, 44, 45, 51, 54), + 1.9 D was used in one study (45), + 1.50 D were used in three studies (47, 52, 55), and + 1.0 D was used in one study (45).

Trial Quality

Quality assessment of the included studies was performed by the Newcastle–Ottawa Quality Assessment Scale items (**Table 3**). This includes 15 items with following three domains: Selection (representativeness), comparability (because of design or analysis), and outcomes (assessment and follow-up). One study can be awarded a maximum of one star for each numbered item within the selection and outcome categories. A maximum of two stars can be given for comparability. The quality of the included RCTs was generally high, the scores from all trials are ≥6.

The Risk of Bias of the Including Trials

The risk of bias (**Figures 2**) of the included studies was assessed by Revman 5.3 according to the following points: (1) Random sequence generation (selection bias); (2) Allocation concealment (selection bias); (3) Blinding of participants and personnel (performance bias); (4) Blinding of outcome assessment (detection bias); (5) Incomplete outcome data (attrition bias); (6) Selective reporting (reporting bias); and (7) Other bias. The masking was not adequate in four studies (22, 44, 51, 55) and no allocation concealment was present in one paper (51). In general, the risks of these 15 trials were low (**Figure 2**).

Treatment Effects of Multifocal Lens Assessed for Spherical Equivalent Refraction and Axial Length

The mean differences of SER and AL between MFLs and SVLs were calculated. Since the part of the subgroups shows moderate heterogeneity ($I^2 > 50\%$ and $p < 0.05$) across the studies, we analyzed the data with a random-effect model as the previous studies did.

Annual (12-months) visit group includes six trials and among which four trials finished 3 years' follow up (**Figure 3**). By analyzing SER in this group, the weighted mean differences (WMDs) of myopic progresses with MFLs are 0.29 D (95% CI, 0.21 ∼ 0.37, $p < 0.00001$) slower than SVLs at first year, 0.46 D (95% CI, 0.32 ∼ 0.60, $p < 0.00001$) and 0.64 D (95% CI, 0.40 ∼ 0.88, $p < 0.00001$) at the second and third year, respectively. For the AL (**Figure 4**), the myopic progresses with MFLs are −0.12 mm (95% CI, −0.14 ∼ −0.11, $p < 0.00001$), −0.19 mm (95% CI, −0.22 ∼ −0.16, $p < 0.00001$), and −0.26 mm (95% CI, −0.31 ∼ −0.21, $p < 0.00001$) less compared to SVLs at the first, second, and third year. With annual visit subgroup, we could conclude that the inhibition of the myopic progress of MFLs in both SER and AL are significant and sustained at least for 3 years, which is different with the previous analysis (25, 26). Heterogeneity of this subgroup analysis are moderate in SER (12 months: $p = 0.06$, $I^2 = 51\%$; 24 months: $p = 0.005$, $I^2 = 68\%$; 36 months: $p < 0.002$, $I^2 = 76\%$) and none in AL (12 months: $p = 0.62$, $I^2 = 0\%$; 24 months: $p = 0.42$, $I^2 = 0\%$; 36 months: $p = 0.65$, $I^2 = 0\%$). When the prismatic bifocal

TABLE 2 | Characteristics of included 6-months visit studies in meta-analysis.

Study	Location	Intervention/ Control	Age of participants (years)	No. of participants	Female (%) MSLs, SVLs	Drop-out N (%) MSFs SVLs	Follow-up, months	baseline SER
Lam et al. (46)	China	DIMS, BF, Relative peripheral power + 3.5 Day SVL	8–13 years 10.2 ± 1.47 10 ± 1.45	183 (93 + 90)	41.80 45.70	14 (15) 9 (10)	24	−1.0 ∼ −5.0 Day −2.97 ± 0.97 −2.76 ± 0.96
Garcia-Del Valle et al. (42)	Spain	PALs, add + 2.5 Day SVL	(7–15 years) 12.2 ± 2.22 11.9 ± 2.13	70 (36 + 34)	19 (59.4) 18 (69.2)	4 (11.1) 8 (23.5)	12	−0.5 ∼ −8.75 Day −2.8 ± 1.79 −3.31 ± 1.76
Sankaridurg et al. (47)	China	Relative peripheral power a: I add + 2.5 Day, b: II add + 1.5 Day, SVL	(8–13 years) 10.4 ± 1.3 10.4 ± 1.3 10.5 ± 1.3	306 (103 + 101 + 102)	49 (47.6) 52 (51.5) 43 (42.2)	56 (54.4) 56 (55.4) 52 (50.1)	24	−0.75 ∼ −3.5 Day −2.38 ± 0.82 −2.39 ± 0.79 −2.29 ± 0.75
Cheng et al. (48)	United States	+ SA SVL	(8–11 years) 9.7 ± 1.11 9.7 ± 1.05	127 (64 + 63)	24 (45.3) 27 (45.8)	11 (17.2) 4 (6.8)	24	−0.75 ∼ −4.0 Day −2.52 ± 1.094 −2.44 ± 0.911
Aller (43)	Australia	BF SVL	(8–18 years) 13.0 ± 2.5 13.5 ± 2.2	86 (43+ 43)	27 (62.8) 27 (62.8)	4 (9.30) 3 (6.98)	12	−0.5 ∼ −6.0 Day −2.57 ± 1.34 −2.81 ± 1.46
Lam et al. (49)	China	DISC, BF add + 2.5 Day SVL	(8–13 years) 11.06 ± 1.55 10.87 ± 1.67	221 (111 + 110)	44 (67.7) 39 (61.9)	46 (41.4) 47 (42.7)	24	−1.0 ∼ −5.0 Day −2.9 ± 1.05 −2.80 ± 1.03
Hasebe et al. (50)	China Japan	PAL, a: add + 1.0 Day b: add + 1.5 Day SVL	(6–12 years) 10.6 ± 1.50 10.0 ± 1.50 10.2 ± 1.20	197 (67 + 67 + 63)	30 (45) 20 (32) 24 (36)	9 (13) 12 (19) 710)	24	−1.0 ∼ −4.5 Day −2.52 ± 1.01 −2.80 ± 1.02 −2.55 ± 0.96
Sankaridurg et al. (44)	China	PAL, add + 2.0 Day SVL	(7–14 years) 11.6 ± 1.5 10.8 ± 1.9	100 (60 + 40)	23 (51) 17 (43)	17 (28.3)1 (2.5)	12	−0.75 ∼ −3.5 Day −2.9 ± 1.05 −2.8 ± 1.03
Sankaridurg et al. (45)	China	Relative peripheral power a:Type I add + 1.0 Day b:Type II add + 2.0 Day c:Type III add + 1.9 Day SVL	(6–16 years) 10.7 ± 2.4 11.1 ± 2.2 11.4 ± 2.3 10.0 ± 1.1	210 (50 + 60 + 50 + 50)	27 (54) 26 (43) 25 (50) 22 (44)	2 (4) 2 (3) 4 (8) 1 (2)	12	−0.75 ∼ −3.5 Day −1.82 ± 0.62 −1.81 ± 0.67 −1.82 ± 0.66 −1.87 ± 0.68

BF, bifocal; PAL, progressive addition lens; SVLs, single-vision lenses.

intervention group of the study by Cheng et al. (55) was excluded from the SER analysis, the heterogeneity (I^2) reduced to 39% ($p = 0.14$), 51% ($p = 0.07$), and 69% ($p = 0.02$) at 12-, 24-, and 36 months, respectively. The mean differences reduced to 0.27 D (95% CI, 0.19 ∼ 0.34, $p < 0.00001$), 0.41 D (95% CI, 0.30 ∼ 0.53, $p < 0.00001$), and 0.56 D (95% CI, 0.34 ∼ 0.78, $p < 0.00001$) at 12-, 24-, and 36 months, respectively.

On analyzing SER in 6-months interval visit group (**Figure 5**), the inhibition levels of the myopic progress with MFLs are 0.14 D (95% CI, 0.08 ∼ 0.20, $p < 0.0001$), 0.19 D (95% CI, 0.11 ∼ 0.28, $p < 0.0001$), 0.24 D (95% CI, 0.16 ∼ 0.33, $p < 0.0001$), and 0.31 D (95% CI, 0.18 ∼ 0.44, $p < 0.0001$) at 6, 12, 18, and 24, respectively. For AL reduction levels with MFLs in this group (**Figure 6**) are −0.08 mm (95% CI −0.09 ∼ −0.07, $p < 0.00001$) at 6 months, −0.10 mm (95% CI −0.12 ∼ −0.09, $p < 0.00001$) at 12 months, −0.14 mm (95% CI −0.17 ∼ −0.11, $p < 0.00001$) at 18 months and −0.18 mm (95% CI −0.22 ∼ -0.14, $p < 0.00001$) at 24 months. We could show that a slightly decreased treatment effect was observed after first visit in both SER and AL, which is consistent with the previous meta-analysis (25, 26). However, we also observed an obvious rebound in AL at the following data points. A small or moderate heterogeneity in SER (6 months: $p = 0.002$, $I^2 = 61\%$; 12 months: $p < 0.0001$, $I^2 = 72\%$; 18 months: $p = 0.3$, $I^2 = 18\%$, 24 months: $p = 0.07$, $I^2 = 50\%$) and a moderate or high heterogeneity in AL analysis (6 months: $p < 0.00001$, $I^2 = 87\%$; 12 months: $p < 0.00001$, $I^2 = 75\%$; 18 months: $p < 0.00001$, $I^2 = 87\%$; 24 months: $p = 0.0002$, $I^2 = 79\%$) of this subgroup is detected. When excluding the study with defocus incorporated multiple segments (DIMS) spectacle lenses in this subgroup from Lam et al. (46), the heterogeneity reduced to a tolerable level or zero in both SER (6 months: $p = 0.004$, $I^2 = 60\%$; 12 months: $p < 0.0002$, $I^2 = 69\%$; 18 months: $p = 0.99$, $I^2 = 0\%$, 24 months: $p = 0.99$, $I^2 = 0\%$) and AL (6 months: $p < 0.00001$, $I^2 = 76\%$; 12 months: $p = 0.0007$, $I^2 = 66\%$; 18 months: $p = 0.19$, $I^2 = 34\%$; 24 months: $p = 0.47$, $I^2 = 0\%$).

TABLE 3 | Quality assessment of cohort studies included in the meta-analysis using Newcastle–Ottawa quality assessment scale.

	Selection				Outcome				
	Exposed cohort representative	Non-exposed cohort selection	Exposure ascertainment	Outcome not present at star	Comparability of cohorts	Assessment	Follow-up length	Follow-up adequacy	NOS score
Study									
Lam et al. (46)	★	★	★	★	★★	★	★	★	9
Garcia-Del Valle et al. (42)	★	★	★	★	★★	★	★	★	9
Sankaridurg et al. (47)	★	★	★	★	★★	★	★	☆	8.5
Cheng et al. (48)	★	★	★	★	★★	★	★	★	9
Aller (43)	★	★	★	★	★★	★	☆	★	8.5
Lam et al. (49)	★	★	★	★	★★	★	★	☆	8.5
Hasebe et al. (50)	★	★	★	★	★★	★	★	☆	8.5
Sankaridurg et al. (44)	★	★	☆	★	★	☆	★	★	7
Sankaridurg et al. (45)	★	★	★	★	★★	☆	★	★	8.5
Walline et al. (52)	★	☆	★	★	★★	★	★	★	8.5
Chamberlain et al. (53)	★	★	★	★	★★	★	★	☆	8.5
Ruiz-Pomeda et al. (22)	★	☆	★	★	★	★	★	★	7.5
Cheng et al. (55)	★	★	☆	★	★	☆	★	★	7
Walline et al. (51)	★	☆	☆	★	★	☆	★	☆	6
COMET (54)	★	★	★	★	★★	☆	★	★	8.5

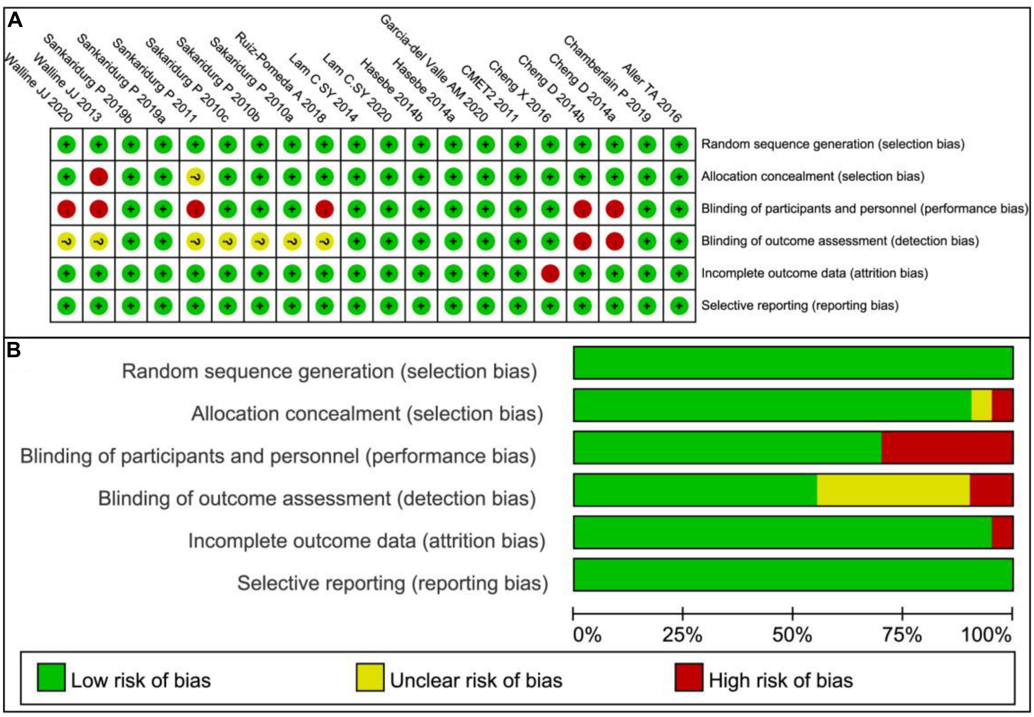

FIGURE 2 | Risk of bias graph. **(A)** Risk of bias summary: Review authors' judgments about each risk of bias item for each included study. **(B)** Risk of bias graph: Review authors' judgments about each risk of bias item presented as percentages across all included studies.

The mean differences of SER (6 months: 0.13 mm, 95% CI 0.07 ∼ 0.19, $p < 0.00001$; 12 months: 0.18 mm, 95% CI 0.09 ∼ 0.27, $p = 0.00001$; 18 months: 0.19 mm, 95% CI 0.10 ∼ 0.28, $p < 0.0001$; 24 months: 0.24 mm, 95% CI 0.14 ∼ −0.34, $p < 0.00001$) and AL (6 months: −0.06 mm, 95% CI −0.09 ∼ −0.04, $p < 0.00001$; 12 months: −0.09 mm, 95% CI −0.12 ∼ −0.05, $p < 0.00001$; 18 months: −0.08 mm, 95% CI −0.13 ∼ −0.04, $p = 0.0002$ and 24 months: −0.13 mm, 95% CI −0.17 ∼ −0.08, $p < 0.00001$) are also reduced a little bit accordingly but without altering the conclusions.

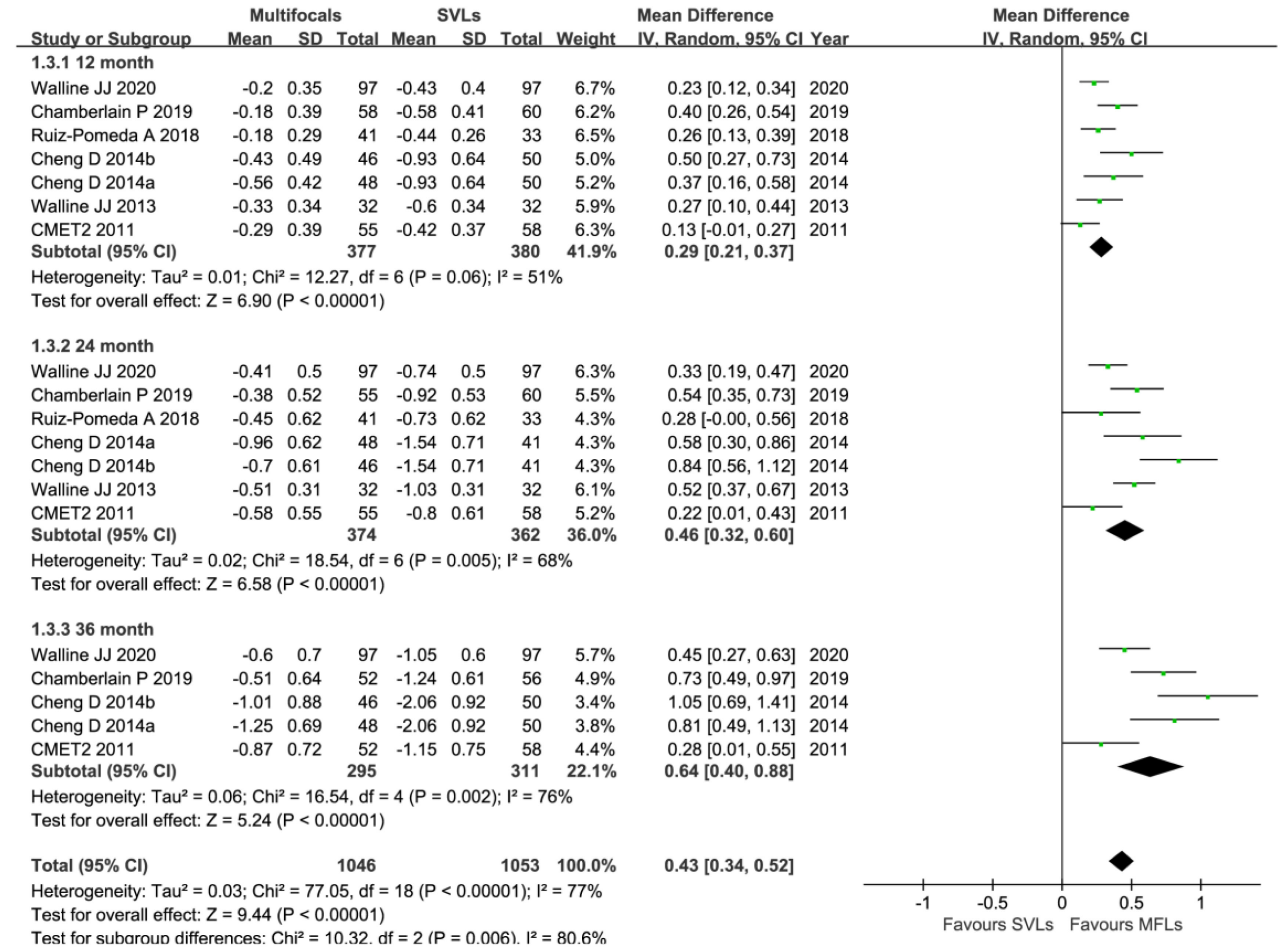

FIGURE 3 | Forest plot about the change of SER in annual interval visit trials.

In short summary, our systematic analysis clearly showed that the treatment effects of MFLs to slow down the myopic progress are positive in both 6-months and annual-visit trials and which could be sustained to 36 months. While a slight weaker treatment effect was observed after the first visit in 6-months visit, a slight rebound was observed at following visit points. Furthermore, the treatment effects in annual visit are more profound than 6-months visit at almost all stages especially in SER although this trend did not reach the statistic difference likely due to the enrolled number of annual studies is not enough. Furthermore, this observation is not altered when excluding the related studies to reduce the heterogeneity, indicating the conclusion is in principle acceptable. Thus, our analysis encourages the MFLs users to maintain a long-term treatment with annual visit.

DISCUSSION

Currently, the most prevalent treatments to control the myopia progress involves in pharmacological agents such as atropine ophthalmologic drops, orthokeratology (OK), and MFL. Atropine ophthalmologic drops could reduce accommodation and increase pupillary diameter, resulting in well-controlled myopia progress (56). However, because of its side-effects such as photophobia, poor near visual acuity, increased pupillary diameter, and headache, many parents terminate the treatment with atropine for their children. In addition, the mechanism why atropine could control myopic progress and whether long-term application of antimuscarinic agents on ocular tissue is harmful or not remain to be determined (38). Orthokeratology is suitable for the low-to-moderate myopia, the children can wear it overnight to remodel the corneal epithelial into a flatter and less powerful refractive surface, achieving a transient emmetropia (57, 58). According to the clinical trials, the axial elongation with OK group could be significantly inhibited and the peripheral refractive status of the cornea could be less hyperopic defocus when comparing with single vision group (59). However, the children who take OK treatments are easy to suffer from microbial keratitis, contact lens irritation, dry eye, and corneal epithelial iron deposition (60, 61).

In this study, we summarized currently available evidences of controlling myopia progression in school-aged children aged 6–18 years from 15 RCTs to dissect the potential roles of MFLs treatment. The effects of MFLs to slow down the myopic progress

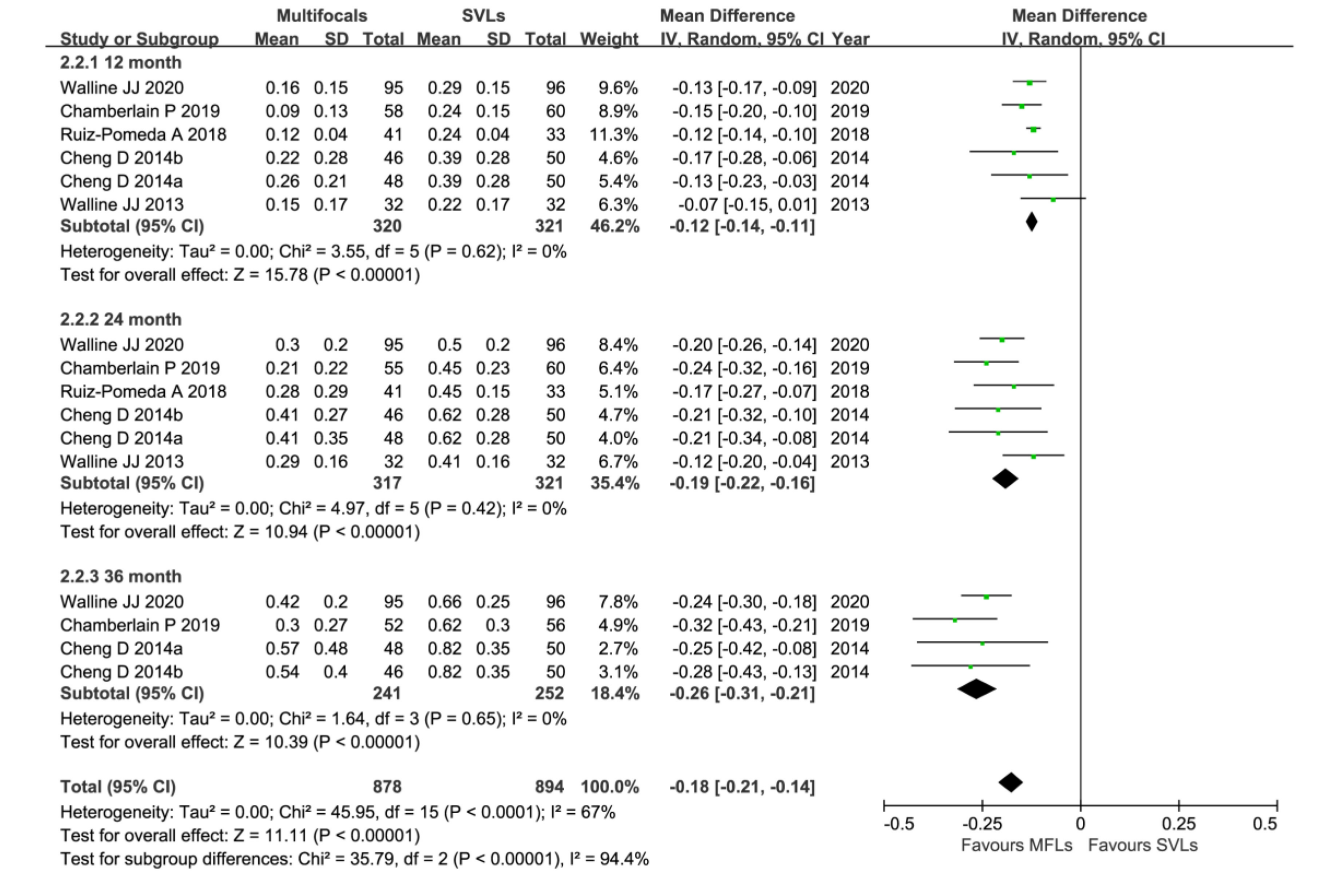

FIGURE 4 | Forest plot about the change of AL in annual interval visit trials.

could be sustained to 36 months but with slightly decreased effects from the second visit. While the treatment effects in both 6-months and annual-visit trials are positive, the annual visit is more profound comparing to 6-months visit group (**Figure 7**) although no statistic difference was detected which is likely due to the variability and small samples.

It is still unknown why a decreased effect happened after first visit in both 6-months visit and annual visit trials not only in our analysis but also in the previous reports (25, 26). Our analysis showed that in annual visit, differences of mean SER change is 0.29 D for the first year, 0.17 D for the 12–24 months and 0.18 D for the 24–36 months; of mean AL change is −0.12 mm for the first year, −0.07 mm for the 12–24 months and −0.17 mm for the 24–36 months. In 6-months visit, the difference of mean SER change is 0.14 D for the first visit and around 0.05–0.07 D for the following visit intervals; of mean AL change is −0.07 mm for the first visit and −0.04 to −0.02 mm for the following visits. Kaphle et al. proposed accommodation adaptation may play a role to explain this phenomenon (25). It was reported that the lag of accommodation gradually increases while a person wearing MFLs (62), the same addition power may not be as effective as it did earlier. Therefore, to maintain the effective treatment for MFLs as they were in the beginning of the trial, the power of the addition should be increased gradually. In addition, they also supposed that the age is a critical factor since myopia usually stabilizes when a child reaches a certain age which means the rate of myopia progression decreases over time in the SVLs control group, and hence the treatment effect of the myopia intervention reduces as it is determined *via* comparison with the progression of the SVLs group. This argument is however not very reliable since the average age of children involved in these clinic trails is around 9.5–12 years old at least in current study (**Tables 1**, **2**), which is far from the stage for the myopia stabilization although a slower and more stable rates of change of myopia after onset was observed (63, 64).

In addition, we clearly present an obvious difference in distinct treatment intervals. Comparing to 6-months trails, the annual visit with MFLs show more profound effects [annual vs. 6-months visit: SER: 0.29 D (95% CI 0.21 ∼ 0.37) vs. 0.19 D (95% CI 0.11 ∼ 0.28) at the first year, 0.46 D (95% CI 0.32 ∼ 0.60) vs. 0.31 D (95% CI 0.18 ∼ 0.44) at the second year; AL: −0.12 (95% CI −0.14 ∼ −0.11) vs. −0.07 (95% CI −0.10 ∼ −0.04) at the first year, −0.19 (95% CI −0.22 ∼ -0.16) vs. −0.10 (95% CI −0.13 ∼ −0.06) at the second year]. One possibility could be that frequent lens power adjustment (less than 1 year) affects the accommodation adaptation response which eventually blocks the treatment effects. Thus, the detailed mechanisms on why frequent lens power adjustment is not conducive to myopia control in this case should be further explored.

Study or Subgroup	Multifocals Mean	Multifocals SD	Multifocals Total	SVLs Mean	SVLs SD	SVLs Total	Weight	Mean Difference IV, Random, 95% CI	Year
1.4.1 6 month									
Lam C.SY 2020	-0.13	0.27	65	-0.37	0.36	55	3.4%	0.24 [0.12, 0.36]	2020
Garcia-del Valle AM 2020	-0.25	0.33	32	-0.46	0.53	26	2.0%	0.21 [-0.02, 0.44]	2020
Sankaridurg P 2019a	-0.23	0.29	66	-0.39	0.25	74	3.7%	0.16 [0.07, 0.25]	2019
Sankaridurg P 2019b	-0.27	0.24	67	-0.39	0.25	74	3.8%	0.12 [0.04, 0.20]	2019
Cheng X 2016	-0.19	0.28	39	-0.39	0.33	38	3.1%	0.20 [0.06, 0.34]	2016
Aller TA 2016	-0.17	0.3	39	-0.48	0.3	40	3.2%	0.31 [0.18, 0.44]	2016
Hasebe 2014a	-0.54	0.68	65	-0.56	0.68	64	2.0%	0.02 [-0.21, 0.25]	2014
Lam C SY 2014	-0.21	0.28	65	-0.26	0.33	63	3.5%	0.05 [-0.06, 0.16]	2014
Hasebe 2014b	-0.45	0.67	63	-0.56	0.68	64	2.0%	0.11 [-0.12, 0.34]	2014
Sankaridurg P 2011	-0.28	0.28	45	-0.57	0.33	40	3.2%	0.29 [0.16, 0.42]	2011
Sakaridurg P 2010a	-0.51	0.34	50	-0.55	0.35	50	3.1%	0.04 [-0.10, 0.18]	2010
Sakaridurg P 2010c	-0.47	0.3	50	-0.55	0.35	50	3.2%	0.08 [-0.05, 0.21]	2010
Sakaridurg P 2010b	-0.6	0.33	60	-0.55	0.35	50	3.2%	-0.05 [-0.18, 0.08]	2010
Subtotal (95% CI)			**706**			**688**	**39.3%**	**0.14 [0.08, 0.20]**	
Heterogeneity: Tau² = 0.01; Chi² = 30.99, df = 12 (P = 0.002); I² = 61%									
Test for overall effect: Z = 4.66 (P < 0.00001)									
1.4.2 12 month									
Garcia-del Valle AM 2020	-0.28	0.35	32	-0.57	0.52	26	2.0%	0.29 [0.06, 0.52]	2020
Lam C.SY 2020	-0.17	0.44	65	-0.55	0.36	55	3.0%	0.38 [0.24, 0.52]	2020
Sankaridurg P 2019b	-0.52	0.36	60	-0.66	0.34	69	3.3%	0.14 [0.02, 0.26]	2019
Sankaridurg P 2019a	-0.46	0.36	63	-0.66	0.34	69	3.3%	0.20 [0.08, 0.32]	2019
Cheng X 2016	-0.55	0.41	39	-0.68	0.52	38	2.2%	0.13 [-0.08, 0.34]	2016
Aller TA 2016	-0.22	0.34	39	-0.79	0.43	40	2.7%	0.57 [0.40, 0.74]	2016
Hasebe 2014a	-0.71	0.56	64	-0.8	0.67	63	2.2%	0.09 [-0.12, 0.30]	2014
Hasebe 2014b	-0.56	0.53	57	-0.8	0.67	63	2.2%	0.24 [0.02, 0.46]	2014
Lam C SY 2014	-0.36	0.37	65	-0.48	0.47	63	3.0%	0.12 [-0.03, 0.27]	2014
Sankaridurg P 2011	-0.54	0.37	45	-0.84	0.47	40	2.5%	0.30 [0.12, 0.48]	2011
Sakaridurg P 2010a	-0.81	0.42	50	-0.78	0.5	50	2.6%	-0.03 [-0.21, 0.15]	2010
Sakaridurg P 2010c	-0.66	0.41	50	-0.78	0.5	50	2.6%	0.12 [-0.06, 0.30]	2010
Sakaridurg P 2010b	-0.81	0.46	60	-0.78	0.5	50	2.6%	-0.03 [-0.21, 0.15]	2010
Subtotal (95% CI)			**689**			**676**	**34.1%**	**0.19 [0.11, 0.28]**	
Heterogeneity: Tau² = 0.02; Chi² = 42.66, df = 12 (P < 0.0001); I² = 72%									
Test for overall effect: Z = 4.31 (P < 0.0001)									
1.4.3 18 month									
Lam C.SY 2020	-0.31	0.53	79	-0.72	0.45	81	2.9%	0.41 [0.26, 0.56]	2020
Sankaridurg P 2019b	-0.7	0.46	48	-0.88	0.46	56	2.6%	0.18 [0.00, 0.36]	2019
Sankaridurg P 2019a	-0.68	0.46	49	-0.88	0.46	56	2.6%	0.20 [0.02, 0.38]	2019
Lam C SY 2014	-0.5	0.43	65	-0.71	0.52	63	2.7%	0.21 [0.04, 0.38]	2014
Hasebe 2014a	-0.97	0.66	60	-1.1	0.9	63	1.6%	0.13 [-0.15, 0.41]	2014
Hasebe 2014b	-0.88	0.63	55	-1.1	0.9	63	1.6%	0.22 [-0.06, 0.50]	2014
Subtotal (95% CI)			**356**			**382**	**14.1%**	**0.24 [0.16, 0.33]**	
Heterogeneity: Tau² = 0.00; Chi² = 6.12, df = 5 (P = 0.30); I² = 18%									
Test for overall effect: Z = 5.53 (P < 0.00001)									
1.4.4 24 month									
Lam C.SY 2020	-0.38	0.54	79	-0.93	0.54	81	2.7%	0.55 [0.38, 0.72]	2020
Sankaridurg P 2019b	-0.88	0.51	45	-1.15	0.51	50	2.3%	0.27 [0.06, 0.48]	2019
Sankaridurg P 2019a	-0.87	0.56	47	-1.15	0.51	50	2.2%	0.28 [0.07, 0.49]	2019
Hasebe 2014a	-1.12	0.71	51	-1.39	0.98	60	1.4%	0.27 [-0.05, 0.59]	2014
Hasebe 2014b	-1.2	0.75	58	-1.39	0.98	60	1.4%	0.19 [-0.12, 0.50]	2014
Lam C SY 2014	-0.59	0.49	65	-0.79	0.56	63	2.5%	0.20 [0.02, 0.38]	2014
Subtotal (95% CI)			**345**			**364**	**12.5%**	**0.31 [0.18, 0.44]**	
Heterogeneity: Tau² = 0.01; Chi² = 10.02, df = 5 (P = 0.07); I² = 50%									
Test for overall effect: Z = 4.74 (P < 0.00001)									
Total (95% CI)			**2096**			**2110**	**100.0%**	**0.19 [0.15, 0.24]**	
Heterogeneity: Tau² = 0.01; Chi² = 109.67, df = 37 (P < 0.00001); I² = 66%									
Test for overall effect: Z = 8.39 (P < 0.00001)									
Test for subgroup differences: Chi² = 7.78, df = 3 (P = 0.05), I² = 61.4%									

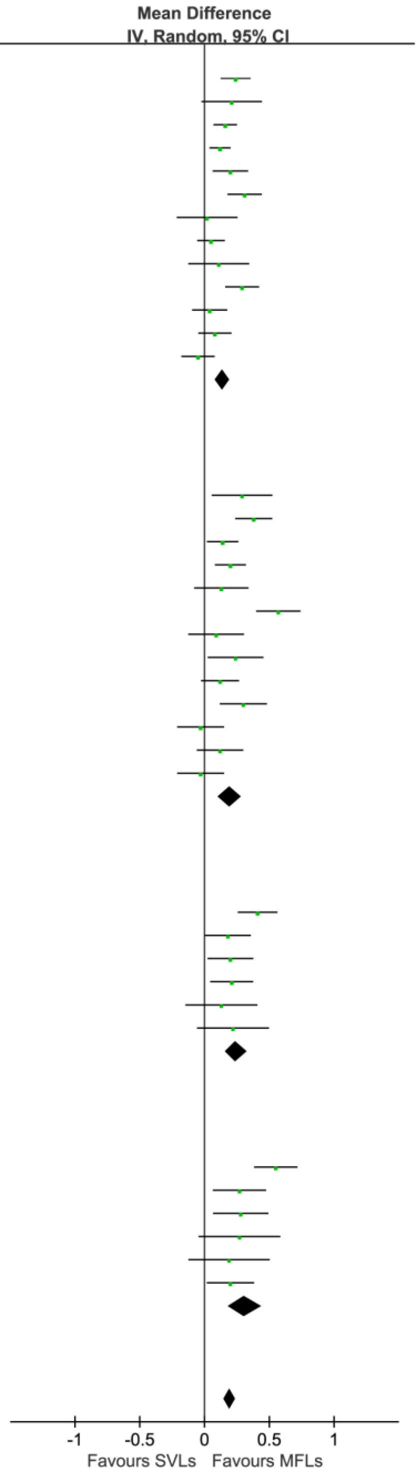

FIGURE 5 | Forest plot about the change of SER in 6-months interval visit trials.

There are several limitations in our study. First, only the RCTs were included in the analysis. We excluded at least one clinic research from Paune et al. (36) which is a prospective, longitudinal, non-randomized study (36). In addition, a few studies, for example the trials from Fujikado et al. (39) and Berntsen et al. (41) met the inclusion criteria, but were not included because of unavailability of data at the required time points.

Study or Subgroup	Multifocals Mean	Multifocals SD	Multifocals Total	SVLs Mean	SVLs SD	SVLs Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
2.3.1 6 month									
Garcia-del Valle AM 2020	0.07	0.1	32	0.09	0.1	26	2.8%	-0.02 [-0.07, 0.03]	2020
Lam C.SY 2020	0.03	0.09	79	0.2	0.09	81	9.7%	-0.17 [-0.20, -0.14]	2020
Sankaridurg P 2019a	0.1	0.08	63	0.19	0.09	74	9.3%	-0.09 [-0.12, -0.06]	2019
Sankaridurg P 2019b	0.12	0.08	64	0.19	0.09	74	9.3%	-0.07 [-0.10, -0.04]	2019
Aller TA 2016	0.03	0.1	39	0.14	0.11	40	3.5%	-0.11 [-0.16, -0.06]	2016
Cheng X 2016	0.06	0.1	39	0.17	0.1	38	3.8%	-0.11 [-0.15, -0.07]	2016
Hasebe 2014a	0.18	0.15	65	0.22	0.14	64	3.0%	-0.04 [-0.09, 0.01]	2014
Hasebe 2014b	0.19	0.13	63	0.22	0.14	64	3.4%	-0.03 [-0.08, 0.02]	2014
Lam C SY 2014	0.07	0.11	65	0.11	0.12	63	4.7%	-0.04 [-0.08, -0.00]	2014
Sankaridurg P 2011	0.09	0.11	45	0.26	0.12	40	3.1%	-0.17 [-0.22, -0.12]	2011
Sakaridurg P 2010b	0.24	0.13	60	0.25	0.13	50	3.2%	-0.01 [-0.06, 0.04]	2010
Sakaridurg P 2010c	0.21	0.1	50	0.25	0.13	50	3.6%	-0.04 [-0.09, 0.01]	2010
Sakaridurg P 2010a	0.24	0.13	50	0.25	0.13	50	2.9%	-0.01 [-0.06, 0.04]	2010
Subtotal (95% CI)			**714**			**714**	**62.3%**	**-0.08 [-0.09, -0.07]**	
Heterogeneity: Chi² = 90.94, df = 12 (P < 0.00001); I² = 87%									
Test for overall effect: Z = 14.70 (P < 0.00001)									
2.3.2 12 month									
Garcia-del Valle AM 2020	0.13	0.12	32	0.22	0.14	26	1.6%	-0.09 [-0.16, -0.02]	2020
Lam C.SY 2020	0.11	0.18	79	0.32	0.18	81	2.4%	-0.21 [-0.27, -0.15]	2020
Sankaridurg P 2019a	0.19	0.16	63	0.33	0.13	69	3.0%	-0.14 [-0.19, -0.09]	2019
Sankaridurg P 2019b	0.23	0.16	60	0.33	0.13	69	2.9%	-0.10 [-0.15, -0.05]	2019
Aller TA 2016	0.05	0.14	39	0.24	0.17	40	1.6%	-0.19 [-0.26, -0.12]	2016
Cheng X 2016	0.23	0.15	39	0.37	0.16	38	1.6%	-0.14 [-0.21, -0.07]	2016
Hasebe 2014b	0.33	0.18	57	0.38	0.2	63	1.6%	-0.05 [-0.12, 0.02]	2014
Hasebe 2014a	0.37	0.21	64	0.38	0.2	63	1.5%	-0.01 [-0.08, 0.06]	2014
Lam C SY 2014	0.13	0.11	65	0.21	0.19	63	2.6%	-0.08 [-0.13, -0.03]	2014
Sankaridurg P 2011	0.24	0.17	45	0.39	0.19	40	1.3%	-0.15 [-0.23, -0.07]	2011
Sakaridurg P 2010c	0.31	0.1	50	0.36	0.22	50	1.7%	-0.05 [-0.12, 0.02]	2010
Sakaridurg P 2010b	0.35	0.2	60	0.36	0.22	50	1.2%	-0.01 [-0.09, 0.07]	2010
Sakaridurg P 2010a	0.36	0.22	50	0.36	0.22	50	1.0%	0.00 [-0.09, 0.09]	2010
Subtotal (95% CI)			**703**			**702**	**24.0%**	**-0.10 [-0.12, -0.09]**	
Heterogeneity: Chi² = 47.83, df = 12 (P < 0.00001); I² = 75%									
Test for overall effect: Z = 11.44 (P < 0.00001)									
2.3.3 18 month									
Lam C.SY 2020	0.15	0.18	79	0.43	0.18	81	2.4%	-0.28 [-0.34, -0.22]	2020
Sankaridurg P 2019a	0.34	0.21	49	0.47	0.19	56	1.3%	-0.13 [-0.21, -0.05]	2019
Sankaridurg P 2019b	0.35	0.18	48	0.47	0.19	56	1.5%	-0.12 [-0.19, -0.05]	2019
Hasebe 2014b	0.48	0.2	55	0.53	0.31	63	0.9%	-0.05 [-0.14, 0.04]	2014
Lam C SY 2014	0.2	0.2	65	0.29	0.22	63	1.4%	-0.09 [-0.16, -0.02]	2014
Hasebe 2014a	0.53	0.2	60	0.53	0.31	63	0.9%	0.00 [-0.09, 0.09]	2014
Subtotal (95% CI)			**356**			**382**	**8.3%**	**-0.14 [-0.17, -0.11]**	
Heterogeneity: Chi² = 38.88, df = 5 (P < 0.00001); I² = 87%									
Test for overall effect: Z = 9.31 (P < 0.00001)									
2.3.4 24 month									
Lam C.SY 2020	0.21	0.18	79	0.53	0.27	81	1.5%	-0.32 [-0.39, -0.25]	2020
Sankaridurg P 2019a	0.41	0.24	47	0.6	0.22	50	0.9%	-0.19 [-0.28, -0.10]	2019
Sankaridurg P 2019b	0.46	0.24	45	0.6	0.22	50	0.9%	-0.14 [-0.23, -0.05]	2019
Hasebe 2014b	0.6	0.28	51	0.69	0.38	60	0.5%	-0.09 [-0.21, 0.03]	2014
Hasebe 2014a	0.63	0.3	58	0.69	0.38	60	0.5%	-0.06 [-0.18, 0.06]	2014
Lam C SY 2014	0.25	0.23	65	0.36	0.24	63	1.1%	-0.11 [-0.19, -0.03]	2014
Subtotal (95% CI)			**345**			**364**	**5.4%**	**-0.18 [-0.22, -0.14]**	
Heterogeneity: Chi² = 24.24, df = 5 (P = 0.0002); I² = 79%									
Test for overall effect: Z = 9.44 (P < 0.00001)									
Total (95% CI)			**2118**			**2162**	**100.0%**	**-0.10 [-0.11, -0.09]**	
Heterogeneity: Chi² = 236.94, df = 37 (P < 0.00001); I² = 84%									
Test for overall effect: Z = 22.08 (P < 0.00001)									
Test for subgroup differences: Chi² = 35.05, df = 3 (P < 0.00001), I² = 91.4%									

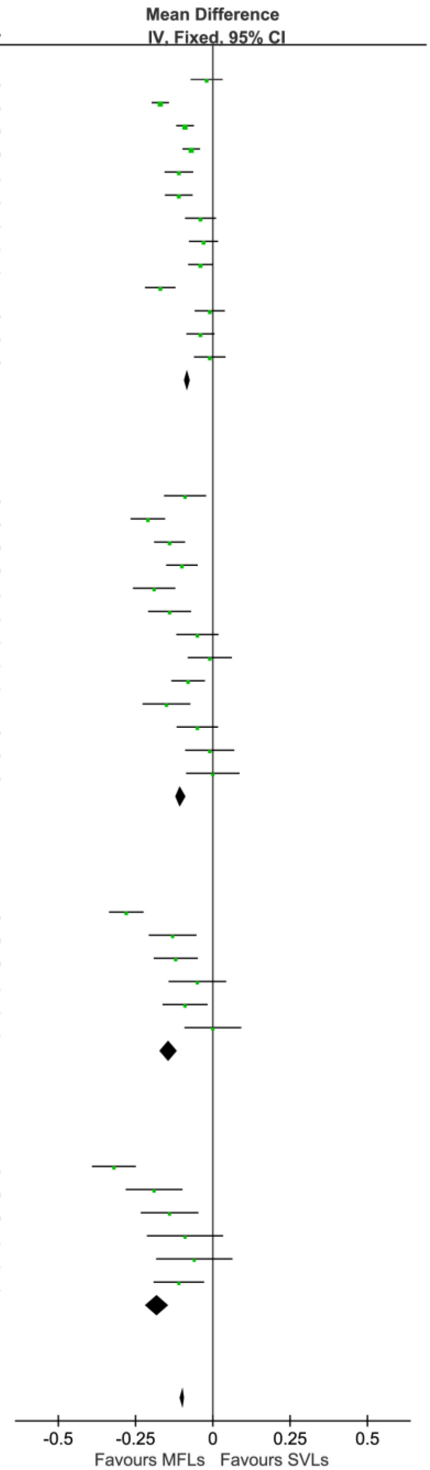

FIGURE 6 | Forest plot about the change of AL in 6-months interval visit trials.

In addition, much fewer (only 4 in 15 RCTs) studies finished 3-year observation. One trial from Lam et al. (46) was a part of the data from Lam (35) by year of 2021. However, the data at 36 months from the trail of Lam et al. (35) was discarded because it lacks of control data since the control group of this trial was switched from SVLs to MFLs at this time point. Besides, we could not exclude the possibility that the third-year interval was terminated due to either good or no obvious treatment effects

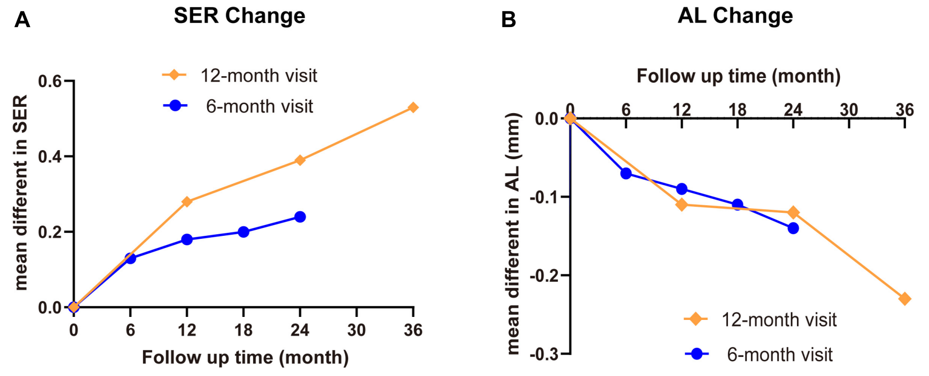

FIGURE 7 | The summary of SER and AL change with MFL treatment in school-aged children. The mean differences of SER **(A)** and AL **(B)** between MFLs (intervention) and SVLs (control) with different visit intervals were summarized.

at the first and/or especially the second year, which could affect the treatment effects in the meta-analysis. In this analysis, we could reach the data of 3-year treatments with annual visit but not 6-months visit. Therefore, the difference between annual and 6-months visit for a long-term treatment effect is not determined.

Third, our analysis may also have publication bias since the studies we selected were peer-reviewed. Currently, the studies with positive treatment effects are much easy to be published comparing to the studies with negative or no obvious treatment effects. Besides, some clinic trails may be terminated because no significant treatment effects are observed at early stage. This likely would overestimate the treatment effect of intervention.

Lastly, heterogeneity is a common problem for meta-analysis and it is difficult to deal with especially when the enrolled studies is selected in certain cases. In current study, we noticed a high heterogeneity which promotes us to do subgroup analysis. By analyzing the potential factors such as the county/region, added power and visit intervals (6-months and annual-visit), we found that subgroup with the visit intervals shows smaller and tolerable heterogeneity. Actually, this factor is exactly the one we would like to analyze because it seems distinct visit intervals did affect the treatment effects from literatures and in clinic practice. However, the part of data still shows moderate heterogeneity after subgroup. Therefore, a random-effect model for analysis was selected as other previous studies conducted. In addition, it is also possible to eliminate/reduce the heterogeneity by excluding certain studies. Thus, we found that by excluding the studies from Lam et al. (46) and Cheng et al. (55) could significantly reduce the heterogeneity. However, excluding specific study is not applicable when no decent reasons arising. Nevertheless, we found that the mean differences when including or excluding these two studies are only tiny changed, which did not alter any of the interpretations. Furthermore, a meta-regression could be also performed to find the potential factors that arise the heterogeneity. However, the meta-regression would not eventually dissolve the problem since we have failed to reduce the heterogeneity when subgroup with country/region and added power and we are mainly focusing on the treatment effects from distinct visit intervals in current study.

In conclusion, our analysis showed that the treatment effect of MFLs is positive in either 6-months or annual visit although annual visit shows more profound effects. In addition, it also highlights that while a slightly decreased effect was observed from the second visit in both 6-months and annual visit, a longer treatment likely acquires a better effect. Thus, the data encourages the MFLs users to maintain the long-term treatment (at least for 36 months) with annual visit. Due to the presence of heterogeneity in this analysis, a standardized large scale multi-center clinical trial should be conducted to provide an explicit direction.

DATA AVAILABILITY STATEMENT

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

MC and YW designed and supervised the project. MC performed literature review, data analysis, figure preparation, and prepared the manuscript with contributions from all authors. LX and CH prepared the tables. HL, FC, and HW reviewed the literatures and datasets. All authors contributed to the article and approved the submitted version.

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The assessment of future RSV immunizations: How to protect all infants?

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KEYWORDS

infant and child health, infant mortality, respiratory syncytial virus (RSV), RSV-acute lower respiratory illness, monoclonal antibody, infant hospitalization, infant immunization, respiratory disease

Introduction: RSV burden concerns all infants

Respiratory syncytial virus (RSV) infects nearly all infants at least once by their second birthday (1). It spreads through coughs, sneezes, or close physical contact (2). RSV infections are associated with morbidity and mortality, ranging from mild upper respiratory illness to life threatening lower respiratory tract infections (LRTIs). More than 97% of RSV-attributable deaths occur in low- and middle-income countries (LMICs) (3), reflecting that healthcare infrastructure and resources in these countries is limited and may present issues in dealing with RSV disease burden.

Severe RSV infection is more likely during the first months of life (4). RSV causes a substantial burden for infants below 12 months of age. It is estimated that 12.9 million RSV LRTI episodes, 2.2 million RSV-associated hospitalizations and 66,300 RSV-attributable deaths occurred globally in 2019 (3). RSV also causes a significant outpatient burden worldwide, with RSV being associated with 21% of infants aged <24 months brought to the emergency department and 18% in pediatric practices according to one study (5).

RSV is a leading cause of hospitalization among infants in their first year of life, whether they are born during or before the RSV season (6). Severe RSV cases are difficult to predict. Although preterm infants or infants with co-morbidity have a higher risk of having a severe infection, ~80% of infants hospitalized with RSV are otherwise healthy, i.e., with no underlying medical conditions, and born at term (7). The percentage can be even higher in some countries. For example, it was reported in Japan that 98% of infants hospitalized for RSV were otherwise healthy (8). In addition, roughly 50% of all children hospitalized with RSV are born outside of the RSV season (9). Quantifying individual RSV risk is far more complicated than assessing population level RSV risk due to a number of interrelated risk factors (10). Multiple factors appear to put some children at higher risk of a severe RSV infection, such as having older siblings; having a parent who smokes; exposure to pollution; poor living conditions; living in the suburbs or large communities; siblings attending school or daycare; socio-economic status and a low level of parental education; maternal age; and a familial history of atopy.

RSV represents a significant economic burden. RSV infection increases the length of hospital stay and admissions to the intensive care department compared to non-RSV-related infections (11). RSV in premature and at-risk infants (i.e., those with congenital heart disease, chronic lung disease, neuromuscular impairment, immunodeficiency and Down's syndrome) incurs an individual economic burden that is comparatively higher than a healthy, full-term infant (12, 13). However, in an annual cohort of infants, RSV disease burden and associated costs (including hospitalization and outpatient visit costs) are created mostly by RSV in infants who were healthy prior to the acute RSV illness, due to the far higher number of hospitalizations observed in this infant population (14). Infant RSV infection also resulted in significant 5-year long-term healthcare-resource utilization impact (15). The etiological link between RSV infection and the development of asthma has long been debated. Many studies assume that RSV infection is a trigger of a pre-existing predisposition to asthma and can trigger further economic burden (3, 14, 16, 17).

RSV infections also place a significant burden and emotional impact on affected families and caregivers (18–20). Parents may feel powerless due to a lack of knowledge on RSV and its related complications. Given the overwhelming service needs during RSV season, which may overlap with other infectious disease's seasonality, healthcare staff are also impacted, often manifesting as stress and burnout (21).

Abbreviations: ALRI, Acute lower respiratory illness; mAbs, monoclonal antibodies; RSV, Respiratory syncytial virus; RSV-ALRI, RSV-associated acute lower respiratory illness; WHO, World Health Organization; ICU, Intensive Care Units; LMICs, Low- and middle-income countries.

COVID-19 has impacted RSV circulation and reinforces the need for new prevention solutions

The COVID-19 pandemic has disrupted the epidemiology of many infectious diseases—including RSV. RSV usually peaks across the late autumn and winter in temperate countries (typically November to March) (22). While typically being more evenly distributed across the year in tropical regions, most countries in this region show a peak toward late summer (23). A minority of countries—almost all equatorial LMICs—report multiple peaks, or consistent RSV circulation year-round (23).

Non-pharmaceutical COVID-19 interventions such as social distancing reduced transmission, leading to an unusual reduction of RSV cases throughout 2020 in many countries (22). In 2021, following the removal of lockdown measures, uncommon resurgences during *spring and* summer were first reported in southern hemisphere countries such as Australia (24). Similar trends were then observed in some northern hemisphere countries, such as France, Spain, Germany and the UK (25).

The out-of-season peaks resulted in a significant disruption of healthcare systems and overwhelmed pediatric services due to RSV-related complications and potential hospital-acquired infections. In Germany, children aged 6 months to 1 year were hospitalized due to RSV across the summer of 2021 at a higher rate than they had been in previous years (26). Due to reduced circulation of RSV during the winter months of 2020, older infants and toddlers showed an increased risk of severe RSV-associated illness in 2021 (up to 5 years of age) (27).

Future immunization solutions should be assessed with the objective of protecting all infants against RSV

All infants should ideally be protected during their first RSV season as long as the prevention solution provided is proven safe and cost-effective. The only currently available preventative measure is a mAb, palivizumab (AstraZeneca) which is indicated and approved in many high-income countries for some infants born preterm, and/or who have existing heart or lung disease and must be injected monthly throughout the RSV season (28).

Several active and passive immunization options are in late-stage development. These include new monoclonal antibodies and both pediatric and maternal vaccines. Clinical trials are ongoing (29). It is of utmost importance to have data on the efficacy and duration of protection for these new immunization options in order for Immunization Technical Advisory Groups to assess them properly, with the objective of protecting all infants against RSV and reducing the overall RSV burden.

A long-acting mAb, which is likely to be the first licensed new preventative intervention, has shown promising results and there is a growing body of evidence suggesting it can protect all infants from RSV through their first RSV season with a single dose (30–34) (Figure 1). A baby born during or *just before* the RSV season should be immunized with a mAb as early as possible. The timing and location in which the immunization is administered is likely to differ depending on the country due to the differences in the postnatal practices and systems. Where possible, immunization should occur directly after birth, whether in the hospital, birth centers or in primary care settings (31, 35–37). Approaches that work within pre-existing immunization routine visits and structures are essential to ensuring uptake and to avoiding additional appointments for parents. The closest medical appointment to the start of the RSV season will be the optimal time for administration of the mAb to infants born before it (35). There is a degree of flexibility in the administration timing due to the rapid onset of protection with a mAb. Although acceptability of the RSV mAb palivizumab is currently high for infants at risk, it is unknown to what extent parents of healthy, full-term infants will accept long-acting mAbs against RSV (38–40).

Maternal vaccination is another option which might have great potential (41–43), even though the protected population might be more limited in cases of extreme prematurity where the infant may not receive the full benefit of antibody transfer (44), and for infants born out of season (35) (Figure 1). It may be that some health systems will offer parents a choice of prevention technologies: if a maternal vaccine is licensed, for babies born close to or in season, the mother may be offered the choice of receiving a vaccine during the third trimester or of the baby receiving a mAb shortly after birth. In countries and communities with poor maternal vaccine coverage, implementation of a RSV maternal vaccine could be challenging.

Both options (mAbs and maternal immunization) could be combined with RSV pediatric vaccines—which will likely be available at a much later date—to extend the duration of RSV protection throughout childhood (35) (Figure 1). This combined approach would grant immune coverage throughout the first months of life before immune system maturity is developed.

Need for an increased awareness of the risk that RSV poses to all infants: A prerequisite for the assessment of new immunizations

Currently there is a general lack of education about the burden of RSV and especially about all infants' cohorts being at potential risk. Consequently, there is a lack of awareness about the differences and complementarities between future preventative solutions. Knowledge was even noted to be low among non-specialist medical practitioners (45).

Parents must be properly informed about the benefit and reassured about the safety profile of any preventative solution in appropriate language. Some of this education will be given by health practitioners including midwives, nurses, family doctors, pharmacists and pediatricians, depending on the country.

The current momentum of discussion surrounding infectious diseases must not be wasted. COVID-19 has sensitized policymakers to respiratory infectious diseases and their necessary prevention. In many countries, these are now high on the political agenda. Policymakers should be informed of the burden of RSV in all infants, the value of the different prevention solutions and how they can support public health objectives, and prioritize the assessment of new RSV immunization routine strategies. Overall, strategies to increase the uptake of immunization, as well as efforts to dispel harmful misinformation (46) must also be promoted.

Even though a lot of data is already available, there is still a need for improved national surveillance systems for respiratory viral infections. New epidemiological data will come from increased use of multiplex PCR and rapid tests in the wake of COVID-19. Policymakers and healthcare professionals should also consider collecting more data on rehospitalizations and outpatients visits due to the long-term sequelae of RSV infection in infancy, such as recurrent wheezing and asthma. These data may be important in aiding evidence-based decisions about prevention.

Discussion

It is difficult to identify which infants will experience the most severe RSV illness and the vast majority of infants hospitalized with severe RSV are otherwise healthy and born at term. Beyond hospitalizations, RSV causes a significant outpatient burden. Policy recommendations to protect all infants against RSV should be discussed by Immunization Technical Advisory Groups. In each country, the development of recommendations will demand a careful assessment of the new RSV immunization programs and an analysis on the ease of implementation of these measures.

New immunization perspectives can protect more infants compared with the current standard of care. New long-acting mAbs are likely to be licensed first and can protect all infants, through administration at or close to birth for those infants born during the RSV season or alongside pre-scheduled immunization visits for those born before the season. That point of view is supported by additional publications released since the RSV Experts Group Event held in October 2021 (47, 48). Reducing RSV could relieve

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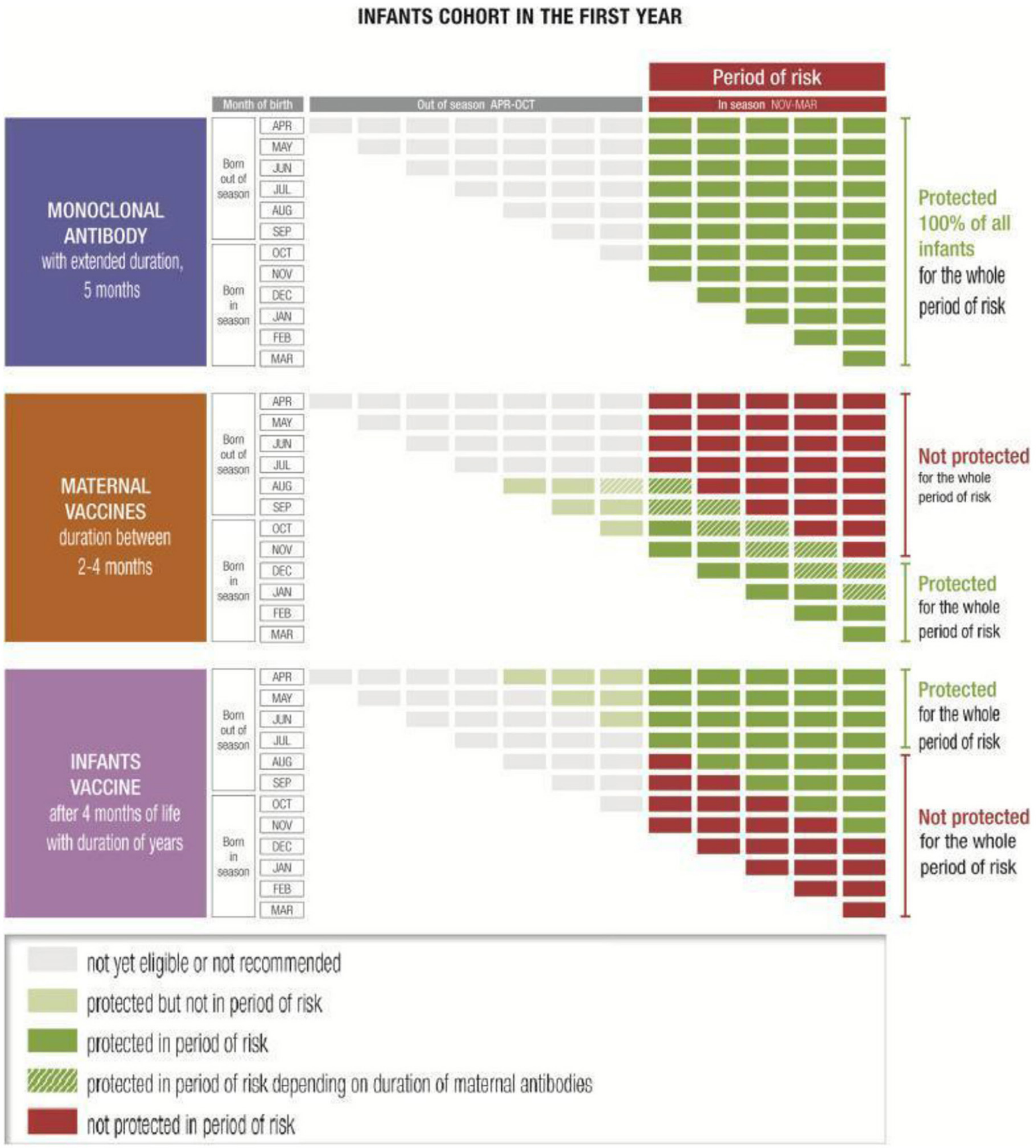

FIGURE 1
Examples of immunization coverage of infants through the first year of life against the November–March seasonality typical of temperate Northern hemisphere countries (35).

recurrent pressure on healthcare systems, leading to more efficient use of resources and contributing to the sustainability of healthcare systems.

The uptake of new RSV immunization strategies depends on the level of awareness of RSV among healthcare professionals, policymakers, and parents.

Although more is needed, awareness of RSV is improving. COVID-19 has played a huge role in this, with multiplex testing also checking for RSV cases in some countries. The data generated have made healthcare workers more aware of the volume of cases. The pandemic has also highlighted how crucial adequate immunization coverage is to maintaining both the health of the targeted population and the functioning of healthcare systems. As a consequence, many governments are now prioritizing the prevention of respiratory infectious diseases. As the burden of RSV is much higher than that of other pediatric infectious diseases, it is crucial to make the assessment of new RSV preventative measures for all infants a priority.

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Prevalence and associated factors of diarrhea among under-five children in the Jawi district, Awi Zone Ethiopia, 2019. Community based comparative cross-sectional study

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Introduction: Although most deaths are preventable with simple and inexpensive measures, death from diarrhea accounts for one out of nine deaths in children worldwide which makes it the disease with the highest mortality rate in children under the age of five. Therefore, this study is aims to investigate diarrhea prevalence and risk factors among children under the age of five in Jawi district, Awi Zone, Ethiopia.

Materials and methods: A comparative cross-sectional study was done among 440 study participants from March to June 2019. Data were collected with a face-to-face interviewer-administered questionnaire. Data was entered into EPI Info version 7 software and cleaned and analyzed using SPSS version 20 software. Binary logistic regression was done to assess independent factors associated with the dependent variable. A significant association was determined using an adjusted odds ratio at a confidence level of 95% and a *p*-value of less than or equal to 0.05.

Results: In the current study, the overall under-five children diarrheal disease was found to be 15.5%. Diarrheal disease prevalence in model and non-model households was 10.9 and 20%, respectively. Shallow water [AOR: 6.12, 95%CI; (1.52, 24.58)], and maternal diarrhea [AOR: 4.11, 95%CI; (1.75, 9.61)] were determinants of childhood diarrhea. Place of birth [OR: 2.52, 95%CI (1.16, 5.49)] and maternal diarrhea [AOR: 3.50; 95%CI (1.28, 9.56)] in non-model households were also determinants of childhood diarrhea.

Conclusion: Under-five children diarrheal disease was found to be high in the Jawi District. Thus, to decrease the disease prevalence in the study area, the health extension workers aim to better educate the mothers on how to handle diarrheal diseases. It is also better for concerned stakeholders to promote institutional delivery and to give access to safe water for the community.

KEYWORDS

childhood diarrhea, model and non-model households, Jawi district, Ethiopia, under-five children

Background

According to World Health Organization (WHO), diarrhea is defined as "the passing of three or more loose or liquid stools per day or passing more frequently than is normal for the individual (1)." Although most deaths from diarrhea are preventable with simple, inexpensive measures, one in nine deaths in children worldwide is due to diarrhea. This means 2,195 children are dying per day due to diarrhea, which is equivalent to losing 32 school buses full of children each day or 801 thousand child deaths from diarrhea every year worldwide (2). According to a WHO report in 2015, diarrhea in children aged less than five causes 0.53 million deaths worldwide per year, which accounts for four in 1,000 live births (3) which makes it the most common cause of death worldwide (4). Another report surprisingly showed that child death is 15 times more in sub-Saharan Africa than in the developed world (5). Even though reports showed the decline of death due to childhood diarrhea in Ethiopia from 2000 to 2016, it still accounts for about 8% of deaths of under-five children and the number is still unacceptable (6). Some studies had been conducted in different parts of Ethiopia, but there were a large gap in the burden of disease and determinants between studies and showed a range of 11–31% (7–12). The recent findings suggested that interventions such as pure water consumption, good hygiene and sanitation, breastfeeding, complementary feeding, zinc and vitamin A supplementation, and Rota vaccination were effective to prevent diarrhea in children under five (13). Despite these suggestions, the burden of disease in children is high, and community-based studies are limited, especially in the proposed district. Even these limited studies had great differences in disease burden and factors related to child diarrhea.

Therefore, this study aimed to assess the prevalence and determinants of diarrheal diseases in children under 5 years of age residing in modeled households and non-modeled HHs in the Jawi district, Amhara regional state. Thus, the results of the study will be used to develop prevention strategies at the community level in the district. The findings of this study will also be used to put priority settings on the prevention of under-five diarrheal diseases in the community level.

Abbreviations: HHs, households; WHO, World Health Organization; AOR, adjusted odds ratio; CI, confidence interval; COR, crude odds; SD, standard deviation; SPSS, statistical package for social science.

Materials and methods

A community-based comparative cross-sectional study was conducted from May to June 2019. The Jawi district is found in the Western Amhara region 540 km away from Addis Ababa, the capital of Ethiopia, and 200 km away from Bahir Dar, the capital city of Amhara regional state. A total of 163,102 people live in this district, of which 50% are female. From the total population, about 19,399 are under-five children. There are about 35 governmental health institutions (28 health posts, six health centers, and one primary hospital) and 38 non-governmental health institutions (four medium clinics and 34 primary clinics) in the district. The total health workforces were about 215 of which 63 were found to be health extensions in the district. The water source of the district was mainly shallow (425), followed by a hand pump (100) and a water pipe in three kebeles (**Figure 1**). All under-five children were included, but any children whose caregivers were mentally ill and had a hearing problem were excluded from the study.

The sample size was determined by using a double population proportion formula considering, 6.4% the proportion of diarrhea in extension modeled HHs and 25.5% the proportion of diarrhea in extension none modeled HHs among under-five children (11), 95% confidence level and 80% power.

In the study that was conducted in the Sheko district the n1 was 275 and n2 was 550 with a ratio of two, based on this information I was calculated and pulled p and q values. The pulled p-value is 0.1913 and q is 0.809.

$$n_1 = n_2 = \frac{[Z\alpha/2\ 2p^{-}q^{-} + z1 - \beta((p1q1) + (p2q2))]^2}{(P1 - p2)}$$

$$n_1 = n_2 = \frac{[1.962(0.1913)(0.809) + 0.842((6.4)\ (25.5) + (0.936)(0.745)]^2}{(0.064 - 0.255)^2}$$

$$= 100$$

Therefore, by considering the design effect of 2 and 10 percent non-response rates, the total sample size was 440.

n1 = number of exposed (number of model households).

n2 = number of non-exposed (number of non-model households).

p1 = proportion of diarrheal case among children living model households.

p2 = proportion of diarrheal case among children living in non-model households $^{-}$p = pulled *p*-value; $^{-}$q = pulled *q* value.

The largest sample size obtained using the associated factor for this study was 148. By considering 10% of non-response and two design effects, the largest sample size was estimated to be 326 which was less than the sample size calculated above. Therefore, the final sample size for this study was 440.

In the study district, there were two health extension modeled and 26 non-modeled kebeles. The kebeles were stratified to health extension modeled and not modeled. From the non-model kebeles, three kebeles were randomly selected using the lottery method and two kebeles from the modeled stratum were surveyed. From each selected kebele, households that have at least one child were enumerated by data collectors. Then, systematic random sampling was used to select households. The lottery method was used if there was more than one child in the household. When a household was closed during data collection, the next household was included.

Diarrhea was defined as passing three or more loose or watery stools in 24 h in the household within the 2 weeks before the survey, as reported by the mother/caretaker of the child (14). Model household was defined as having a household head/caregiver who had taken basic training for 96 h and graduated on the 16 health extension packages (15). Non-model family was defined as having a household head/caregiver who had not taken basic training on the 16 health extension packages (15). Handwashing at a critical time was based on whether a mother/caregiver practiced all simple hand washings before food preparation, before child feeding, after child cleaning, and after latrine visiting. If these criteria were met, it was considered to be "all practiced" otherwise it was considered to be "partially practiced (16)." Proper refuse disposal was defined as a way of disposal of refuse which includes burning, buried in a pit or stored in a container, composting, and disposed of at a designated site, whereas disposal in an open field was considered as improper refuse disposal (14).

A pretested, face-to-face interviewer-administered structured questionnaire was used to collect the desired sample size. The tool was first developed in English and translated to the local language then back to English to keep the tool consistent. The data was collected by four nurses and there was one health officer for supervision. Data was collected from the mother, father, or other caregivers using an interviewer-administered questionnaire. Data collector nurses and a supervisor were trained on basic interviewing techniques. The data were checked daily for its completeness by supervisors and principal investigators. The tool was pre-tested in 5% of the sample in deke 01 kebele. Data was entered into EPI Info version 7 software and cleaned and analyzed using SPSS version 20 software. Frequency, percentage, and mean were used to describe the characteristics of study participants. Binary logistic regression was carried out to assess independent factors associated with the dependent variable. A significant association was determined using an adjusted odds ratio at a confidence level of 95% and a *p*-value of less than or equal to 0.05.

Results

Socio-demographic characteristics of study participants

In the current study, a total of 440 study participants were included making the response rate 100%. Among the total study participants, half of them were from model households. The mean age of the study participants was 27.7 (±14.8 SD) months in model households and 33.6 (±13.9 SD) months in non-model households. Of the total study participants, the mean height was 84.6 (±11.4 SD) centimeters in model and 82.3 (±12.8 SD) centimeters in non-model HHs (**Table 1**).

Environmental and personal factors

All study households had a latrine, of which 167 (75.9%) of model HHs and 5 (2.3%) of non-model HHs used an improved type of latrine. Of these, 193 (87.7%) and 82 (37.3%) latrines were clean among model and non-model households respectively. 95 (44.5%) model households had a hand washing facility on their latrine but only 5 (2.3%) non-model households had a hand washing facility. Among 220 model and 220 non-model households, 210 (95.5%) and 165 (75%) households used separate kitchens, respectively. The median distance to fetch water for model households was 6 m with a minimum distance of 1 m and a maximum distance of 100 m away from their home, and for non-model households the median was 10 m with a minimum distance of 2 m and a maximum distance of 100 m away from their home. The mean distance of the latrine from the HHs was 14.3 (±7.8SD) meters from which the mean distance away from the model and non-model HHs was 12 (±5.38SD) meters and 16.6 (±9.13SD) meters respectively (**Table 2**).

Maternal and child health condition

Maternal diarrheal prevalence was 6.4% (95%CI, 4.1, 8.6), of which the prevalence based on the model type was 4.1% in model and 8.6% in non-model HHs. Among the study

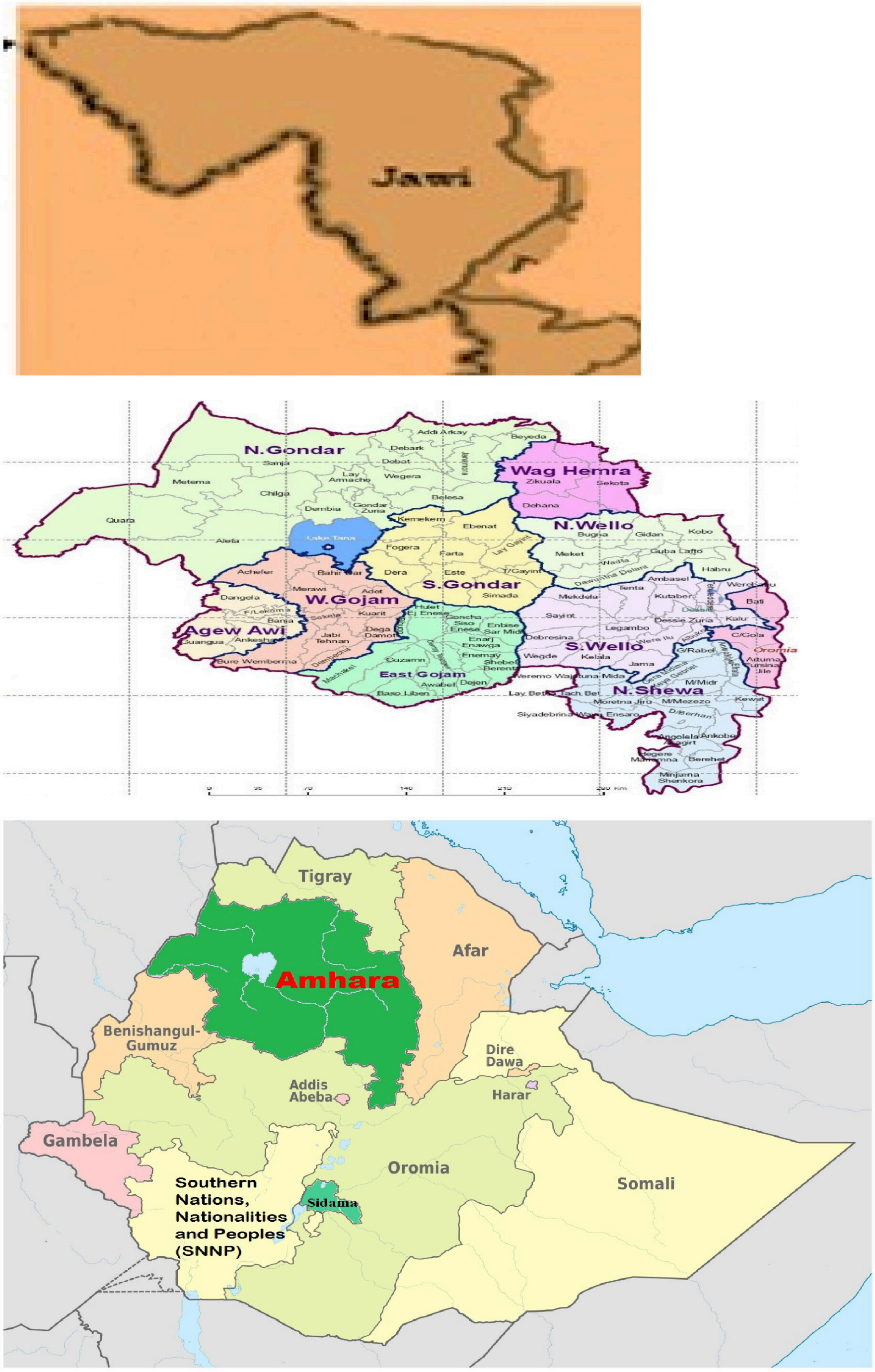

FIGURE 1
Map showing Jawi District, Awi Zone, Ethiopia.

participants, 313 were greater than or equal to 2 years during the study period among them 196 (62.6%) were dewormed with albendazole. Of which 65 (33.2%) were from model households and 131 (66.8%) were from non-model households. 405 (92.0%) of the children were above the age of 9 months, of which 391 (96.5%) were vaccinated against measles and among them, 188 (85.5%) were from model households and 203 (92.3%) were from non-model households. 434 (98.6%) of the study participants were older than 6 weeks, and among them 425 (97.9%) were vaccinated against Rota, of which half of the children were in model and non-model HHs (Table 2).

TABLE 1 Socio demographic characteristics of respondents in Jawi district, Awi Zone, southwest Ethiopia, 2019.

Variables	Model HHs		Non-model HHs	
	Diarrhea			
	Yes (%)	No (%)	Yes (%)	No (%)
Sex of child				
Male	10 (41.7)	92 (46.9)	21 (47.7)	85 (48.3)
Female	14 (58.3)	103 (52.6)	23 (52.3)	91 (51.7)
Place of birth				
Home	3 (12.5)	35 (17.9)	13 (29.5)	26 (14.8)
Institution	21 (87.5)	161 (82.1)	31 (70.5)	150 (85.2)
Ethnicity				
Amhara	17 (70.8)	151 (77.0)	21 (47.7)	95 (54.0)
Awi	7 (29.2)	45 (23.0)	23 (52.3)	81 (46.0)
Religion				
Orthodox	16 (66.7)	159 (81.1)	43 (97.7)	174 (98.9)
Muslim	8 (33.3)	37 (18.9)	1 (2.3)	2 (1.1)
Maternal education status				
No education	10 (41.7)	74 (37.8)	30 (68.2)	131 (74.4)
Primary	11 (45.8)	99 (50.5)	14 (31.8)	44 (25.0)
Secondary & above	3 (12.5)	23 (11.7)	0 (0.0)	1 (0.6)
Maternal occupation				
House wife	17 (70.8)	134 (68.4)	9 (20.5)	12 (6.8)
Farmer	3 (12.5)	25 (12.8)	33 (75.0)	160 (90.9)
Government employed	2 (8.3)	12 (6.1)	0 (0.0)	1 (0.6)
Non-governmental organization	2 (8.3)	15 (7.7)	1 (2.3)	3 (1.7)
Not employed	0 (0.0)	10 (5.1)	1 (2.3)	0 (0.0)
Father's occupation				
Government employed	8 (33.3)	19 (9.7)	0 (0.0)	2 (1.1)
Non-governmental organization	7 (29.2)	94 (48.0)	4 (9.1)	4 (2.3)
Farmer	8 (33.3)	71 (36.2)	39 (88.6)	168 (95.5)
Not employed	1 (4.2)	12 (6.1)	1 (2.3)	2 (1.1)
Father's education status				
No education	7 (29.2)	36 (18.4)	20 (45.5)	99 (56.3)
Primary	9 (37.5)	122 (62.2)	24 (54.5)	75 (42.6)
Secondary & above	8 (33.3)	38 (19.4)	0 (0.0)	2 (1.1)
Age of caregiver				
15–24	8 (33.3)	52 (26.5)	4 (9.1)	24 (13.6)
25–34	10 (41.7)	111 (56.6)	24 (54.5)	99 (56.3)
35–49	6 (25.0)	33 (16.8)	16 (36.4)	53 (30.1)
Number of under 5 children/HHs				
One	14 (58.3)	138 (70.4)	32 (72.7)	138 (78.4)
Two	10 (41.7)	57 (29.1)	11 (25.0)	37 (21.0)
Three	0 (0.0)	1 (0.5)	1 (2.3)	1 (0.6)
Family size				
Less than or equal to five	19 (79.2)	155 (79.1)	24 (54.5)	97 (55.1)
Greater than five	5 (20.8)	41 (20.9)	20 (45.5)	79 (44.9)

HHs, households.

Knowledge and behavioral factors of caregivers

Of the total caregivers, 272 (61.96%) of them know at least one mode of transmission of diarrhea, of which 160 (58.8%) of them were residing in model HHs and 112 (41.2%) were residing in non-model HHs. The caregivers were asked when they started supplementary food for their children 423 (96.1%)

TABLE 2 Environmental and personal factors, and maternal and child health condition of respondents in Jawi district, Awi Zone, southwest Ethiopia, 2019.

Variables	Model HHs		Non-model HHs	
	Diarrhea			
	Yes (%)	No (%)	Yes (%)	No (%)
Type of latrine				
Improved	17 (70.8)	150 (76.5)	1 (2.3)	4 (2.3)
Unimproved	7 (29.2)	46 (23.5)	43 (97.7)	172 (97.7)
Clean latrine				
Yes	22 (91.7)	171 (87.2)	21 (47.7)	61 (34.7)
No	2 (8.3)	25 (12.8)	23 (52.3)	115 (65.3)
Latrine has hand washing				
Yes	9 (37.5)	89 (45.4)	1 (2.3)	4 (2.3)
No	15 (62.5)	107 (54.6)	43 (97.7)	172 (97.7)
Waste disposal pit				
Yes	17 (70.8)	102 (52.0)	1 (2.3)	2 (1.1)
No	7 (29.2)	94 (48.0)	43 (97.7)	174 (99.9)
Domestic animal live in house				
Yes	1 (4.2)	6 (3.1)	1 (2.3)	1 (0.6)
No	23 (95.8)	190 (96.9)	43 (97.7)	175 (99.4)
Water source for domestic use				
Pipe	9 (37.5)	126 (64.3)	1 (2.3)	1 (0.6)
Water pump	9 (37.5)	31 (15.8)	0 (0.0)	1 (0.6)
Shallow	6 (25.0)	39 (19.9)	43 (97.7)	174 (98.9)
Maternal diarrhea				
Yes	3 (12.5)	6 (3.1)	8 (18.2)	11 (6.3)
No	21 (87.5)	190 (96.9)	36 (81.8)	165 (93.7)
Albenedazole				
Yes	7 (29.2)	58 (29.8)	31 (70.5)	100 (56.8)
No	6 (25.0)	64 (32.7)	5 (11.4)	42 (23.9)
Age < 2 years	11 (45.8)	74 (37.8)	8 (18.2)	34 (19.3)
Rota vaccine taken				
Yes	24 (100)	189 (96.4)	42 (95.5)	170 (96.6)
No	0 (0.0)	4 (2.0)	1 (2.3)	4 (2.3)
Age < 6 weeks	0 (0.0)	3 (1.5)	1 (2.3)	2 (1.1)
Measles vaccine taken				
Yes	17 (70.8)	171 (87.2)	40 (90.9)	163 (92.6)
No	2 (8.3)	7 (3.6)	2 (4.5)	3 (1.7)
Age < 9 month	5 (20.8)	18 (9.2)	2 (4.5)	10 (5.7)

HHs: households.

answers were at or after the age of 6 months, of which 407 (96.2%), 3 (0.7%), and 12 (2.8%) answers at 6, 8, and 12 months, respectively (Table 3).

Prevalence of diarrhea

Diarrheal disease prevalence of under-five children in the study district in the 2 weeks prior to the interview was 15.5% (95% CI, 12.5–18%). The occurrence of diarrheal disease morbidity in model and non-model HHs was 10.9% (95% CI; 6.8–15.0%) and 20% (95%CI; 15.0–25.5%), respectively.

Independent factors associated with childhood diarrhea

To avoid excess numbers and unstable estimates, variables were screened by bivariable logistic regression, and variables with a *p*-value $\leq$ 0.25 were included in multivariable logistic regression analysis. Accordingly, the odds of child diarrhea from HHs who use shallow water were 6.12 times more likely compared to those who use water pump as water source [AOR: 6.12, 95%CI; (1.52, 24.58)]. The odds of child diarrhea were 12.8 times more likely in the Orthodox Christian religion compared to the Muslim religion [AOR: 12.8, 95%CI; (3.3, 50)]. The odds of child diarrhea were 4.1 times more common in HHs in which the mother had diarrhea [AOR: 4.11, 95%CI; (1.75, 9.61)] as shown in Table 4.

TABLE 3 Knowledge and behavioral factors of respondents in Jawi district, Awi Zone, southwest Ethiopia, 2019.

Variables	Model HHs		Non-model HHs	
	Diarrhea			
	Yes (%)	No (%)	Yes (%)	No (%)
Mode of transmission				
Yes	19 (79.2)	141 (71.9)	22 (50.0)	90 (51.1)
No	5 (20.8)	55 (28.1)	22 (50.0)	86 (48.9)
Method of prevention				
Yes	18 (75.0)	133 (67.9)	14 (31.8)	75 (42.6)
No	6 (25.0)	63 (32.1)	30 (68.2)	101 (57.4)
Homemade treatment				
Yes	6 (25.0)	70 (35.7)	3 (6.8)	16 (9.1)
No	18 (75.0)	125 (63.8)	41 (93.2)	160 (90.9)
Critical time for hand washing				
Yes	21 (87.5)	156 (79.6)	40 (90.9)	168 (95.5)
No	3 (12.5)	40 (20.4)	4 (9.1)	8 (4.5)
Supplementation				
At $\geq$ 6 month	21 (87.5)	183 (93.4)	43 (97.7)	176 (100)
At < 6 month	3 (12.5)	13 (6.6)	1 (2.3)	0 (0.0)

HHs, households.

TABLE 4 Independent factors associated with childhood diarrhea of respondents in Jawi district, Awi Zone, southwest Ethiopia, 2019.

Variables	Child diarrhea		COR	AOR
	Yes	No		
Maternal diarrhea				
Yes	11	17	4.03 (1.80,9.04)	**4.11 (1.75,9.61)****
No	57	365	1	1
Source of water				
Shallow	49	213	1.22 (0.55, 1.43)	**6.12 (1.52,24.58)***
Pipe	10	127	0.34 (0.17, 0.70)	0.526 (0.15, 1.83)
Water pump	9	32	1	1
Religion				
Orthodox	59	333	1.3 (0.6, 2.8)	12.8 (3.3, 50)*
Muslim	9	9	1	1
Household type				
Model	24	196	1	1
Non-model	44	176	2.04 (1.19,3.49)	1.54 (0.50, 4.79)
Type of latrine				
Improved	18	154	1	1
Unimproved	50	218	1.96 (1.10,3.49)	1.13 (0.40, 3.19)
Ethnicity				
Awi	30	126	1.54 (0.91,2.61)	1.18 (0.66, 2.11)
Amhara	38	248	1	1
Place of birth				
Home	16	61	1.57 (0.84, 2.93)	1.72 (0.88, 3.35)
Institution	52	311	1	1
Hand washing facility				
Yes	10	93	1	1
No	58	279	1.93 (0.95, 3.94)	1.30 (0.52, 3.25)
Mebendazole supplementation				
Yes	38	158	2.32 (1.13, 4.73)	2.13 (0.90, 4.54)
No	11	106	1	1

*Significance at *p*-value $\leq$ 0.05, **significance at *p*-value $\leq$ 0.001; COR, crude odds ratio; AOR, adjusted odds ratio. The bold letter-significant association at *P*-value < 0.05.

Determinants of childhood diarrhea among model and non-model households

After stratifying study subjects into model and non-model HHs, bivariate screening was done and variables with a *p*-value $\leq$ 0.25 were included in multivariable logistic regression. No variable had an association with childhood diarrhea in model HHs. On the other hand, among non-model households, the risk of getting diarrhea in children who delivered at home was 2.5 times higher compared to children who delivered at the institution [OR: 2.52, 95%CI (1.16, 5.49)]. The odds of child

TABLE 5 Independent factors associated with childhood diarrhea among non-model households (HHs) of respondents in Jawi district, Awi Zone, southwest Ethiopia, 2019.

Variables	Child diarrhea		COR	AOR
	Yes	No		
Maternal diarrhea				
Yes	8	11	3.33 (1.25, 8.88)	**3.50 (1.28, 9.56)**
No	36	165	1	1
Place of birth				
Home (33.3) (66.7)	13	26	2.42 (1.12, 5.23)	**2.52 (1.16, 5.49)**
Institution	31	150	1	1
Clean latrine				
Yes	23	115	1	1
No	21	61	1.72 (0.88, 3.35)	1.61 (0.8, 3.23)
Mebendazole supplementation				
Yes	31	100	2.60 (0.95, 7.14)	2.70 (0.95, 7.69)
No	5	42	1	1

COR, crude odds ratio; AOR, adjusted odds ratio. The bold letter-significant association at P-value < 0.05.

diarrhea were 3.5 times more likely among children whose mother had diarrhea as compared to those whose mother did not have diarrhea in non-model HHs [OR: 3.50; 95%CI (1.28, 9.56)] as shown in **Table 5**.

Discussion

In the current study, the overall prevalence of under-five children diarrheal disease was found to be 15.5%. The result was relatively lower than the study done in Arba Minch district (31%) (17). The prevalence of diarrheal disease is also lower compared to other studies conducted in Ethiopia: 19.6% in Shebedino District (18), 21.5% in Jabithennan (19), 22.0% in Ethiopia (20), 22.1% in Benishangul Gugmuz (21), 22.5% in Eastern Ethiopia (10), 26% in Mbour, Senegal (22), 26.1% in Nomadic (23), 27% in Jigjiga district (24), and 30.5% in Arba Minch (17). The variation may be related to the differences in caregivers' basic environmental and behavioral characteristics. However, the result was high compared to the study conducted in Addis Ababa (11.9%) (25).

A possible explanation for the discrepancy is the difference in socioeconomic development, there could be better awareness about diarrhea prevention mechanisms which could decrease the disease prevalence, and this showed that more attention needs to be paid to the reduction of child morbidity in the area to reduce child death.

The diarrheal morbidity of children under 5 years of age among model and non-model HHs was about 11 and 20% respectively. This figure was higher than a comparative study done in Hawassa (9%) and (14%) among model and non-model HHs (11). This might be because the current study includes residences from both urban and rural areas. The methods of health education and health service delivery between rural and urban residents are possibly different. Urban residents might have better information on how to handle waste products and how to care for their child by considering prevention mechanisms of diarrhea.

However, this study had a higher prevalence among model HHs and a lower prevalence among non-model HHs compared to a study done in Sheko district, southwest Ethiopia (6.4% and 25.5%, respectively) (16). This difference could be due to different socio-demographic characteristics of the mothers and differences in weather conditions.

The source of water used for household utility had a significant impact on diarrheal diseases. This study showed that using shallow water is a risk factor for developing diarrhea compared to using water from a water pump. This is because shallow water is unprotected from contamination with animal and human waste, which may contain a range of pathogenic microorganisms causing an increased risk of a range of diarrheal diseases. This is in line with other studies (23, 24).

Maternal diarrhea was another variable that was associated with childhood diarrhea morbidity. Children whose mothers had diarrheal diseases had a high chance of developing diarrhea. This is because mothers with a disease contaminate the food, water, and utensils and directly when handling their children. This is consistent with other study findings (11).

In the study, the place of birth of their index child was significantly associated with childhood diarrhea among non-model households. Home delivery of their index child increased the likelihood of developing a diarrheal disease compared to delivery at an institution. This can be explained by the fact that mothers who give birth at an institution can have better information on how to care for their children and on how to prevent diarrheal disease. Moreover, mothers who gave birth in an institution are given information on exclusive breast feeding, which might decrease the chance of getting an infection that may lead to diarrheal disease. This was not associated significantly in the study done in Shebedino District (18) and in other studies.

Limitation

Caregivers of the child were asked about their children's health status in the 2 weeks before the survey which might measure their perceptions rather than actual morbidity that might affect the result. Perceptions of illness may not be the same in different caregivers.

Conclusion

Childhood diarrhea was found to be prevalent in the study District. The factors that were associated with childhood diarrhea were maternal diarrhea, the source of water for domestic use, and religion. Factors associated with childhood diarrhea among non-model HHs were the place of birth for their index child and maternal diarrhea.

Thus, to decrease childhood diarrhea in the study area, the health extensions should better educate the community on how to dispose of solid and liquid wastes, the pit they are going to use for waste disposal, and how mothers can handle the contraction of a diarrheal disease. for concerned stakeholders, it is also better to promote institutional delivery and to give access to the community for safe water.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the University of Gondar internal review board with a reference number of V/P/RCS/05/2710/2019. Written informed consent was obtained from the study participants before commencing the data collection.

Author contributions

Both authors contributed to the conception of the study to final approval of the version to be published.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Predicting South Korean adolescents vulnerable to obesity after the COVID-19 pandemic using categorical boosting and shapley additive explanation values: A population-based cross-sectional survey

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Objective: This study identified factors related to adolescent obesity during the COVID-19 pandemic by using machine learning techniques and developed a model for predicting high-risk obesity groups among South Korean adolescents based on the result.

Materials and methods: This study analyzed 50,858 subjects (male: 26,535 subjects, and female: 24,323 subjects) between 12 and 18 years old. Outcome variables were classified into two classes (normal or obesity) based on body mass index (BMI). The explanatory variables included demographic factors, mental health factors, life habit factors, exercise factors, and academic factors. This study developed a model for predicting adolescent obesity by using multiple logistic regressions that corrected all confounding factors to understand the relationship between predictors for South Korean adolescent obesity by inputting the seven variables with the highest Shapley values found in categorical boosting (CatBoost).

Results: In this study, the top seven variables with a high impact on model output (based on SHAP values in CatBoost) were gender, mean sitting hours per day, the number of days of conducting strength training in the past seven days, academic performance, the number of days of drinking soda in the past seven days, the number of days of conducting the moderate-intensity physical activity for 60 min or more per day in the past seven days, and subjective stress perception level.

Conclusion: To prevent obesity in adolescents, it is required to detect adolescents vulnerable to obesity early and conduct monitoring continuously to manage their physical health.

KEYWORDS

obesity, COVID-19 pandemic, CatBoost, machine learning, adolescent

Introduction

Obesity is an important health problem among adolescents. Adolescent obesity has been increasing worldwide over the past 20 years (1). The prevalence of obesity among adolescents has been steadily increasing from 9.1% in 2016 to 11.1% in 2019 in South Korea as well (2). Since obesity increases not only the size of adipocytes but also the number of adipocytes, obesity in adolescence is highly likely to develop a chronic disease in adulthood (3). In addition, the obesity of adolescents is highly associated with emotional problems such as depression (4).

Meanwhile, SARS-CoV-2, named coronavirus disease 2019 (COVID-19), appeared in December 2019 (5). As COVID-19 spreads rapidly all over the world, the World Health Organization declared a pandemic caused by COVID-19 on March 11, 2020 (5), and the pandemic is still ongoing as of March 2022. As a result, the global population has faced changes in lifestyle due to the COVID-19 pandemic in the world at large, including social distancing. Particularly, home-based classes have become common in South Korea as the classes for adolescents have shifted from face-to-face classes to online classes during the COVID-19 pandemic (6). There is a possibility that health problems such as obesity may appear among adolescents due to the restriction on school attendance. For example, the balanced school meal is replaced by home meals. Nevertheless, only a few studies have evaluated factors for predicting obesity in adolescents under the disaster due to a pandemic infectious disease such as the COVID-19 pandemic.

Meanwhile, machine learning has been widely used in the disease prediction field in recent years (7). Machine learning has several advantages: it can handle multidimensional and multivariate data and it can discover specific patterns in big data.

In particular, categorical boosting (CatBoost) is the most recently developed model among machine learning models based on gradient boosting, and it uses the ordered boosting technique (8). It has been reported that it minimizes model overfitting and has superior predictive performance in predicting categorical variables than XGBoost and LightGBM (8).

This study used 53,534 adolescents who participated in the national survey in South Korea in 2020. This study identified factors related to adolescent obesity during the COVID-19 pandemic by using machine learning techniques and developed a model for predicting high-risk obesity groups among South Korean adolescents based on the result.

Materials and methods

Subjects

This study was a secondary data analysis study that analyzed the Korea Youth Risk Behavior Survey (KYRBS) conducted from August 1 to November 30, 2020. The KYRBS is a part of the national chronic disease monitoring system construction plan (9). It is an anonymous online self-report survey jointly conducted by the Ministry of Health and Welfare, the Ministry of Education, and Korea Disease Control and Prevention Agency to understand the current status and level of South Korean adolescents' health risk behaviors and to evaluate health indicators for promoting adolescents' health (9). The KYRBS consists of items covering 15 health behavior-associated domains, such as smoking, drinking, obesity, eating habits, and physical activity. The KYRBS divided South Korea into 16 districts (cities and provinces) and then clustered them into 64 city units according to city size. Afterward, this study extracted 800 survey units (400 middle schools and 400 high schools) by using the systematic extraction method as much as the number of samples allocated to each cluster. This study targeted students between seventh grade and twelfth grade across South Korea. The response rate of the 2020 KYRBS was 94.8%. This study analyzed 50,858 subjects (male: 26,535 subjects, and female: 24,323 subjects) out of all subjects (54,948 subjects) of the 2020 KYRBS between 12 and 18 years old after excluding 1,414 subjects who did not respond to height or weight and 2,676 subjects who were underweight (a body mass index below the 5th percentile).

Variable measurements

Outcome variables were classified into two classes (normal or obesity) based on body mass index (BMI). BMI was calculated by using recently measured height and weight responded by the subject to the first decimal place. BMI was calculated by dividing weight (kg) by squared height (m^2). This study classified subjects into percentiles according to BMI by gender and age using the 2020 standard growth chart for children and adolescents (10). This study excluded those with a BMI less than the 5th percentile from the analysis to avoid over-interpretation due to the possibility of false-positive in the process of calculating a BMI (11). This study classified adolescents with a BMI of 25 or higher as obese based on the Obesity Treatment Guidelines (12) of the Korean Society for the Study of Obesity.

The explanatory variables included demographic factors, mental health factors, life habit factors, exercise factors, and academic factors. Demographic factors were gender (male or female), grade, area of residence (urban or rural), and subjective household economic level (high, medium, or low). Mental health factors were stress perception rate (high, moderate, or low), the experience of depressive feeling (sadness and hopelessness for more than 2 weeks) in the past 12 months (yes or no), and smartphone overdependence (experienced a severe conflict in friend or social relationships due to excessive smartphone use: yes or no). Life habit factors were smoking in the past 30 days (yes or no), drinking more than 1 shot of soju, beer, or whiskey in the past 30 days (yes or no), the number of days of having breakfast in the past seven days (none, 1–3 days, 4–6 days, or every day), the number of days of eating fruit in the past seven days (none, 1–2 days, or 3 days or more), the number of days of drinking soda in the past seven days (none, 1–2, 3–4, or 5°days or more), the number of days of having fast food in the past seven days (none, 1–2 days, or 3 days or more), mean sleeping hours per day (less than 4, 5, 6, 7, or 8 h or more), and mean sitting hours per day (6 h or less, or 6 h and more). Exercise factors were the number of days of conducting strength training in the past seven days (none, 1–2, 3–4, or 5 days or more), and the number of days of conducting the moderate-intensity physical activity for 60 min or more per day in the past seven days (physical activities that increase the heart rate to 50–70% higher than the maximum heart rate, such as bicycle riding and power walking) (none, 1–2 days, or 3 days or more). An academic factor was grade (high, medium-high, medium, middle-low, or low).

Categorical boosting

Categorical boosting (CatBoost) is the most recently announced boosting algorithm, and its performance exceeds the performance of existing XGBoost and LightGBM (8). Particularly its unique characteristic is that it is designed to efficiently handle categorical variables while minimizing model overfitting by using an ordered boosting technique. CatBoost can be used without converting categorical variables into numbers. Especially, it improves performance by automatically applying encoding techniques (one-hot encoding, target encoding, mean encoding, and response encoding) suitable for categorical variables. Moreover, since CatBoost optimizes hyperparameters using an internal algorithm without a separate hyperparameter optimization process, it is easier to use compared to other algorithms that require hyperparameter tuning, which is an advantage of this algorithm. While running CatBoost, this study set the number of trees to 100, learning rate to 0.300, regularization's Lambda to 3, and the limit depth of individual trees to 6.

Shapley additive explanation

The correct interpretation of machine learning-based predictive model results has always been a subject of interest. In particular, a more complex model has lower interpretability (black box) even though it can improve predictive power. However, the interpretability of a developed machine learning model is very important for health care workers who apply the model results (13). It is essential in terms of helping people gain insights regarding how to advance models and understand the model development process (13).

The tree-based boosting algorithm used in this study can utilize the function of calculating the variable importance based on impurity criteria provided by scikit-learn. At this time, the variable importance is calculated based on the mean decrease in impurity. Therefore, it can evaluate how much each individual variable contributes to improving the predictive performance of the model in the training data. However, it does not reflect the importance of data not included in the training. Moreover, it tends to consider the cardinality of the variable more importantly. It has another limitation that it cannot identify the variable importance of each individual data point and can check the global variable importance of the entire model.

Shapley additive explanation (SHAP), a framework, has been proposed recently to solve this problem (13). This is developed based on game theory, and it is a model-agnostic method (13). The model-agnostic method can explain the specific contribution of each variable to the target data (13). It was used for interpreting the model results of this study especially because its major advantages were contrastive explanation (i.e., identifying the interdependency between individual variables or between an individual variable and the target variable) and variable importance of each data point (i.e., understanding the importance of a local variable).

Development and validation of a logistic nomogram

This study developed a model for predicting adolescent obesity by using multiple logistic regressions that corrected all confounding factors to understand the relationship between predictors for South Korean adolescent obesity by inputting the seven variables with the highest Shapley values found in

TABLE 1 General characteristics of subjects by the prevalence of obesity, n (%).

Variable	Obesity		p
	No (n = 41,777)	Yes (n = 9,081)	
Gender			< 0.001
Male	20,009 (75.4)	6,526 (24.6)	
Female	21,768 (89.5)	2,555 (10.5)	
Grade			< 0.001
7th grade	7,530 (85.4)	1,288 (14.6)	
8th grade	7,405 (85.0)	1,307 (15.0)	
9th grade	7,225 (82.9)	1,493 (17.1)	
10th grade	6,867 (81.7)	1,539 (18.3)	
11th grade	6,798 (80.2)	1,676 (19.8)	
12th grade	5,952 (77.0)	1,778 (23.0)	
Area of residence			0.437
Urban	17,949 (82.0)	3,942 (18.0)	
Rural	23,828 (82.3)	5,139 (17.7)	
Subjective household economic level			< 0.001
High	16,379 (83.0)	3,358 (17.0)	
Medium	20,304 (82.7)	4,243 (17.3)	
Low	5,094 (77.5)	1,480 (22.5)	
Stress perception level			0.002
High	13,981 (81.3)	3,213 (18.7)	
Moderate	18,728 (82.7)	3,920 (17.3)	
Low	9,068 (82.3)	1,948 (17.7)	
Experience of depressive feeling			0.005
No	31,226 (81.9)	6,915 (18.1)	
Yes	10,551 (83.0)	2,166 (17.0)	
Experienced a conflict with an acquaintance due to smartphone overdependence			0.725
No	40,106 (82.1)	8,725 (17.9)	
Yes	1,671 (82.4)	356 (17.6)	
Smoking in the past 30 days			< 0.001
No	37,585 (82.5)	7,980 (17.5)	
Yes	4,192 (79.2)	1,101 (20.8)	
Drinking in the past 30 days			< 0.001
No	37,444 (82.5)	7,926 (17.5)	
Yes	4,333 (79.0)	1,155 (21.0)	
Number of days of having breakfast in the past seven days			0.874
0 day (none)	8,722 (82.2)	1,886 (17.8)	
1–3 days	10,548 (81.9)	2,330 (18.1)	
4–6 days	10,533 (82.2)	2,284 (17.8)	
7 days (everyday)	11,974 (82.3)	2,581 (17.7)	
Number of days of eating fruit in the past seven days			< 0.001
None	5,219 (79.7)	1,331 (20.3)	
1–2 days	24,460 (81.7)	5,469 (18.3)	
3 days or more	12,098 (84.1)	2,281 (15.9)	
Number of days of drinking soda in the past seven days			< 0.001

(Continued)

TABLE 1 (Continued)

Variable	Obesity		p
	No (n = 41,777)	Yes (n = 9,081)	
0 day (none)	9,475 (83.6)	1,858 (16.4)	
1–2 days	17,623 (81.9)	3,893 (18.1)	
3–4 days	9,105 (81.0)	2,139 (19.0)	
5 days or more	5,574 (82.4)	1,191 (17.6)	
Number of days of having fast food in the past seven days			0.009
None	7,484 (81.5)	1,700 (18.5)	
1–2 days	23,838 (82.0)	5,238 (18.0)	
3 days or more	10,455 (83.0)	2,143 (17.0)	
Mean sleeping hours per day			0.945
Less than 4 h	5,173 (82.2)	1,118 (17.8)	
5 h	7,402 (82.0)	1,621 (18.0)	
6 h	8,613 (81.8)	1,814 (18.2)	
7 h	7,081 (81.8)	1,579 (18.2)	
8 h or more	7,523 (82.1)	1,645 (17.9)	
The number of days of conducting the moderate-intensity physical activity for 60 min or more per day in the past seven days			< 0.001
None	16,169 (83.8)	3,136 (16.2)	
1–2 days	12,225 (82.2)	2,652 (17.8)	
3 days or more	10,731 (79.9)	2,707 (20.1)	
Mean sitting hours per day			< 0.001
Less than 6 h	35,491 (82.4)	7,565 (17.6)	
6 h or more	5,502 (80.6)	1,326 (19.4)	
The number of days of conducting strength training in the past seven days			< 0.001
None	20,947 (82.9)	4,316 (17.1)	
1–2 days	10,320 (80.7)	2,462 (19.3)	
3–4 days	5,180 (81.2)	1,200 (18.8)	
5 days or more	5,330 (82.9)	1,103 (17.1)	
Academic performance			< 0.001
High	5,293 (84.9)	941 (15.1)	
Medium-high	10,549 (84.4)	1,948 (15.6)	
Medium	12,743 (82.5)	2,694 (17.5)	
Medium-low	9,301 (79.4)	2,417 (20.6)	
Low	3,891 (78.3)	1,081 (21.7)	

CatBoost. In multiple logistic regressions, adjusted odds ratio (aOR) and 95% confidence interval (CI) were presented to identify the independent relationships between predictors and adolescent obesity.

The developed adolescent obesity predictive model visualized the probability of adolescent obesity using a nomogram based on logistic regression so that medical workers could easily interpret the adolescent groups with a high obesity probability. The nomogram refers to a two-dimensional diagram showing the relationship between multiple risk factors to calculate the predictive probability of disease simply and efficiently. It consists of a point line, a risk factor line, a probability line, and a total point line. The point line is placed at the top of the nomogram to derive the score corresponding to the class of each risk factor. The number of risk factor lines was six, corresponding to the number of risk factors for adolescent obesity in this study. The total point line means the sum of the scores of risk factors. The probability line is the final probability of adolescent obesity prediction calculated based on the total score line, and it is placed at the bottom of the nomogram.

The predictive performance of the finally developed adolescent obesity prediction nomogram was evaluated and analyzed using 10-fold cross-validation. F-measure, the area under the curve (AUC), general accuracy, precision, recall, and calibration plots were used as indicators for evaluating predictive performance. All analysis was performed using Python version 3.8.2.[1]

Results

General characteristics of subjects according to the prevalence of obesity after the onset of the COVID-19 pandemic

Table 1 shows the results of the chi-square test, which analyzed the differences between obese adolescents and normal-weight adolescents by general characteristics. Among 50,858 subjects, obese adolescents were 9,081 (17.9%). The results of the chi-square test showed that obese adolescents and normal-weight adolescents were significantly ($p < 0.05$) different in gender, grade, subjective household economic level, stress perception level, the experience of depressive feeling, smoking in the past 30 days, drinking in the past 30 days, the number of days of eating fruit in the past seven days, the number of days of drinking soda in the past seven days, the number of days of having fast food in the past seven days, the number of days of conducting the moderate-intensity physical activity for 60 min or more per day in the past seven days, mean sitting hours per day, the number of days of conducting strength training in the past seven days, and academic performance.

Predictors for obesity in South Korean adolescents

Figure 1 presents the calculated SHAP value of a factor related to obesity in South Korean adolescents by using CatBoost. In this study, the top seven variables with a high impact on model output (based on SHAP values) were gender, mean sitting hours per day, the number of days of conducting strength training in the past seven days, academic performance, the number of days of drinking soda in the past seven days, the number of days of conducting the moderate-intensity physical activity for 60 min or more per day in the past seven days, and subjective stress perception level.

Table 2 shows the results of logistic regression analysis for predicting obesity in South Korean adolescents using the top seven variables with high impact on model output in

1 https://www.python.org

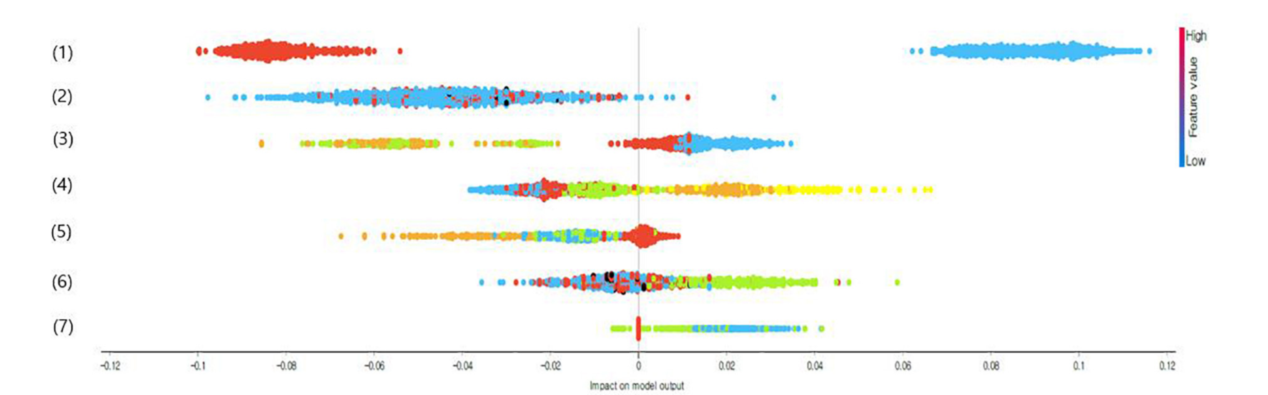

FIGURE 1
Impact on model output of adolescent obesity predictors using categorical boosting (CatBoost's) shapley additive explanation (SHAP) values (only top seven variables are presented); (1) Gender (1 = male or 2 = female), (2) mean sitting hours per day (1 = less than 6 h or 2 = 6 h or more), (3) number of days of conducting strength training in the past seven days (1 = none, 2 = 1–2 days, 3 = 3–4 days, or 4 = 5 days or more), (4) academic performance (1 = high, 2 = medium-high, 3 = medium, 4 = medium-low, or 5 = low), (5) the number of days of drinking soda in the past seven days (1 = none, 2 = 1–2 days, 3 = 3–4 days, or 4 = 5 days or more), (6) the number of days of conducting the moderate-intensity physical activity for 60 min or more per day in the past seven days (1 = none, 2 = 1–2 days, or 3 = 3 days, and more), and (7) stress perception level (1 = high, 2 = moderate, or 3 = low).

TABLE 2 Predictors for obesity in South Korean adolescents: aOR and 95% CI.

Variable	AOR	95% CI	*p*
Gender			
Male	3.39	3.20, 3.58	< 0.001
Female (reference)	1	1	
Stress perception level			
High	1.33	1.25, 1.43	< 0.001
Moderate	1.08	1.01, 1.15	0.015
Low (reference)	1	1	
Number of days of drinking soda in the past seven days			
0 day (reference)	1	1	
1–2 days	1.25	1.15, 1.37	< 0.001
3–4 days	1.28	1.18, 1.38	< 0.001
5 days or more	1.21	1.11, 1.31	< 0.001
The number of days of conducting the moderate-intensity physical activity for 60 min or more per day in the past seven days			
None	1.21	1.14, 1.29	< 0.001
1–2 days	1.06	1.01, 1,12	0.045
3 days or more (reference)	1	1	
Mean sitting hours per day			
Less than 6 h (reference)	1	1	
6 h or more	1.08	1.01, 1.16	0.016
The number of days of conducting strength training in the past seven days			
None	1.81	1.65, 1.99	< 0.001
1–2 days	1.55	1.41, 1.70	< 0.001
3–4 days	1.25	1.13, 1.39	< 0.001
5 days or more (reference)	1	1	
Academic performance			
High (reference)	1	1	
Medium-high	1.12	1.02, 1.23	0.011
Medium	1.33	1.22, 1.45	< 0.001
Medium-low	1.61	1.47, 1.76	< 0.001
Low	1.65	1.48, 1.83	< 0.001

CatBoost. The results of the adjusted model for predicting suicidal ideation in South Korean adolescents revealed that independent influence factors were male (AOR = 3.39, 95% CI: 3.20, 3.58), stress perception level moderate or higher (moderate: AOR = 1.08, high: AOR = 1.33), the number of days of drinking soda in the past seven days (1–2 days: AOR = 1.25, 3–4 days: AOR = 1.28, and 5 days or more: AOR = 1.21), the number of days of conducting the moderate-intensity physical activity for 60 min or more per day in the past seven days (1–2 days: AOR = 1.06 and none: AOR = 1.21), number of days of conducting strength training in the past seven days (3–4 days: AOR = 1.25, 1–2 days: AOR = 1.55, and none: AOR = 1.81), and academic performance (medium-high: AOR = 1.12, medium: AOR = 1.33, medium-low: AOR = 1.61, and low: AOR = 1.65) ($p < 0.05$).

Development and validation of a nomogram for predicting groups vulnerable to obesity in South Korean adolescents

Figure 2 presents the nomogram for predicting groups vulnerable to obesity among South Korean adolescents. The nomogram predicted that the probability of male students who currently felt a lot of stress, had poor academic performance, drank soda for 3–4 days in the past seven days, did not conduct the moderate-intensity physical activity for 60 min or more per day or strength training, and sat for 6 h or more per day on average having obesity was 77%.

The developed nomogram for predicting adolescent obesity examined its predictive performance using AUC, general accuracy, F1, recall, precision, and calibration plot (**Figure 3**). When the predicted probability and the observed probability were compared by using calibration plots and a chi-square test for the obese group and the non-obese group (**Figure 3**), the predicted probability and the observed probability were not significantly different ($p < 0.05$). The results of 10-fold cross validation showed that the AUC of the adolescent suicidal ideation prediction nomogram was 0.68, the general accuracy of it was 0.82, the precision of it was 0.77, the recall of it was 0.82, and the F-[Frame1] measure of it was 0.78.

Discussion

This study identified influencing factors associated with obesity in adolescents after the COVID-19 pandemic. The results of this study showed that the obesity rate of adolescents was 17.9%. It was a 2.5% increase from the 2019 national survey (15.4%). Studies in other countries, such as the United States (14) and China (15), also reported an increase in adolescent obesity rates after the declaration of the COVID-19 pandemic. Ministry of Education, Ministry of Health and Welfare, Korea Disease Control, and Prevention Agency (14) showed that the prevalence of obesity among U.S. adolescents increased by more than 15% during the COVID-19 pandemic due to school closures. The prevalence of obesity among Chinese adolescents between 15 and 17 years also increased from 10.5 to 12.9%, more than 2.4% (15). Stavridou et al. (16) systematically reviewed 15 studies (17,028,111 subjects in total) related to adolescent obesity during the COVID-19 pandemic and reported that the obesity rate increased because adolescents had less physical activities as outdoor activities were restricted due to lockdown.

The WHO declared a pandemic on March 11, 2020, as COVID-19 began to spread globally from January 2020 (5). South Korea also implemented intensive social distancing such as shifting schooling from in-person to online classes and

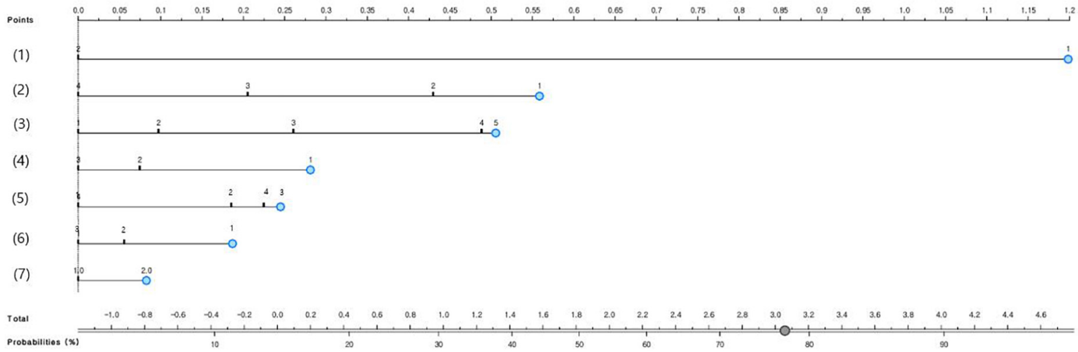

FIGURE 2
The nomogram to predict groups vulnerable to obesity in South Korean adolescents; (1) Gender (1 = male or 2 = female), (2) number of days of conducting strength training in the past seven days (1 = none, 2 = 1–2 days, 3 = 3–4 days, or 4 = 5 days or more), (3) academic performance (1 = high, 2 = medium-high, 3 = medium, 4 = medium-low), (4) stress perception level (1 = high, 2 = moderate, or 3 = low), (5) the number of days of drinking soda in the past seven days (1 = none, 2 = 1–2 days, 3 = 3–4 days, or 4 = 5 days or more), (6) the number of days of conducting the moderate-intensity physical activity for 60 min or more per day in the past seven days (1 = none, 2 = 1–2 days, or 3 = 3 days and more), and (7) mean sitting hours per day (1 = less than 6 h or 2 = 6 h or more).

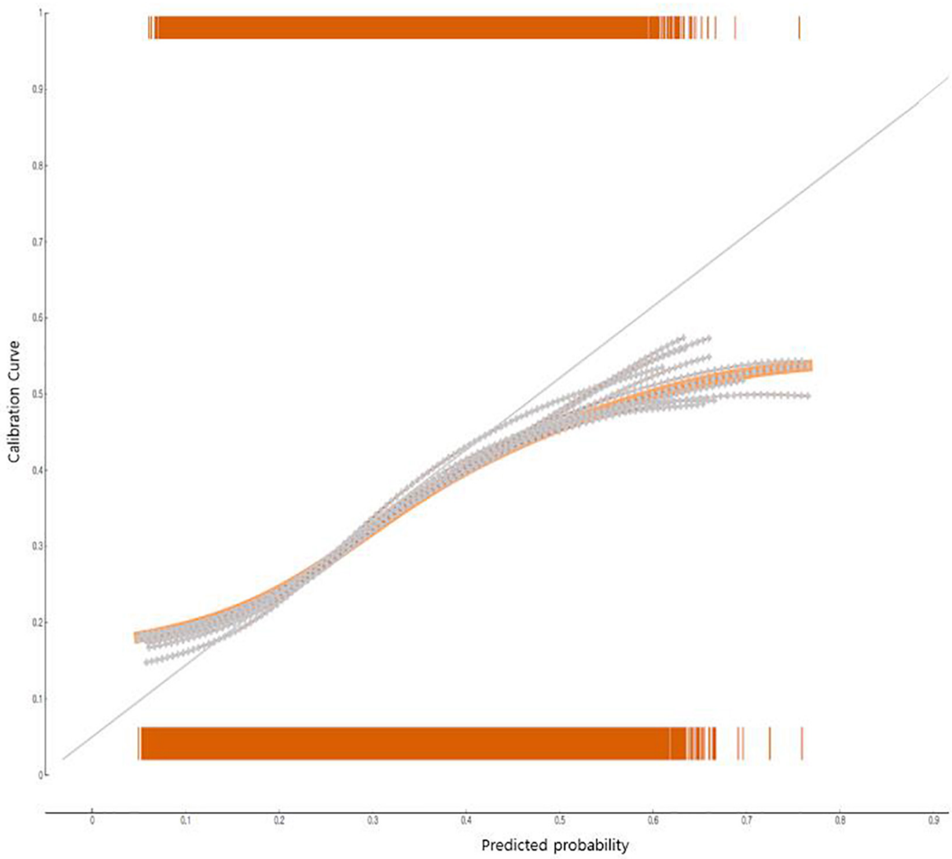

FIGURE 3
The performance of the nomogram to predict groups vulnerable to obesity in South Korean adolescents: calibration plot.

restricting indoor and outdoor physical activities to prevent the spread of the infectious disease (17). It has been reported that adolescent obesity is affected by various factors including social and environmental factors and lifestyle factors as well as biological factors. It is believed that the extended COVID-19 pandemic has induced changes in lifestyles such as restrictions on outdoor activities to affect the physical health of adolescents such as obesity as well as their mental health.

In this study, gender was a major predictor of adolescent obesity. The obesity rate of South Korean male adolescents and that of South Korean female adolescents were similar until 2010, but the former tended to be higher than the latter after 2011 (9). In particular, this epidemiologic study examined the obesity rate of South Korean adolescents after the COVID-19 pandemic and showed that male students (24.6%) had a 2.5 times higher obesity rate than female students (10.5%). Therefore, it is necessary to develop obesity management guidelines considering the characteristics of gender to prevent adolescent obesity.

In this study, soda intake was a major risk factor for adolescent obesity. The social distancing restrictions after COVID-19 changed dietary life such as an increase in food delivery and instant food intake (18–21). Four out of 10 Palestinian adolescents gained weight due to increased consumption of soda, fried dishes, and sweets (18). Ing and Ing (19) and Bertens et al. (20) also showed that Italy, Spain, Chile, Colombia, and Brazil adolescents consumed soda and snacks up to 20.7% more than usual during the lockdown period. Particularly, obese adolescents with a high BMI consumed a lot of soda. Absorption of excessive sugar increases lipid synthesis in the liver, which increases the risk of cardiovascular disease and obesity (22). A large-scale epidemiologic study is required to determine the causal relationship between increased soda consumption and adolescent obesity during the COVID-19 pandemic.

Another finding of this study was that a decrease in moderate-intensity physical activity and strength training and an increase in sitting hours were significantly associated with adolescent obesity after the COVID-19 pandemic. Fernandez-Rio et al. (23) revealed that the weight gain of adolescents after the COVID-19 pandemic was significantly related with a decrease in moderate-intensity or higher physical activity, which agreed with the results of this study. In particular, intensive social distancing was implemented in South Korea during the COVID-19 pandemic (24). For example, the business of fitness centers and group sports facilities was restricted during the period (24).

Moreover, Dunton et al. (25) reported that sedentary behaviors increased while the physical activity of adolescents decreased during the lockdown period. Previous studies (26, 27) revealed that screen-based sedentary behavior such as watching TV was closely related to obesity in children and adolescents. Especially, Kwak and Ickovics (27) showed that maintaining a sedentary behavior (e.g., watching TV) for more than 2 h a day also increased the risk of type 2 diabetes, in addition to obesity. Kang et al. (28) on South Korean adolescents also reported that adolescents who spent 35 h or more per week in screen-based sedentary behavior had a higher chance of metabolic disease morbidity than those who spent 16 h or less per week.

Since lockdown included not only indoor social distancing but also restrictions on outdoor activities such as sports, the decrease in strength training or the change in physical activity habits during the COVID-19 pandemic was likely to act as major influencing factors for adolescent obesity. Sekulic et al. (29) showed that a decrease in the physical activity level due to social distancing negatively influenced basic physical strength. In particular, Sekulic et al. (29) observed reduced stamina among male students in relation to their participation in organized sports. As non-face-to-face activities have increased during the COVID-19 pandemic, adolescents had fewer physical activities. As a result, to prevent adolescent obesity, it is necessary to prepare a physical activity promotion program for adolescents vulnerable to obesity.

This study developed a model for predicting adolescent obesity after the COVID-19 pandemic while considering multiple health risk factors. The model showed that the probability of male students who currently felt a lot of stress, had poor academic performance, drank soda for 3–4 days in the past seven days, did not conduct the moderate-intensity physical activity for 60 min or more per day or strength training, and sat for 6 h or more per day on average having obesity was 77%, which was very high. Previous studies showed that an increase in sedentary hours and a decrease in physical activity adversely influenced the stamina and sense of balance of adolescents (30) and decreased physical activities induced stress and obesity in adolescents (31, 32). These results implied the risk of adolescent obesity due to multiple health behaviors. However, it is difficult to compare these results with the results of this study directly. Obese subjects are vulnerable to infectious diseases, and obesity is a major influencing factor for chronic diseases (33). Therefore, to promote the health of adolescents, it is required to develop customized health promotion programs considering the multiple health risk behaviors of adolescents vulnerable to obesity and conduct monitoring continuously at the school level (34). Furthermore, since only a few studies analyzed multiple health risk factors of adolescent obesity, additional epidemiological studies are needed to analyze multiple health risk factors in obese adolescents considering various factors.

The limitations of this study are as follows. First, since this study used an online survey as a data source, this study could underestimate the percentage of obesity. A large-scale epidemiological study is needed to measure adolescent obesity more accurately by using body measurements such as height, weight, and waist circumference. Second, there can be other potential explanatory variables, in addition to the explanatory variables included in this study, that may affect obesity after the COVID-19 pandemic. It is required to develop models for predicting adolescent obesity while including various potential variables that are likely to influence obesity, such as adolescent mental health. Third, the raw data of this study did not have information whether obese adolescents were obese before the COVID-19 pandemic. Therefore, it is difficult to interpret that the obesity observed in this epidemiological study occurred after the COVID-19 pandemic. A retrospective cohort study comparing obesity before and after the COVID-19 pandemic is needed in the future. Fourth, since it was a cross-sectional study, the results of this study could not be interpreted as a cause-effect relationship. Additional cohort studies are needed to determine causality between factors.

Conclusion

This epidemiological study predicted that male students who currently felt a lot of stress, had poor academic performance, drank soda for 3–4 days in the past seven days, did not conduct the moderate-intensity physical activity for 60 min or more per day or strength training, and sat for 6 h or more per day on average were vulnerable to obesity. Consequently, to prevent obesity in adolescents, it is required to detect adolescents vulnerable to obesity early and conduct monitoring continuously to manage their physical health. Furthermore, schools need to prepare a customized support system that considers the characteristics of multiple health risk behaviors in the high-obesity-risk group.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Korea Disease Control and Prevention Agency (protocol code 117075 and date: 2021.07.01). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

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Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.955339/full#supplementary-material

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Instrument referral criteria for PlusoptiX and SureSight based on 2021 AAPOS guidelines: A population-based study

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Objective: The study aims to assess two refractive instrument-based methods of vision screening (SureSight and PlusoptiX) to detect refractive amblyopia risk factors (ARFs) and significant refractive errors in Chinese preschool children and to develop referral criteria according to the 2021 AAPOS guidelines.

Methods: Eye examinations were conducted in children aged 61 to 72 months ($n = 1,173$) using a PlusoptiX photoscreener, SureSight autorefractor, and cycloplegic retinoscopy (CR). The Vision Screening Committee of AAPOS's preschool vision screening guidelines from 2021 were adopted for comparison. Paired *t*-test analysis and Bland–Altman plots were used to assess the differences and agreement between the PlusoptiX photoscreener, SureSight autorefractor, and CR. In addition, the validity of the cut-off values of the several ARFs measured with the SureSight and PlusoptiX was estimated using receiver operating characteristic (ROC) curves and compared to the age-based 2021 AAPOS examination failure levels.

Results: A total of 1,173 children were tested with comprehensive eye examinations. When the referral numbers based on the 2013 (43/3.67%) and 2021 (42/3.58%) AAPOS guidelines were compared, significant differences between the values of astigmatism (72.09 vs. 52.38%) and anisometropia (11.63 vs. 38.10%) were found. The 95% limits of agreement (LOA) of the spherical value and the cylindrical value between PlusoptiX and CR were 95.08 and 96.29%. It was 93.87 and 98.10% between SureSight and CR. Considering refractive failure levels, the ROC curves obtained the optimal cut-off points. However, the PlusoptiX and the SureSight showed lower efficiency in hyperopia (Youden index, 0.60 vs. 0.83) and myopia (Youden index, 078 vs. 0.93), respectively. After adjusting the above cut-off points, the optimized NES (Nanjing Eye Study) referral criteria for myopia, hyperopia, astigmatism, and anisometropia were −0.75, 1.25, −1.0, and 0.5 with PlusoptiX and −1.25, 2.75, −1.5, and 0.75 with SureSight.

Conclusions: SureSight and PlusoptiX showed a good correlation with CR and could effectively detect refractive ARFs and visually significant refractive errors. There were obvious advantages in detecting hyperopia using SureSight and myopia using PlusoptiX. We proposed instrumental referral criteria for age-based preschool children based on AAPOS 2021 guidelines.

KEYWORDS

amblyopia risk factors, vision screening, failure criteria, referral criteria, AAPOS 2021

Introduction

Amblyopia is a common neurodevelopmental vision disorder with at least 1–2% prevalence (1, 2). Amblyopia not only compromises visual acuity but also contrast sensitivity, stereopsis, and motion perception. Early interventions for amblyopia show promisingly high cure rates. However, the efficacy decreases with age (3). Amblyopia risk factors (ARFs) include amblyogenic factors, such as strabismus, anisometropia, refractive error, and vision deprivation, and they can interrelate with each other (3). Therefore, the US Preventive Services Task Force (USPSTF) recommends that children aged 3 to 5 years could be screened for ARFs at least once (4). The American Association for Pediatric Ophthalmology and Strabismus (AAPOS) published the AAPOS 2021 guidelines, dividing the targets for vision screening into ARFs and visually significant refractive errors by age. In addition, the AAPOS 2021 guidelines adjust refractive thresholds to reduce over-referral and provide new guidance and requirements for revising instrument referral criteria.

Current screening methods based on a visual acuity chart may have limited accuracy due to children's poor cooperation and examiners' lack of experience (3, 5). Instrument-based screening uses autorefraction or photorefraction, which identifies the presence and magnitude of refractive error instead of measuring visual acuity. Therefore, compared to a visual acuity chart, instrument-based vision screening is quicker to administer as it requires minimal child cooperation. The American Academy of Pediatrics recommends instrument-based vision screening when available (6). Therefore, some user-friendly vision screeners have been employed.

The SureSight Vision Screener has been used as a handheld autorefractor for years, especially in developing countries, with well-established refractive error referral criteria. The PlusoptiX Photoscreener is also used as one of the photorefraction devices. Both devices are now being used simultaneously in different medical institutions in many regions. However, a few studies have compared the two devices and validated their accuracy. Meanwhile, the optimum refractive error referral criteria for two devices are yet to be determined based on 2021 AAPOS guidelines.

Based on the updated preschool vision screening guidelines from the Vision Screening Committee of AAPOS for 2021, we evaluated the accuracy of the SureSight Vision Screener and the PlusoptiX Photoscreener in detecting refractive ARFs and visually significant refractive errors. In addition, we tried to develop and optimize customized instrument referral criteria based on the Nanjing Eye Study (NES).

Materials and methods

Study population

NES is a population-based cohort study aiming to longitudinally observe the onset and progression of childhood ocular diseases in eastern China. As previously described (7), the children born between September 2011 and August 2012 in Yuhuatai District, Nanjing, China, who entered a kindergarten in Yuhuatai District were invited to participate in NES to undergo comprehensive eye examinations annually. The primary data presented in this paper were obtained in 2017 when these children were 60 to 72 months old.

Examinations

A team of six trained ophthalmologists and four optometrists conducted a comprehensive eye examination on all participants. Children's roster and basic information, including name, sex, and birth date, were obtained from each kindergarten's principal and were checked during the examination. Examinations including anthropometric parameters, distance visual acuity (VA, including uncorrected visual acuity, UCVA; presenting visual acuity, PVA and best corrected visual acuity, BCVA), anterior segment and fundus examination, instrument-based vision screening using automated technology, table-mounted autorefractor before and after cycloplegia, stereo acuity test, ocular alignment and motility, ocular biometric parameters, intraocular pressure, accommodative response, and optical coherence tomography were performed in the setting of every kindergarten. In addition, instrument-based vision screening was performed using automated technology before cycloplegia, including a handheld autorefractor (SureSight, Welch-Allyn, Inc, Skaneateles Falls, NY) and handheld photoscreener (PlusoptiX A12C, PlusoptiX GmbH, Nuremberg, Germany). Children with suspected or confirmed eye problems were referred to senior ophthalmologists and underwent further examinations.

The SureSight Vision Screener was placed 35 cm in front of the children. When the child is attracted by a circle of eight flashing green LEDs surrounding a small, central red light, the device measures refractive error monocularly along two meridians. After both eyes were measured individually, the SureSight displayed refractive values of both eyes and confidence numbers. The confidence number indicates the number of good readings obtained and their consistency, ranging from 1 to 9. The manufacturer's recommended minimum confidence number is 6. As recommended by the manufacturer for children younger than age 6 years, the SureSight was used in the "Child" mode, which adds a constant to the sphere value obtained, to correct the accommodative response of the non-cycloplegic child during testing. The spherical value ranged from –5.00D to +7.00D, and the cylindrical value ranged from –3.00D to + 3.00D. A +9.99 or −9.99 indicates a reading outside the unit's measurement range.

The PlusoptiX photoscreener was placed in front of the children at a distance of 1 meter under dim light, using a smiling face as a fixation target. The examination was performed simultaneously on both eyes while the non-cycloplegic child stared at the fixation target. This device's spherical and cylindrical value ranged from –7.00D to +5.00D in 0.25D increments, with asymmetry ranging from 0 to 25° in increments of 0.1°. The screener would show "Myopia" or "Hyperopia" directly when the spherical equivalent (SE) was over range. The test was performed at least 10 times until success.

Cycloplegic refraction was performed on (1) voluntary children and (2) children with suspected or confirmed eye problems, using retinoscopy. One drop of topical 1.0% cyclopentolate (Cyclogyl, Alcon Pharmaceuticals) was administered to each eye two times at a 5-min interval. After 15 min, the third drop of cyclopentolate was administered if the pupil size was <6 mm or the pupillary light reflex was still present.

Definition

Defined by the updated 2021 AAPOS guidelines, cycloplegic confirmatory examination failure levels for children aged >48 months should detect myopia >-2.00 D, hyperopia >4.00 D, astigmatism >-1.75 D, and anisometropia >1.25 D (8).

Data analysis

Except for the anisometropia calculation, only data for the right eye was analyzed to avoid enantiomorphism bias. Therefore, SE was calculated as spherical plus half of the cylindrical error. Consistent with AAPOS 2021 guidelines, we used the myopic meridional refractive power for myopic refractions, the hyperopia meridional refractive power for hyperopic refractions, and the magnitude of the difference of the lesser meridian for anisometropic determination (8).

Data analysis was performed using the IBM Statistical Package for the Social Sciences program V13.0 (SPSS, Chicago, IL, USA), and $P < 0.05$ was considered statistically significant. Descriptive data were presented as mean ± standard deviation (SD). Paired *t*-test analysis and Bland–Altman plots were used to assess the differences and agreement between the PlusoptiX photoscreener, SureSight autorefractor, and CR separately. The validity of the cut-off values of the several ARFs measured with the SureSight and with PlusoptiX was estimated by receiver operating characteristic (ROC) curves using CR as a reference and compared with the age-based 2021 AAPOS examination failure levels (8). The final optimized referral criteria, NES referral criteria, were obtained after adjusting the failure levels based on the ROC curve's different effectiveness of cut-off values. We calculated the sensitivity (Se), specificity (Sp), Youden index, positive predictive value (PPV), and negative predictive value (NPV) of NES referral criteria, Arnold referral criteria, and AAPOS 2021 referral criteria (using the numeric values of AAPOS 2021 failure criteria), which were compared to criterion standard confirmatory examinations by ophthalmologists (9).

Results

A total of 1,609 children (aged 66.84 ± 3.39 months) were tested with instrument-based vision screening, including 889 boys and 720 girls. Cycloplegic refraction was performed in 1,173 children (72.90%, 1,173/1,609). According to referral criteria of 2013 AAPOS and 2021 AAPOS, 43/42 (3.67%/3.58%) children were confirmed to have refractive ARFs, including 4/6 (9.30%/14.29%) with myopia, 12/11 (27.91%/26.19%) with hyperopia, 31/22 (72.09%/52.38%) with astigmatism, and 5/16 (11.63%/38.10%) with anisometropia (Table 1). Several children had two or more different refractive ARFs and visually significant refractive errors. Both guidelines obtained similar referral rates (3.67%/3.58%), but the number of referrals decreased for astigmatism and increased for anisometropia based on AAPOS 2021. Nineteen children were defined as inconclusive screenings from whom SureSight ($N = 10$) and PlusoptiX ($N = 10$) could not get conclusive results. One child was inconclusive in both devices. Seven inconclusive screenings were true positive for SureSight, and only one child was true positive for PlusoptiX. Based on the available results,

TABLE 1 Comparison of referrals based on the AAPOS 2013 and AAPOS 2021.

ARFs and visually significant refractive errors	Cases present	
	2013	2021
Hyperopia	12	11
Myopia	4	6
Astigmatism	31	22
Anisometropia	5	16
All refractive ARFs	43	42

inconclusive screenings were not predictably associated with a high refractive error or ophthalmic diseases.

Data of the right eye of 1,159 children were compared by paired *t*-test (Table 2) and Bland–Altman plots (Figure 1), consisting of 1,154 children with conclusive screenings and 5 children with inconclusive but numerical screenings of both devices. Compared with CR, PlusoptiX underestimated the mean cylindrical value (-0.42 ± 0.36 vs. −0.44 ± 0.45, average difference: −0.02 ± 0.30, $P = 0.01$) and the mean spherical value (0.34 ± 0.51 vs. 1.36 ± 0.78, average difference: 1.02 ± 0.72, $P < 0.001$). Statistical differences between SureSight and CR were found in mean cylindrical value (−0.55 ± 0.38 vs. −0.44 ± 0.45; average difference: 0.12 ± 0.33 D; $P < 0.001$) and the mean spherical value (1.64 ± 0.71 D vs. 1.36 ± 0.78 D; average difference: −0.28 ± 0.92 D; $P < 0.001$). According to the 95% LOA of the mean spherical value and the cylindrical value, the proportion of people within this range to the total was 95.08 and 96.29% between PlusoptiX and CR (Figures 1A,B), and was 93.87 and 98.10% between SureSight and CR (Figures 1C,D), respectively.

We conducted ROC analyses according to the results with specific values for each screening tool tested against the presence/absence of refractive examination failure levels, and ROC curves are shown in Figures 2A–H. Table 3 provides the area under the curve (AUC), a measurement for comparing the screening tools' diagnostic benefits, sensitivity, specificity values, Youden index, and PPV. The PlusoptiX obtained a better AUC value and indicated better diagnostic power than the SureSight. The two instruments have higher accuracy in astigmatism (Youden index, plusoptiX = 0.91, SureSight = 0.92), which were the most common disorder ($N = 22$). Anisometropia ($N = 16$) gained a relatively poor Youden index (plusoptiX = 0.71 vs. SureSight = 0.59), on the contrary, myopia scored well (0.93 vs. 0.78), although it had the fewest positive screenings ($N = 6$). PlusoptiX had 100% sensitivity and lower specificity in detecting refractive factors except for anisometropia, and the screening effectiveness was inferior to the SureSight (Youden index: 0.60 vs. 0.83) in the aspect of hyperopia.

Considering refractive failure levels based on ROC curves, the optimal cut-off points which corresponded to the maximum Youden index for myopia, hyperopia, astigmatism, and anisometropia with PlusoptiX were −0.63, 0.38, −0.88, and 0.38, and with SureSight were 0.56, 2.63, −1.38, and 0.69. Considering clinical practice and the low Sp (59.93%) and Youden index (0.60) of the best cut-off value for detecting hyperopia with PlusoptiX, we chose the second-best cut-off value of 0.88 (Sp = 88.55%, Youden index = 0.59) to replace 0.38. Then, we obtained a more appropriate instrument referral criteria (myopia ≤ −0.75, hyperopia ≥ 1.00, astigmatism ≤ −1.00, anisometropia ≥ 0.5), called NES referral criteria (Table 4). Similarly, we adjusted the cut-off value of myopia for the SureSight and obtained the corresponding NES referral criteria (myopia ≤ −1.25, hyperopia ≥ 2.75, astigmatism ≤ −1.50, anisometropia ≥ 0.75).

Table 4 shows Se, Sp, PPV, and NPV for detecting refractive ARFs for the referral criteria of AAPOS 2021, Arnold referral criteria, and the NES referral criteria. Based on the referral criteria of AAPOS 2021, the Sp obtained were relatively high (PlusoptiX = 98.93%, SureSight = 94.24%). The AAPOS 2021 missed half of the diagnosis (Se = 46.34%) and showed poor screening efficiency (Youden index = 0.45) for the PlusoptiX, while SureSight performed better (Se = 68.57%, Youden index = 0.63). Se (24.39%) and the Youden index (0.24) of Arnold referral criteria declined significantly. Overall, NES referral criteria reduced missed diagnosis (Se = 92.68% for PlusoptiX, 88.57% for SureSight) and misdiagnosis (Sp = 71.66, 71.99%) and achieve acceptable screening efficiency (Youden index = 0.64, 0.61).

Discussion

The present study assessed two refractive instrument-based methods of vision screening (SureSight and PlusoptiX) based on the 2021 AAPOS guidelines and proposed instrumental referral criteria for PlusoptiX (myopia ≤ −0.75, hyperopia ≥ 1.25, astigmatism ≤ −1.0, anisometropia ≥ 0.5) and SureSight (myopia ≤ −1.25, hyperopia ≥ 2.75, astigmatism ≤ −1.5, anisometropia ≥ 0.75), named NES referral criteria. The criteria were proposed recommendations for PlusoptiX and Suresight referral (manufacturer or user) based on AAPOS 2021 guidelines for the ARFs and visually significant refractive errors.

Instrument-based vision screening is appropriate for developing and populous countries where grassroots community medical personnel is short. Applying instrument- and age-specific pass/fail refractive error criteria based on the patient population, economic status and frequency of screening could improve the efficiency of screening. Two studies have compared Se and Sp of the PlusoptiX and the SureSight with CR and found that they were both reliable (10, 11). However, few studies have been conducted assessing their accuracy in the same population

TABLE 2 Comparison of SureSight, PlusoptiX, and cycloplegic retinoscopy in 1,159 children.

	Sphere (D)					Cylinder (D)				
	Mean	SD	95% CI		*P*	Mean	SD	95% CI		*P*
CR	1.36	0.78	1.31	1.4	N/A	−0.44	0.45	−0.47	−0.41	N/A
The plusoptiX	0.34	0.51	0.31	0.37	N/A	−0.42	0.36	−0.44	−0.4	NA
SureSight	1.64	0.71	1.6	1.68	N/A	−0.56	0.39	−0.58	−0.53	N/A
CR-Plus	1.02	0.72	0.98	1.06	<0.001	−0.02	0.3	−0.04	−0.01	0.01
CR-SureSight	−0.28	0.92	−0.34	−0.23	<0.001	0.12	0.33	0.1	0.13	<0.001

CR, Cycloplegic retinoscopy; D, Diopter; SD, Standard Deviation; CI, Confidence Interval; N/A, not applicable.

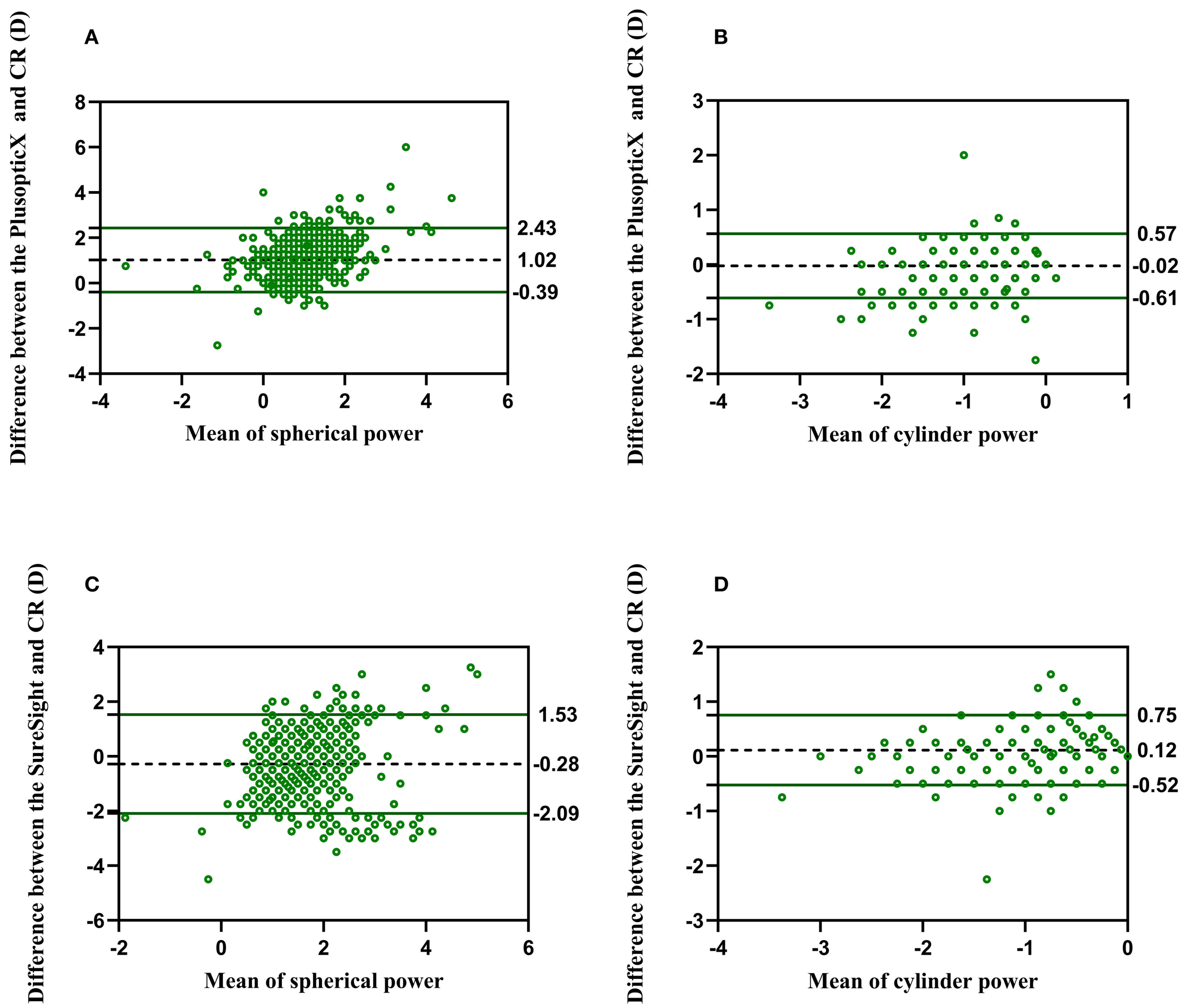

FIGURE 1
Bland–Altman plots show the agreement between PlusoptiX, SureSight, and cycloplegia retinoscopy. The difference between sphere and cylinder between **(A,B)** PlusoptiX and CR and **(C,D)** SureSight and CR.

and improving referral criteria, especially based on the failure levels of updated AAPOS 2021, which significantly revised the threshold (8).

The 2013 and 2021 AAPOS guidelines got similar referrals (43 vs. 42) in the same population. The referrals showed a reduction in astigmatism (22/42 vs. 31/43) and an increase

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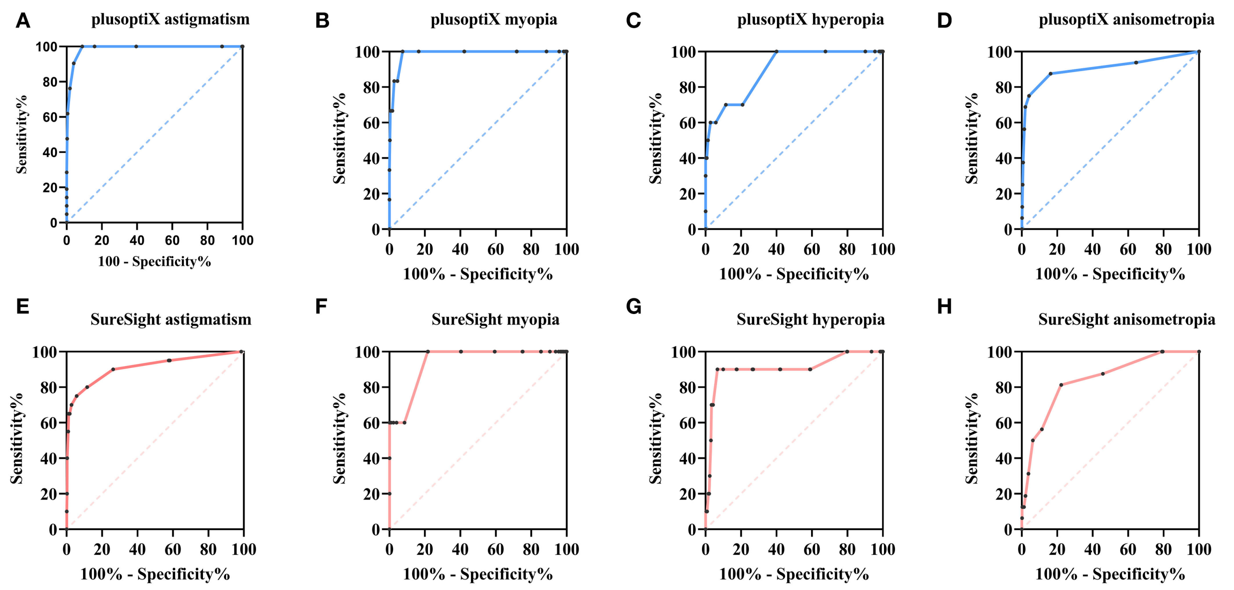

FIGURE 2
Receiver operating characteristic (ROC) curve for refractive results obtained by PlusoptiX and SureSight. ROC curve for **(A-D)** refractive results obtained by PlusoptiX and **(E-H)** refractive results obtained by SureSight.

in anisometropia (16/42 vs. 5/43) based on the 2021 AAPOS guideline, which showed the effectiveness of threshold adjustment (8). The two instruments screened 10 children each who were classified as inconclusive screenings, and 70% for SureSight and 10% for PlusoptiX met failure levels, so we recommended referring inconclusive screenings, especially for SureSight (12, 13). Inconclusive screenings were not predictably associated with a high refractive error or ophthalmic diseases but may be attributable to covered pupils, poor cooperation, or inattention (13).

In the present study, most children were hyperopic. Compared with CR (1.36 ± 0.78D), PlusoptiX (0.34 ± 0.51D) underestimated the mean spherical value, and accommodation caused by fixation (PlusoptiX was performed simultaneously on both eyes) may result in this myopic tendency (14). In addition, the cylinder value was lower in PlusoptiX (−0.02 ± 0.30) and higher in SureSight (0.12 ± 0.33) than in CR. Our results suggested that SureSight overestimated astigmatism, consistent with other studies (12, 15).

Except for the sphere of SureSight, both instruments showed a good correlation with CR, and 95% LOA was more than 95%. One study showed that 95% LOA of SE between SureSight and CR was about 90% (16). As the previous study suggested, adding a constant factor to correct the fixation myopia induced by the SureSight may not solve the problem because each child's degree of accommodation is unforeseeable (17). We thought that this arbitrary addition of 1.50D may be one of the reasons why worse agreement and biases appear in the spherical value of SureSight.

In this population-based study, only 42 successfully tested children were confirmed to have refractive ARFs or visually significant refractive errors, thus increasing the difficulty in analyzing the screening accuracy. The AUC value of PlusoptiX was superior to SureSight for each refractive error, indicating that the former was more powerful and reliable in predicting refractive ARFs. We consider it difficult to precisely obtain myopia cut-off because the children tend to be hyperopia at an early age (14), especially for SureSight, which obtained a higher sphere value than CR. Only six children had myopia according to AAPOS 2021 guidelines, and the small number of positive cases could reduce screening efficiency (14). PlusoptiX, surprisingly, obtained a relatively meaningful myopia cut-off value. Some articles argued that PlusoptiX underestimated hyperopia and overestimated myopia in cases of normal accommodation (18, 19), which might result in a poor Youden index for hyperopia and a better Youden index for myopia. Contrary to expectations, the efficiencies of obtained anisometropia cut-off value were not good, which may be related to different calculation methods of anisometropia and the fewer true positive cases.

When proposing a new referral criterion, the best cut-off value (0.38D) of hyperopia for PlusoptiX resulted in numerous misdiagnoses (Sp = 59.93%). Considering that the PlusoptiX tended to underestimate hyperopia (18, 19), the hyperopia criterion was raised to 0.88, corresponding to the second largest of the Youden index. The SureSight worked well in astigmatism and hyperopia. Therefore, we adjusted the criteria of myopia, choosing the cut-off value with the highest Youden index in myopia refraction. As the severity of the anisometropia ARFs

TABLE 3 Characteristics of ROC curves for refractive ARFs obtained by two refractive instrument-based methods compared with cycloplegic retinoscopy.

ARFs		AUC	P	95% CI	Cut-off (D)	Se (%)	Sp (%)	Youden index	PPV (%)	NPV (%)	
Hyperopia ($N = 11$)	PlusoptiX	0.90	<0.001	0.81	0.98	0.38	100.00	59.93	0.60	2.12	100.00
	SureSight	0.90	<0.001	0.78	1.00	2.63	90.00	93.28	0.83	10.34	99.91
Astigmatism ($N = 22$)	PlusoptiX	0.99	<0.001	0.98	1.00	−0.88	100.00	91.16	0.91	17.21	100.00
	SureSight	0.96	<0.001	0.88	1.00	−1.38	95.24	97.13	0.92	37.74	99.91
Myopia ($N = 6$)	PlusoptiX	0.99	<0.001	0.97	1.00	−0.63	100.00	92.57	0.93	6.52	100.00
	SureSight	0.94	<0.001	0.87	1.00	0.56	100.00	78.39	0.78	1.95	100.00
Anisometropia ($N = 16$)	PlusoptiX	0.90	<0.001	0.80	1.00	0.38	87.50	83.70	0.71	6.97	99.79
	SureSight	0.84	<0.001	0.74	0.94	0.69	81.25	77.91	0.59	4.87	99.67

ROC, receiver operator characteristic curve; ARFs, amblyopia risk factors; AUC, area under the curve; Se, Sensitivity; Sp, Specificity; CI, Confidence Interval; D, Diopter; PPV, positive predictive value; NPV, negative predictive value.

TABLE 4 Assessment and optimization of two refractive instrument-based methods for detecting refractive ARFs.

Device	Referral criteria	Hyper	Myopia	Astig	Aniso	Se (%)	Sp (%)	Youden index	PPV (%)	NPV (%)	FPR(%)	FNR(%)
PlusoptiX	AAPOS 2021	>4.00	<-2.00	<-1.75	>1.25	46.34	98.93	0.45	61.29	98.06	1.07	53.66
	Arnold referral criteria	≥3.00	≤-2.50	≤-2.50	≥1.75	24.39	99.38	0.24	58.82	97.29	0.62	75.61
	NES referral criteria	≥1.00	≤-0.75	≤-1.00	≥0.50	92.68	71.66	0.64	10.67	99.63	28.34	7.32
SureSight	AAPOS 2021	>4.00	<-2.00	<-1.75	>1.25	68.57	94.24	0.63	26.97	98.98	5.76	31.43
	NES referral criteria	≥2.75	≤-1.25	≤-1.50	≥0.75	88.57	71.99	0.61	8.93	99.51	28.01	11.43

Se, Sensitivity; Sp, Specificity; PPV, positive predictive value; NPV, negative predictive value; FPR, false positive rate; FNR, false negative rate.

causes amblyopia (8, 20), we preferred not to modify the criterion. After replacing them with equivalent and more general values, we obtained the final NES referral criteria (Table 4).

The 2021 AAPOS guidelines are intended to be used with the gold-standard examination to identify true positives and to serve as a standard for comparison of referral criteria. For Suresight, the NES referral criteria got a similar Youden index to the referral criteria of AAPOS 2021 (0.61 vs. 0.63), as the former was more sensitive (88.57 vs. 68.57%) and got less specificity (71.99 vs. 94.24%). For PlusoptiX, the referral criteria of AAPOS 2021 trended to significantly miss ARFs and visually significant refractive errors (Se: 46.34 vs. 92.68%), supporting the recommendation that the 2021 AAPOS referral criteria not be used directly in photoscreening device criteria. NES referral criteria were more cautious and sensitive, screening for more positive cases but reducing the percentage of true positives. Some studies suggested that most children with ARFs do not develop amblyopia (21). Preschool vision screening for amblyopia requires attention to lower misdiagnosis and referral rates, especially in economically developed areas. However, if we fail to detect ARFs at the age of 5–6 years may delay the control and treatment of amblyopia (3, 4). Moreover, due to the high morbidity of myopia in China (22), the NES criteria met the basic requirements that the screening of children (>4 years) should focus on the control of myopia caused by near-distance learning. More sensitive and careful screening with NES referral criteria is more beneficial for these age-specific children.

However, it is unsuitable for comparing our results with relevant studies adopting the guidelines of AAPOS 2013. Therefore, a further study employing the 2021 referral guideline of AAPOS is warranted. Recently, Arnold et al. revised the instrument referral criteria of three photoscreeners based on the 2021 AAPOS guidelines, including PlusoptiX (9). In the present study, the NES referral criteria obtained the maximum efficiency and performed better than the Arnold referral criteria in Chinese eastern preschool children. The diverse consequences of the Arnold referral criteria may result from participant heterogeneity, including location, sample source and age, and device models. Altogether, the application of instrument- and age-specific referral criteria should consider the characteristics of the population, economic status, and frequency of screening.

The strength of this study included its large sample size of preschool children in a population-based study, a particular age range in a specific race, a large sample size of a cycloplegic refraction, the application of the updated AAPOS guidelines, relatively comprehensive indexes, and power of the test for refractive ARFs and visually significant refractive error with two refractive instrument-based methods.

The limitations of this study include the fact that 27% of children without cycloplegia may cause bias. Besides, SureSight has been discontinued for sale, although it is still used in many places. Furthermore, because of the small number of patients, particularly those with myopia, it was difficult to assess the cut-off value in this preschool population accurately. More research is needed to assess the cost-effectiveness, convenience, and accuracy of refractive instrument-based methods in children of various ages and races.

Nonetheless, this investigation revealed several valuable findings. First, the sphere and cylinder were consistent between the PlusoptiX and CR in preschool children aged 61–72 months. Second, there was no significant difference in the number of cases between the AAPOS guidelines from 2021 to 2013, but the latter focused more on anisometropia and reduced referrals for astigmatism. Third, there were obvious advantages in detecting hyperopia using SureSight and myopia using PlusoptiX. Finally, based on the AAPOS 2021 uniform guidelines, evidence-based instrument referral criteria derived from ROC curves were provided to children ≥4 years of age and would guide the screening of ARFs and visually significant refractive errors.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of The First Affiliated Hospital with Nanjing Medical University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

HL and DH designed the study. QY, RL, and YXQ participated in manuscript preparation. QY and XL prepared tables and figures. QY, RL, and DH performed data interpretation and analysis. RL, YW, XZhao, XZhang, QS, QH, HT, YuZ, ZL, and YaZ performed the ocular examinations and questionnaire. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Socioeconomic status and other factors associated with HIV status among OVC in Democratic Republic of Congo (DRC)

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Background: Orphans and vulnerable children (OVC) are a high-risk group for HIV infection, particularly in Sub-Saharan Africa.

Purpose: This study aims to portray the socioeconomic profile of OVC and examine the association of household and parent/guardian characteristics with the HIV status of OVC.

Methods: For this quantitative retrospective study, we obtained data from ICAP/DRC for a total of 1,624 OVC from households enrolled for social, financial, and clinical services between January 2017 and April 2020 in two provinces of the Democratic Republic of Congo, Haut-Katanga and Kinshasa. We computed descriptive statistics for OVC and their parents' or guardians' characteristics. We used the chi-square test to determine bivariate associations of the predictor variables with the dichotomous dependent variable, HIV positivity status. To analyze the association between these independent variables and the dichotomous dependent variable HIV status after controlling for other covariates, we performed firth's logistic regression.

Results: Of the OVC included in this study, 18% were orphans, and 10.9% were HIV+. The chi-square analysis showed that among parents/guardians that were HIV+, a significantly lower proportion of OVC (11.7%) were HIV+ rather than HIV- (26.3%). In contrast, for parents/guardians with HIV- status, 9.0% of OVC were HIV-negative, and 11.7% of OVC were OVC+. The firth's logistic regression also showed the adjusted odds of HIV+ status were significantly lower for OVC with parents/guardians having HIV+ status themselves (AOR, 0.335; 95% CI, 0.171–0.656) compared with HIV-negative parents/guardians. The adjusted odds of HIV+ status were significantly lower for OVC with a monthly household income of < $30 (AOR, 0.421; 95% CI, 0.202–0.877) compared with OVC with a monthly household income > $30.

Conclusions: Our results suggest that, with the exception of a few household and parent/guardian characteristics, the risk of HIV+ status is prevalent across all groups of OVC within this study, which is consistent with the existing body of evidence showing that OVC are in general vulnerable to HIV infection. With a notable proportion of children who are single or double orphans in DRC, HIV+ OVC constitute a high-risk group that merits customized HIV services. The findings of this study provide data-driven scientific evidence to guide such customization of HIV services.

KEYWORDS

HIV, DRC, orphans, vulnerable children, socioeconomic status

Introduction

Human immunodeficiency virus (HIV) infection control programs need scientific evidence on HIV risk factors in vulnerable populations such as orphans and vulnerable children (OVC) to eliminate new HIV infections and to customize HIV prevention, treatment, and management services (1). Public health and non-profit organizations continue to set and pursue aggressive targets for the elimination of HIV/AIDS; therefore, understanding the profile of OVC is critical, given that they have a significantly higher risk of HIV infection than other children (2). The premature deaths of people living with HIV (PLHIV), many of whom are parents, directly exacerbate the vulnerability of their children (3, 4). In 2019, there were approximately 405,000 PLHIV in the Democratic Republic of the Congo (DRC). Of those, approximately 51,000 were OVC (5). In the DRC, orphans are defined as children (under 18 years of age) that have lost either one or both parents to war and disease (6, 7). Vulnerable children are people under 15 years of age who are prone to abuse, violence, and economic hardship because of their circumstances of birth or immediate environment. They are often deprived of basic needs, care, and protection and are disadvantaged compared to their peers (8–10).

The HIV epidemic continues to be a global health problem, specifically in resource-limited countries in Sub-Saharan Africa, such as the DRC. This remains particularly true for pediatric HIV patients, some of whom are OVC; over 90 percent of all pediatric HIV patients reside in Sub-Saharan Africa (11). PEPFAR/DRC has been continually intensifying its efforts in epidemic control and strengthening services to support the National AIDS Control Program (PNLS), which moves them closer to the UNAIDS' 95-95-95 targets in the provinces of Haut-Katanga and Lualaba (5). Among their highest priorities are their efforts to support OVCs and their families with a comprehensive set of services, including health, economic, and educational services, especially concerning strengthening the care continuum (5). There is strong evidence that such customized interventions specifically designed for high-risk subgroups produce positive outcomes and are cost-effective (12).

Vulnerability and other factors such as orphan status, isolation and stress, social stigma, and hardship are detrimental to OVC's physical and emotional health (2) and increase the risk of HIV infection and treatment failure (13). The level of social support patients greatly influences adult and adolescent health outcomes from the "network of family, friends, neighbors, and community members that is available in times of need to give psychological, physical, and financial help." Among the OVC in resource-limited countries, the amount of social support is either very limited or non-existent (11, 14, 15). The burden of HIV infection encompasses medical, social, and economic issues. It thus presents a very complex range of psychosocial challenges for not only the patients but also for their caregivers. These challenges become even more complex and cumbersome when the patients are pediatric patients (14). Recent studies have found that pediatric patients with low socioeconomic status and thus reduced access to transportation, education, and economic opportunities are less likely to adhere to antiretroviral therapy (ART) (15).

Parents and caregivers significantly impact children's and youths' treatment adherence (16). In their 2017 study, Nichols, Steinmetz, and Paintsil found that parents or caregivers would not disclose to the child their HIV status if it were positive, fearing the negative psychological impact children may experience after knowing their status (11). Since 2017, health personnel in the DRC have had guidelines for managing HIV disclosure to children with the consent and cooperation of the parents/guardians (17). Unfortunately, non-disclosure leads to children's inability to understand the reasons for taking medication or the risks of certain behaviors, which may result in non-adherence to treatment and preventative care (11, 18). Additionally, households with parents or caregivers that are also HIV+ experience an additional negative socioeconomic impact. Some of the children in these households, especially OVCs, are forced to abandon their education and work very early to meet their basic needs (15). Furthermore, OVCs that are taken care of by a sick parent or caregiver are more likely to engage in unsafe or risky behaviors (19).

The DRC's HIV+ OVC face the same challenges as those in other resource-limited Sub-Saharan countries. Currently, over 700,000 children in the DRC have been left orphaned due to HIV (20). With the majority of the population living in extreme poverty and the slowed economic growth of recent years (21), the DRC has an increased need to understand how household socioeconomic status and parent/guardian characteristics impact the health status (HIV status) of OVC. Evidence-based decision-making in HIV interventions is especially critical for OVC. Research studies on OVC's HIV status elsewhere show that the socioeconomic status of households and caregivers' demographic and clinical characteristics are among significant risk factors, but such studies in the DRC are scant (2, 22–24). To contribute to such scientific evidence, we have two goals in the current research: (a) to portray the profile of OVC in two provinces of DRC and (b) to explore risk factors for HIV+ status in OVC. These risk factors include characteristics of OVC and socioeconomic characteristics of the households and parents/guardians.

Methods

Data

Based on secondary data, this quantitative retrospective study analyzed de-identified individual-level programmatic records obtained from ICAP/DRC for 1,624 OVC enrolled between January 2017 and April 2020 in two provinces of the Democratic Republic of Congo, Haut-Katanga ($n = 175$), and Kinshasa ($n = 1{,}449$). This study focused on OVC as the non-OVC data were unavailable in this database. Per PEPFAR definitions, the age range for OVC is from 0 to 17 years. The source of the OVC dataset was household records, created from several different household files linked through household identification numbers. The data for these files came from household members' screening and assessment for eligibility and enrollment in various social, financial, and clinical services and from the monitoring of each household beneficiary's services. Household eligibility was assessed based on the presence of one or more of the following: (a) HIV+ children/adolescents newly started on ART, (b) HIV+ children or adolescents suspected of treatment failure, (c) children exposed to HIV who were <2 years of age, (d) children or adolescents living with an HIV+ adult at an advanced stage of the disease, and (e) high-risk teenage girls. High-risk teenage girls have an older sex partner, multiple sex partners, and/or adolescent sex workers. This high-risk group also included sexually exploited or abused adolescent girls. This dataset included both male and female OVC enrolled in the system, regardless of HIV status. HIV+ children who have already been on ART and had no treatment failure were not included in this database per the HIV program decision.

Measures

Dependent variable—HIV status of OVC

The dependent variable OVC HIV status had two attributes, HIV-negative (coded as 0) and HIV+ (coded as 1). The proportion of OVC for whom the HIV status was not declared was relatively small in the final dataset (i.e., 31 or 1.9%), so they were excluded from the multivariable analyses. To ascertain the extent to which this exclusion may have caused any bias, we used the chi-square to see if those with HIV status declared vs. undeclared differed by OVC characteristics. There were small though statistically non-significant differences by age and sex; the differences were statistically significant by urban health zones and formal schooling.

Independent variables

Three sets of independent variables were included in the analysis. The first set consisted of child characteristics. The OVC *age at the time of enrollment* was computed by calculating the difference between the date of birth and the date of enrollment and subsequently grouped into four categories: <5 years, 5 to <10 years, 10 to < 15 years, and 15 years or older. *A child's sex* was a dichotomous variable with attributes of both males and females. Whether the *child is in school* and the *child's handicap status* were both dichotomous variables with yes and no categories, as noted in the casework database.

The second set of independent variables comprised guardian/parent and household characteristics. The *main source of drinking water* originally had three categories – (a) private hand pumps, (b) public taps, drilling, rainwater, well/protected source, and catchment scheme, and (c) river, stream, lake, pond, well, or unprotected spring. This variable was coded as dichotomy by combining (a) and (b) above. *Toilet type* was a dichotomous variable with "no toilet/latrine" and "toilet with or without flush" as two attributes. The household having a monthly income of < $30 was recorded as yes or no. Both variables, *sex of the parent/guardian* and *parent's/guardian's HIV status,* were dichotomous with the attributes of male or female and HIV-negative or HIV+, respectively. The variable a*ge of the parent/guardian* was coded as <40 years of age, 40–49 years of age, 50 years or older, and not reported. The third set of characteristics consisted of facility characteristics, one of which was included in the analysis, the *rurality or urbanicity of the health zone*, coded as "rural or semi-rural" and "urban".

Analytical methods

We computed descriptive statistics such as frequencies and percentages after stratification by OVC orphan status to describe the characteristics of OVC and their parents or guardians. We examined the bivariate associations between the categorical independent variables and the dichotomous dependent variable OVC HIV status using the chi-square test and a *p*-value of 0.05 or lower to determine statistical significance. To examine the association between these independent variables and the dichotomous dependent variable HIV status after controlling for other covariates, we performed firth's logistic (FL) regression to compute three separate FL models, first for the OVC characteristics as covariates, the second with parent/guardian or household socioeconomic characteristics, and the third one for the facility characteristics. Firth's logistic regression was deemed appropriate to reduce bias in the estimation of maximum likelihood (ML) coefficients resulting from small samples or extremely disproportionate binary outcomes (e.g., the model overfitting) resulting from extremely disproportionate attribute distribution of the outcome variable—HIV status (HIV+, 163 OVC vs. 1,338 HIV-) (25). Puhr et al. (2017) describe how firth's penalization in logistic regression reduces bias in the estimation of rare events (25). We performed all the analyses for this study using Stata 15 (StataCorp, LLC, College Station, TX) (26). Georgia Southern University's Institutional Review Board (IRB) approved the study under project protocol number H l9260.

Results

Orphans constituted 18% of the OVC included in this study (Table 1). One-in-10 (10.9%) were HIV+. The mean age at enrollment was 9.3 years. Twenty-two percent of OVC were <5 years old, 29.7% were ages 5 to <10 years, 34.5% were aged 10 to < 15 years, and the remaining 13.7% were 15 years or older. Over half, or 51.6%, were females, and 2.8% of all OVCs had some disability or handicap. Only 32.5% of the OVC were in school, 56.7% were not, and the current enrollment status for the remaining 10.8% was unknown.

Most OVC (87.2%) had access to water sources comprising public taps, drilling, rainwater, wells, or other protected sources, whereas the remaining 12.8% had another source of water such as a river, stream, lake, pond, well, or unprotected spring. The majority of OVC had a toilet with or latrine without a flush/pit toilet (62.4%), whereas 3.1% had no toilet in their homes. The majority (62.3%) of OVC households had a monthly income of <$30, whereas 3.2% had a monthly income of $30 or more; for the remaining 34.5%, the household income was unknown. Forty-three percent of the parents/guardians were female, 20.3% were male, and 37.0 had no documented sex.

One-in-four parents or current guardians were HIV+, a small proportion (i.e., 8.9%) were HIV-, and for the remaining 66.4%, their HIV status was not reported. A majority (87.7%) lived in an urban health zone, whereas the remaining 12.3% were in rural or semi-rural health zones. The mean age of the parents or guardians was 44.6 years. The age distribution of the parents or guardians showed that 20.8% were <40 years of age, 21.4% were 40–49 years of age, 20.4% were 50 years old or older, and the remaining 37.4% did not have their age documented. The stratification of these characteristics is shown in Table 1.

Bivariate associations tested with chi-square statistics, depicted in Table 2, show that the risk of HIV was uniform across OVC regardless of child characteristics, with one exception. Whether the child was in school was unknown for a much larger proportion of HIV+ children than HIV-negative, 30.7% vs. 9.1 ($P < 0.001$). There was no significant statistical difference in HIV status among OVC regardless of household socioeconomic characteristics such as type of toilet, monthly household income below $30, or the source of drinking water. The risk of HIV was no different across OVC by different parent/guardian characteristics such as age or sex. However, significant variation ($P < 0.001$) in OVC's HIV status was observed in parents/guardians' own HIV status. Among parents/guardians that were HIV+, a significantly lower proportion of OVC (11.7%) were HIV+ rather than HIV-negative (26.3%). In contrast, for parents/guardians with HIV- status, 11.7% of OVC were HIV+, and 9.0% of OVC were HIV-. For parents with unknown (i.e., unreported) HIV status, 64.7% of OVC were HIV-, and 76.7% of OVC were OVC+.

For further assessment of the associations based on chi-square tests, the results of firth's logistic regression are presented in Table 3. After controlling for children's characteristics such as age at the time of enrollment, sex, and handicap status, the odds of HIV+ status were significantly higher for OVC with unknown school enrollment status (adjusted odds ratio (AOR), 4.140; 95% CI, 2.745–6.244) compared with OVC not in school. The odds of HIV status were not significantly different for OVC in different sex or age categories; these characteristics are considered important in HIV patients.

The odds of HIV+ status were significantly lower for OVC with a monthly household income of < $30 (AOR, 0.421; 95% CI, 0.202–0.877) compared with OVC with a monthly household income of > $30, after controlling for other households and parent/guardian characteristics. The adjusted odds of HIV+ status were also significantly lower for OVC with HIV+ parents/guardians (AOR, 0.335; 95% CI, 0.171–0.656) compared with HIV-negative parents/guardians. The odds of HIV+ status were significantly lower for OVC in urban areas (AOR 0.608; 95% CI, 0.387–0.954) compared to OVC in rural and semi-rural areas.

Discussion

HIV/AIDS prevention, care, and treatment programs rely heavily on empirical evidence to improve the quality and effectiveness of their services. To contribute to such critically needed research evidence for HIV/AIDS programs in the DRC, we, in the current study, focused on analyzing individual-level programmatic data about OVC enrolled in an HIV/AIDS program based on various criteria. The data were from clinics supported by the Centers for Disease Control and Prevention (CDC) with President's Emergency Plan for AIDS Relief (PEPFAR) funding in Haut-Katanga and Kinshasa provinces. Although the national strategic plan for the response to AIDS has always taken OVC into account and underlined its importance in several strategic areas, this study sheds light

TABLE 1 Descriptive statistics for OVC, stratified by orphan status, Jan. 2017 to Apr. 2020.

Child, parent/guardian, and facility characteristics	Child is an orphan						All OVC	
	Yes		No		Undeclared			
	No.	%	No.	%	No.	%	No.	%
HIV results								
HIV-	200	67.6%	708	84.6%	430	87.6%	1338	82.4%
HIV+	69	23.3%	59	7.0%	35	7.1%	163	10.0%
Not Reported	27	9.1%	70	8.4%	26	5.3%	123	7.6%
Age of child								
<5 year of age	65	22.0%	208	24.9%	86	17.5%	359	22.1%
5–9.9 years of age	93	31.4%	248	29.6%	142	28.9%	483	29.7%
10–14 years of age	88	29.7%	275	32.9%	197	40.1%	560	34.5%
15 years or older	50	16.9%	106	12.7%	66	13.4%	222	13.7%
Child's sex								
Female	150	50.8%	428	51.2%	258	52.7%	836	51.5%
Male	145	49.2%	408	48.8%	232	47.3%	785	48.3%
Child in school								
No	165	55.7%	521	62.2%	235	47.9%	921	56.7%
Yes	95	32.1%	248	29.6%	185	37.7%	528	32.5%
Not reported	36	12.2%	68	8.1%	71	14.5%	175	10.8%
Child disabled								
No	224	75.7%	563	67.3%	231	47.0%	1018	62.7%
Yes	11	3.7%	26	3.1%	9	1.8%	46	2.8%
Not reported	61	20.6%	248	29.6%	251	51.1%	560	34.5%
Main source of drinking water								
Other source	27	11.5%	77	13.1%	32	13.3%	136	8.4%
Public taps, drilling, rainwater, well/protected source, catchment scheme	208	88.5%	512	86.9%	208	86.7%	928	57.1%
Toilet type								
No toilet/latrine	10	11.5%	33	13.1%	7	13.3%	50	3.1%
Toilet with flush, or latrine without flush/pit toilet	225	88.5%	556	86.9%	233	86.7%	1014	62.4%
Household income <$30/month								
No	12	4.1%	32	3.8%	8	1.6%	52	3.2%
Yes	223	75.3%	557	66.5%	232	47.3%	1012	62.3%
Not Reported	61	20.6%	248	29.6%	251	51.1%	560	34.5%
Sex of parent/guardian								
Female	178	60.1%	348	41.6%	168	34.2%	694	42.7%
Male	42	14.2%	223	26.6%	64	13.0%	329	20.3%
Not reported	76	25.7%	266	31.8%	259	52.7%	601	37.0%
HIV status of parent/guardian								
HIV-	21	7.1%	76	9.1%	47	9.6%	144	8.9%
HIV+	73	24.7%	254	30.3%	75	15.3%	402	24.8%
Not reported	202	68.2%	506	60.5%	369	75.2%	1078	66.4%
Child in school								
No	5	1.7%	26	3.1%	3	0.6%	34	56.7%
Yes	31	10.5%	63	7.5%	27	5.5%	121	32.5%
Not reported	260	87.8%	748	89.4%	461	93.9%	1469	10.8%
Urban health zone vs rural health zone								
Rural or Semi-rural	43	14.5%	115	13.7%	42	8.6%	200	12.3%
Urban	253	85.5%	722	86.3%	449	91.4%	1424	87.7%
All OVC	296	18.2	837	51.5	491	30.2	1624	100.0%

HIV-, HIV-Negative; HIV+, HIV-Positive; OVC, orphans and vulnerablechildren.

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TABLE 2 Bivariate Analysis of HIV Status in OVC (Chi-Square), Jan. 2017 to Apr. 2020.

Child, parent/guardian and facility characteristics	HIV Status				*P**
	HIV-		HIV+		
	No.	%	No.	%	
Age of Child					0.801
<5 year of age	294	22.0%	38	23.3%	
5–9.9 years of age (in text we have 5–9)	397	29.7%	52	31.9%	
10–14 years of age	462	34.5%	50	30.7%	
15 years or older	185	13.8%	23	14.1%	
Child sex					0.367
Female	698	52.2%	79	48.5%	
Male	639	47.8%	84	51.5%	
Child in School					**<0.001**
No	752	56.2%	75	46.0%	
Yes	464	34.7%	38	23.3%	
Not reported	122	9.1%	50	30.7%	
Child had disability					0.748
No	846	63.2%	108	66.3%	
Yes	37	2.8%	4	2.5%	
Not reported	455	34.0%	51	31.3%	
Main source of drinking water					0.240
Another source	104	11.8%	9	8.0%	
Public taps, drilling, rainwater, well/protected source, catchment scheme	779	88.2%	103	92.0%	
Toilet type					0.287
No toilet/latrine	36	4.1%	7	6.3%	
Toilet with or latrine without flush/pit toilet	847	95.9%	105	93.8%	
HH monthly income <$30					0.061
$30 or more	37	2.8%	10	6.1%	
Less than $30	846	63.2%	102	62.6%	
Not reported	455	34.0%	51	31.3%	
Sex of parent/guardian					0.799
Female	582	43.5%	75	46.0%	
Male	272	20.3%	33	20.2%	
Not reported	484	36.2%	55	33.7%	
Parent/Guardian HIV status					**<0.001**
HIV-	120	9.0%	19	11.7%	
HIV+	352	26.3%	19	11.7%	
Not reported	866	64.7%	125	76.7%	
Parent/guardian age					0.567
<40 years of age	283	21.2%	42	25.8%	
40-49 years of age	299	22.3%	32	19.6%	
50 years or older	269	20.1%	31	19.0%	
Not reported	487	36.4%	58	35.6%	
Urban vs. rural					**0.035**
Rural or Semi-rural	140	10.5%	26	16.0%	
Urban	1198	89.5%	137	84.0%	

[*] P indicates level of significance based on Chi-Squarestatistics.
HH, Household; HIV-, HIV-Negative; HIV+,HIV-Positive.

TABLE 3 Firth's Logistic regression of HIV Status in OVC, Jan. 2017 to Apr. 2020.

Characteristics	AOR	P	95% CI	
			Lower	Upper
Child characteristics				
Age-group (vs. >5 years)				
5 to <10 years	1.087	0.723	0.683	1.729
10 to <15 years of age	0.963	0.874	0.604	1.533
15 years or older	1.164	0.595	0.663	2.044
Child 's Sex (vs. Male)				
Female	1.172	0.348	0.841	1.632
Child in School (vs. No)				
Yes	0.822	0.356	0.542	1.245
Not reported	4.140	**<0.001**	2.745	6.244
Child with disability or handicap (vs. No)				
Yes	1.065	0.903	0.384	2.953
Not reported	1.036	0.848	0.720	1.490
Household and parent/guardian characteristics				
Main source of drinking water (vs. unprotected water)				
Public taps, drilling, rainwater, and other protected sources	1.688	0.146	0.833	3.420
Toilet type (vs. no toilet/latrine)				
Toilet with or latrine without flush/pit toilet	0.553	0.166	0.240	1.277
HH Monthly Income less than $30 (vs. $30 or higher)				
Less than $30	0.421	**0.021**	0.202	0.877
Sex of parent or guardian (vs. Female)				
Male	0.964	0.879	0.609	1.528
Not reported	0.647	0.453	0.207	2.015
Parent/Guardian HIV status (vs. HIV-)				
HIV+	0.335	**0.001**	0.171	0.656
Not reported	1.169	0.581	0.670	2.041
Parent/guardian age (vs. <40 years)				
40–49 years of age	0.728	0.207	0.445	1.191
50 years or older	0.745	0.261	0.447	1.243
Not reported	1.307	0.578	0.508	3.359
Facility characteristics				
Urbanicity status (vs Rural or Semi-Rural)				
Urban	0.608	**0.031**	0.387	0.954

This table presents results from three separate Firth's Logistic Regression Models.
CI, confidence interval; HH, Household; HIV-, HIV-Negative; HIV+,HIV-Positive.

on OVC's HIV status and associated factors, providing critical practice-relevant evidence.

Our study results show that orphans constituted 18% of the OVC included in this study, of which 10.9% were HIV+. Having an orphan or a child who is not the biological child of the household head in one's home is quite prevalent in the DRC. A national survey from 2013–2014 showed that in the general population, 25% of households had children under 18 years of age who lived without their parents, and 12% of the households had single orphans (one parent deceased), whereas 2.4% of the households had double orphans (both parents deceased) (27).

These OVC are truly vulnerable as they are in poor socioeconomic conditions, with 1,012 of the 1,064 or 95% living with a household income of one dollar a day or less. This is extreme poverty relative to the international poverty line set at $1.90 daily (28). These OVC were also deprived of education because despite only 22% of these children being under the age of 5; a much larger proportion (57%) were not in school. In contrast, 78% of school-age children in the DRC are enrolled in primary school (29) and 46.17% in secondary school (30). This is consistent with a recent study in Zambia that discovered an association between higher psychosocial issues within OVC populations and the limited capacities for care due to poor socioeconomic conditions and lower academic achievements (31).

It is unclear why being in school was higher for OVC HIV+ (30.7%) vs. OVC HIV-negative (9.1%). This uncertainty about school enrollment may have been because 80% of the OVC in the database were referrals by healthcare workers because they lived in a household with one or more HIV+ adults; therefore, when someone other than the parent/guardian is reporting on the child's behalf, they may not know their school enrollment status. Household vulnerability and school dropouts would contribute to low school enrollment. These analyses revealed no variation in the proportion of HIV+ OVC by other characteristics such as age and sex, indicating that OVC of all ages and both sexes needed equal attention. Our findings of the higher proportion of HIV-negative OVC in the parent/guardian group that were themselves HIV+ are noteworthy, and several explanations can be proposed as follows: (1) HIV+ parents/guardians may have had better knowledge and skills to prevent their children or OVC from HIV transmission; (2) When extended families need to place an orphan or vulnerable child with someone other than their parents, the extended family may choose an HIV-negative parent/guardian who likely has some combination of more resources, better health, and less vulnerability vs. an HIV+ person; (3) HIV+ parents, once they know their status, may decide to not have more children to protect their children from infection and stigmatization (32, 33); and (4) DRC's successful PMTCT program, protecting HIV+ women from giving birth to an HIV infected baby likely plays a key role. These results are consistent with the findings of a recent study conducted in Tanzania and South Sudan regarding the impact of the OVC's caregivers and access to clinical care and support services for HIV+ OVC (34–36). These explanations must be substantiated with additional research, perhaps requiring qualitative or mixed methods. Our findings suggest the lower odds of HIV+ status among OVC in households <$30 may be attributable to healthcare accessibility issues for extremely poor OVCs and the resulting inability to get diagnoses; however, this was inconsistent with the Tanzania study that found that OVC in a lower socioeconomic status (34).

The study has some limitations; thus, our findings should be interpreted with those in mind. First, the OVC in the study did not represent all OVC found in the general population in the DRC. Instead, the enrollment with HIV clinics in Haut-Katanga and Kinshasa provinces occurred through multiple entry modes, with 8 out of 10 enrolled because the community-level caseworkers had enrolled an HIV+ adult in the same households. So, the findings may not be generalizable to similar OVC populations. Second, data were not always collected about the OVC from the person most knowledgeable. Third, some variables had a large proportion of cases with missing data, so those variables could not be included as covariates in the statistical model. Fourth, the study utilized a retrospective design, so disaggregation desirable by additional socioeconomic characteristics and type of orphan (single, double, which parent was deceased, or distinction between parent/guardian) was not available. Fifth, there is a potential for a household clustering effect due to some cases of multiple children coming from the same households. However, the secondary data did not include a family-level identifier, which would enable us to make that determination. Finally, many of the OVC and guardian characteristics were unreported, perhaps due to social desirability and social stigma associated with those attributes (e.g., child's schooling status, child's disability status). Regardless of these limitations, the study makes an important contribution in that it is the first of its kind in the DRC, and the findings are important for targeted and efficient interventions for OVC. We have included interpretation of non-significant results for variables that are traditionally seen as very important variables in HIV patient research. When there is no statistically significant difference among one or more of these variables, the authors feel that it is important to report these. It allows other researchers to recognize that a patient's status can be impacted regardless of patient characteristics such as age or sex.

Conclusions

Given the persisting HIV epidemic in Sub-Saharan countries, targeted, data-driven efforts to inform HIV prevention, care, and treatment programs are imperative, particularly in resource-poor countries such as the DRC. The current study describes the profile of OVC in Haut-Katanga and Kinshasa provinces, showing that OVC is a high-risk subgroup that may merit customized and targeted interventions. A notable proportion of these children were HIV+, many of whom may be orphans, and an abnormally high proportion was not in school. OVC whose school enrollment status was unknown were at a greater risk of being HIV+ than other OVC, implying that their enrollment may be unstable due to HIV. Age and sex of OVC were not significantly associated with elevated odds of being HIV+, suggesting that younger age is not as dominant an aspect of vulnerability to HIV infection as the orphan status (37). We also found significant associations among rurality of health zone, household income, and parents'/guardians' HIV status with OVC HIV+ status. Future program priorities in Sub-Saharan countries must include the development of linkages between OVC care and community support and evidence-based research into the effectiveness of cognitive and educational interventions within the OVC populations. These interventions may include direct and indirect programs that assist with financial support,

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improvement of neurocognitive development, and in-home activities that revolve around daily living activities and developmentally appropriate play.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: The program-implementing partners required that data be destroyed after publication. The authors do have data until the publication of the article. The authors can facilitate data access if requested with proper permission from the DRC Ministry of Health. Requests to access these datasets should be directed to Lievain Maluantesa, LMaluantesa@fhi360.org.

Ethics statement

The studies involving human participants were reviewed and approved by Georgia Southern University's Institutional Review Board approved the study under project protocol number H l9260. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

Conceptualization: GS, GE, LM, KW, EE, BB, AM, AT, and OI. Methodology: GS, GE, and LM. Formal analysis: GS and KW. Investigation: GS. Writing—original draft preparation: GS, LM, GE, and KW. Writing—review and editing: GS, GE, LM, KW, EE, AM, OI, AT, BB, and AM. Supervision and funding acquisition: GS. Project administration: GS and LM. All authors made substantial contributions to this manuscript, with the following areas of specific contributions and have read and agreed to the published version of this manuscript.

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Conflict of interest

Author GE was employed by the organization FHI. Authors LM, EE, and AM were employed by the organization FHI 360.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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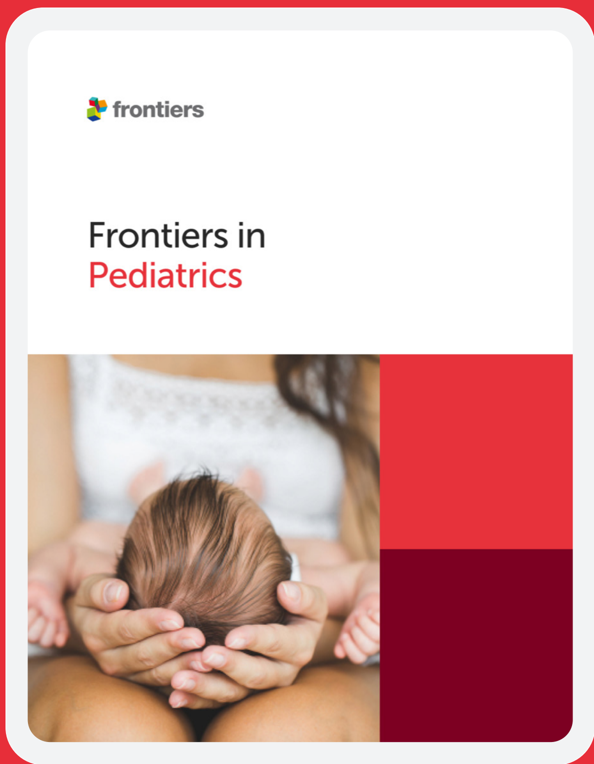

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