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The Association Between Obesity and COVID-19 Severity in Children Differed Between SARS-CoV-2 Variants: A Multicountry Hospital-based Observational Study

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Background: Obesity was a risk factor for severe COVID-19 in children during early outbreaks of ancestral SARS-CoV-2 and the Delta variant. However, the relationship between obesity and COVID-19 severity during the Omicron wave remains unclear.

Methods: This multicenter, observational study included polymerase chain r eaction-confirmed SARS-CoV-2-infected children and adolescents from Australia, Brazil, Italy, Portugal, Switzerland, Thailand, the United Kingdom and the United States hospitalized between January 1, 2020, and March 31, 2022. Data were collected across 3 time periods representing dominant SARS-CoV-2 variants: the ancestral strain (T1), pre-Omicron variants (Alpha and Delta; T2) and Omicron (T3). The primary outcome was the need for supplemental oxygen therapy and/or ventilatory support (respiratory support).

Results: This study included 6176 hospitalized children and adolescents of 2 to <18 years of age. The median age was 11.0 (interquartile range, 6.0–14.0) years, and 2989 (48.4%) were female. Obesity status was available for 5460 (88.4%), of whom 213 (3.9%) met the criteria for having obesity. Obesity was positively associated with the need for respiratory support during T1 [risk ratio (RR), 3.45 (95% CI: 2.02–5.88)] and T2 [RR, 3.24 (95% CI: 1.57–6.67], but this association was lost during T3 [RR, 3.08 (95% CI: 0.85–11.15)]. These findings were similar for unvaccinated children.

Conclusions: Obesity was associated with more severe COVID-19 during the ancestral and pre-Omicron waves but not during the Omicron wave. Importantly, the same phenomenon was observed in unvaccinated children, suggesting that differences in vaccination did not account for the observed changes in the need for respiratory support over time.

Key Words: pediatric obesity, COVID-19 severity, SARS-CoV- 2 variants, risk factor

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Obesity is an important independent risk factor for invasive mechanical ventilation, intensive care unit (ICU) admission and death among adult patients hospitalized with COVID-19.[1,2] This

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may reflect the combined deleterious effect of obesity on both the innate and adaptive immune response to SARS-CoV-2, as well as the biomechanical impact on respiration and/or other obesity associated conditions including type 2 diabetes.[3,4] A similar relationship between obesity and severe COVID-19 has previously been observed in children.[5] Specifically, obesity in children increased the risk of progression to severe COVID-19, ICU admission and the need for respiratory support during the early waves of the pandemic, including those dominated by the ancestral, Alpha and Delta variants.[5–7] Obesity has also been identified as a risk factor for the development of Multisystem Inflammatory Syndrome in Children following SARS-CoV-2 infection.[8]

To date, the majority of studies on pediatric obesity and COVID-19 severity are derived from the early waves of SARS-CoV-2, preceding the emergence of the Omicron variant of concern.[9] Differences in both COVID-19 symptoms and severity have been recorded in children across different waves of the pandemic.[10–13] For example, evidence from South Korea suggests that obesity was not a risk factor for severe COVID-19 in children during the Omicron wave of the pandemic, while it was for earlier variants.[14] In a study of approximately 700 children under the age of 18 years, Choi et al[14] showed that during the Delta wave, obesity was identified as a risk factor for serious illness caused by COVID-19. In contrast, during the Omicron wave, obesity was not found to be a risk factor for serious illness.[14] These findings are consistent with those of Lee et al[15] who showed that during the Delta wave, obesity was a risk factor for both hospitalization and the provision of supplemental oxygen. In contrast, obesity was not associated with hospitalization or supplemental oxygen during the Omicron wave.[15]

These contrasting findings for different variants may indicate a change in the pathogenesis of Omicron compared with previous SARS-CoV-2 variants. Alternatively, it has been speculated that these results may reflect differences in vaccination uptake. Namely, during the Omicron wave, children with obesity received SARS-CoV-2 vaccination and, hence, were less susceptible to severe disease.[14] For example, as of January 30, 2022, shortly after the Omicron wave commenced in South Korea, 59.4% of the population of 12 to 17 years of age had received a primary COVID-19 vaccine course.[15] A similar hypothesis regarding vaccination has been proposed to explain the lack of association between obesity and disease severity during the Omicron wave in adults.[9,16] However, it must be noted that these observations were not a global phenomenon. In China, during the Omicron wave, children who were overweight or obese still had a higher risk of developing moderate/severe illness than those with a normal weight.[17] Therefore, the global association between pediatric obesity and disease severity due to Omicron remains unclear.

In this study, we aim to determine the association between obesity and COVID-19 disease severity in children and adolescents admitted to the hospital, focusing on the Omicron variant in comparison with earlier pandemic waves (ancestral and Delta/Alpha).

METHODS

Study Design

This multicenter, retrospective study used clinical data from hospitalized children and adolescents (2–<18 years of age) who were SARS-CoV-2 positive, as previously described.[10] Participants for this analysis were included only from sites for which data on weight (kg), height (cm) or obesity status was available, ensuring alignment with the study's objective. Children with an incidental positive test for SARS-CoV-2 without disease were excluded.[10] Deidentified data were provided from hospitals in 8 countries: Australia, Brazil, Italy, Portugal, Switzerland, Thailand, the United Kingdom and the United States, covering the period from January 1, 2020, to March 31, 2022.

The timeframes for the dominant SARS-CoV-2 variants, ancestral strain (T1), pre-Omicron variants (Alpha and Delta; T2) and Omicron (T3), varied slightly across participating countries. These were based on national SARS-CoV-2 genome surveillance, with a variant of concern considered dominant if it constituted >70% of collected sequences, as previously described.[10] The primary outcome was the need for respiratory support, defined as oxygen therapy and/or ventilatory support.

Ethical approval was obtained at the coordinating center [the University of Queensland (UQ)], and local approvals were obtained at participating sites. In England and Wales, routine anonymized data from medical records were collected without the need for consent under regulation 3 (4) of the Health Service (Control of Patient Information) Regulations 2002. In Scotland, a waiver of need for consent was obtained from the Public Benefit and Privacy Panel. Ethical approval was given by the South Central-Oxford C Research Ethics Committee in England (reference 13/SC/0149) and the Scotland A Research Ethics Committee (reference 20/SS/0028).

Data Source

Data for this study were provided by 8 participating countries. Each site followed a standardized protocol [the ISARIC Clinical Characterization Protocol (https://isaric.org/)] for data collection and analysis to ensure consistency across the research population. A data transfer agreement between the UQ and each participating site facilitated the secure transfer of deidentified patient data. Specifically, the data collection process at the UK site was conducted in accordance with the data sharing agreement between UQ and the ISARIC Global Coordinating Centre at the University of Oxford. Further details on the data source and protocols have been described previously.[10]

Data Collection

Data were extracted from clinical records at participating centers across the 3 timeframes. The following data were collected for each patient: demographic: date of birth, sex, ethnicity/race, city/country and center; clinical: weight (kg), height (cm), preadmission medications, comorbidities (eg, obesity, asthma, cardiovascular disease, neurological disorders, diabetes and immunosuppression), duration of hospital stay, symptoms and signs at admission, medication and treatment during hospitalization, in-hospital mortality and COVID-19 vaccination status and outcome data: oxygen therapy and ventilatory support (composite outcome).

Obesity was assessed using clinical notations or body mass index (BMI), calculated by dividing weight (in kilograms) by the square of height (in meters). For children and adolescents, BMI percentiles were used, as defined by the Centers for Disease Control and Prevention. Obesity was categorized as a BMI at or above the 95th percentile for age and sex.[18] Preexisting chronic neurological diseases were clinically diagnosed and included epilepsy, cerebral palsy, neurogenetic disorders, neuromuscular disorders, pediatric multiple sclerosis and neurodevelopmental disorders such as attention-deficit/hyperactivity disorder.

Statistical Analysis

Descriptive statistics [n (%), median (interquartile range [IQR])] were used to summarize patient characteristics overall and by age category and obesity status. We compared the characteristics of patients with and without obesity during the 3 timeframes using the χ^2 test for categorical variables, the Fisher exact test for small sample sizes ($n < 5$) and the Student *t* test or the Mann-Whitney *U* test for continuous variables, as appropriate.

To assess the impact of obesity on disease severity across different pandemic waves, we performed multivariable regression analyses. We estimated the relative risk of the primary outcome (respiratory support) by pooling data for obese versus nonobese children during each time period, adjusting for key covariates. Covariates were selected based on biological plausibility and prior evidence linking them to disease severity. Adjusted models were constructed separately for each site, controlling for potential confounders such as age, sex, underlying comorbidities and vaccination status (if available). The effect of obesity on disease severity during the Omicron wave (T3) was compared with the earlier waves (T1 and T2), and the association was further stratified by country or regions. To evaluate whether differences in sample size across time periods contributed to the observed associations, we conducted a sensitivity analysis in which 1100 children were randomly selected from each timeframe (T1, T2 and T3), and the association between obesity and respiratory support was assessed. This number was chosen to reflect the maximum available sample size for T3 with complete data. To determine whether the observed trends were specific to obesity or extended to other comorbidities, we conducted additional analyses evaluating the association of neurological disease, cardiovascular disease and asthma with respiratory support. These conditions were selected due to their high prevalence in the dataset.

Meta-analysis was performed to obtain pooled estimates of the effect of obesity on severe COVID-19 outcomes across all sites. The random-effects models were used to summarize the data, with random-effects estimates presented in the text. All statistical analyses were performed using R software (version 4.4.2).

RESULTS

Characteristics of Patients Included in the Study

This study included 6176 pediatric patients 2 to <18 years of age. The median (IQR) age was 11 (6–14) years, 2989 (48.4%) patients were female and 3187 (51.6%) were male (Table, Supplemental Digital Content 1, https://links.lww.com/INF/G343). Obesity status was available for 5460 (88.4%) children (Table, Supplemental Digital Content 1, https://links.lww.com/INF/G343). Among these patients, the median age was 11.0 (IQR, 6.0–14.0) years, and 2622 (48.0%) were female. A total of 213 (3.9%) pediatric patients met the criteria for obesity across participating centers, and the average country-level prevalence of obesity was 14.26%. Obesity was associated with older age in hospitalized children, with a median age of 14.0 (IQR, 10.0–15.0) years, compared with 10.0 (IQR, 6.0–14.0) years for those without obesity. When stratified by timeframe, 84/1490 children (5.6%) with obesity were hospitalized during T1, 106/2869 (3.7%) during T2 and 23/1101 (2.1%) during T3 (Table, Supplemental Digital Content 2, https://links.lww.com/INF/G343).

Across the 3 timeframes, 1336 (22.0%) of patients required respiratory support, 1088 (18.1%) were admitted to ICU and 59 (1.0%) experienced in-hospital mortality (Table, Supplemental Digital Content 1, https://links.lww.com/INF/G343). ICU admission rates and the need for respiratory support were higher for patients with obesity compared with patients without obesity. Specifically, ICU admission occurred in 77 of 213 patients with obesity (36.5%) versus 946 of 5247 patients without obesity (18.5%; $P < 0.001$; Table, Supplemental Digital Content 2, https://links.lww.com/INF/G343). Similarly, respiratory support was required for 110 of 213 patients with obesity (51.9%) compared with 1118 of 5247 patients without obesity (21.5%; $P < 0.001$; Table, Supplemental Digital Content 2, https://links.lww.com/INF/G343). These differences were also reflected in case fatality rates, with 8 of 213 (3.8%) deaths among children with obesity and 42 of 5247 (0.8%) deaths in those without obesity ($P = 0.01$). However, after stratification by time period, ICU admissions, respiratory support and mortality rates declined during the Omicron wave (T3) compared with earlier waves. Furthermore, no differences in age, sex or ICU admission were observed between children with and without obesity in T3, in contrast to the differences seen in T1 and T2 (Table, Supplemental Digital Content 3, https://links.lww.com/INF/G343). Tables, Supplemental Digital Contents 4–10, https://links.lww.com/INF/G343, show the distribution of pediatric cases for each site in 3 time periods by age, sex on hospital admission, comorbidities, outcomes and COVID-19 vaccination status. There was considerable variability across different countries and sites, for example, findings for the prevalence of COVID-19–related comorbidities and risk factors on hospital admission (Tables, Supplemental Digital Contents 4–10, https://links.lww.com/INF/G343).

Obesity Was Not Significantly Associated With Increased Respiratory Support in Children During the Omicron Wave of the COVID-19 Pandemic

To assess the impact of obesity on COVID-19 severity across the different waves of the pandemic, respiratory support (oxygen therapy and/or ventilation) was assessed in hospitalized children with obesity relative to healthy weight children (while controlling for age, sex and other comorbidities; Fig. 1). Obesity was associated with increased respiratory support during both T1 [risk ratio (RR), 3.45 (95% CI: 2.02–5.88)] and T2 [RR, 3.24 (95% CI: 1.57–6.67)]; this association remained elevated in T3 (RR, 3.08), but the wide confidence interval (95% CI: 0.85–11.15) crossed the null (Fig. 1). Therefore, obesity was no longer a statistically significant risk factor for children during the Omicron wave of the pandemic.

It is important to note that the number of hospitalized children recorded in the Omicron wave was lower than that of T1 and T2. Accordingly, to ensure that these results were not simply reflective of sample size differences, 1100 children were randomly selected from each time period, and the association between obesity and respiratory support was assessed. Once again, obesity was associated with increased respiratory support during both T1 [RR, 3.44 (95% CI: 1.86–6.35)] and T2 [RR, 4.29 (95% CI: 1.82–10.14)], but this association was lost during T3 [RR, 3.08 (95% CI: 0.85–11.15); Fig. 2]. Together, these data suggest that the observed phenotype cannot be solely explained by the reduced numbers in T3.

Obesity Was Not Associated With Increased Need for Respiratory Support in Unvaccinated Children During the Omicron Wave of the COVID-19 Pandemic

To investigate whether the increased prevalence of vaccination during the Omicron wave influenced the trends observed herein, we examined respiratory support in obese and nonobese across the pandemic only in unvaccinated children. Importantly, the same trends were observed in this population as were previously observed in Figure 1. Namely, in unvaccinated children, obesity was associated with increased respiratory support during both T1 [RR, 3.45 (95% CI: 2.02–5.88)] and T2 [RR, 3.90 (95% CI: 2.37–6.41)], but this association was lost during T3 [RR, 3.46 (95% CI: 0.56–21.29); Fig. 3].

Associations Between Other Comorbidities and Respiratory Support in Children During the Omicron Wave of the COVID-19 Pandemic

Finally, we sought to ascertain if these trends were specific to obesity or were observed across other comorbidities in children. Accordingly, respiratory support was assessed in hospitalized

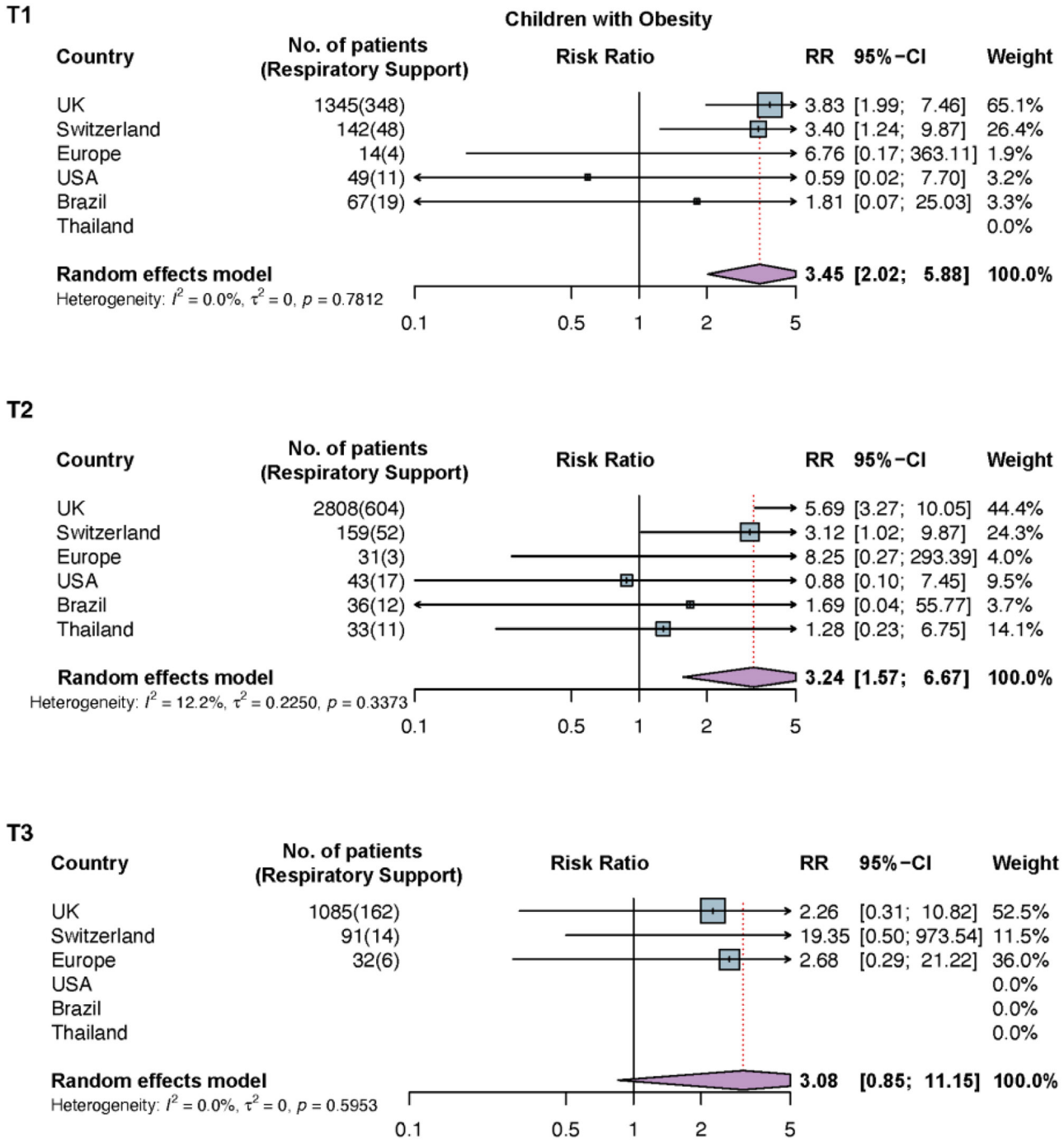

FIGURE 1. Obesity was not associated with increased need for respiratory support in children during the Omicron wave of the pandemic. Meta-analysis RRs for oxygen usage and/or ventilatory support among pediatric patients 2 to <18 years of age. Models were adjusted for age, sex (male/female), preexisting cardiovascular disease (yes/no), asthma (yes/no), neurologic disorder (yes/no), childhood cancer (yes/no), immunologic disease or immunosuppression (yes/no) and diabetes (yes/no) as appropriate.

children with neurological disease, cardiovascular disease and asthma relative to children without these conditions (while controlling for age, sex and other comorbidities; Figs. 4–6). These comorbidities were chosen as they were the most prevalent in our dataset. In contrast to our previous observations in obese children, children with neurologic disease had an increased disease risk of respiratory support at all 3 timepoints (Fig. 4). In contrast, cardiovascular disease was only associated with an increased risk of respiratory support at T2 (Fig. 5), while asthma was only associated with an increased risk of respiratory support at T3 (Fig. 6). Taken together, these data show that the pattern of obesity and the need for respiratory support over time are not seen with other comorbidities.

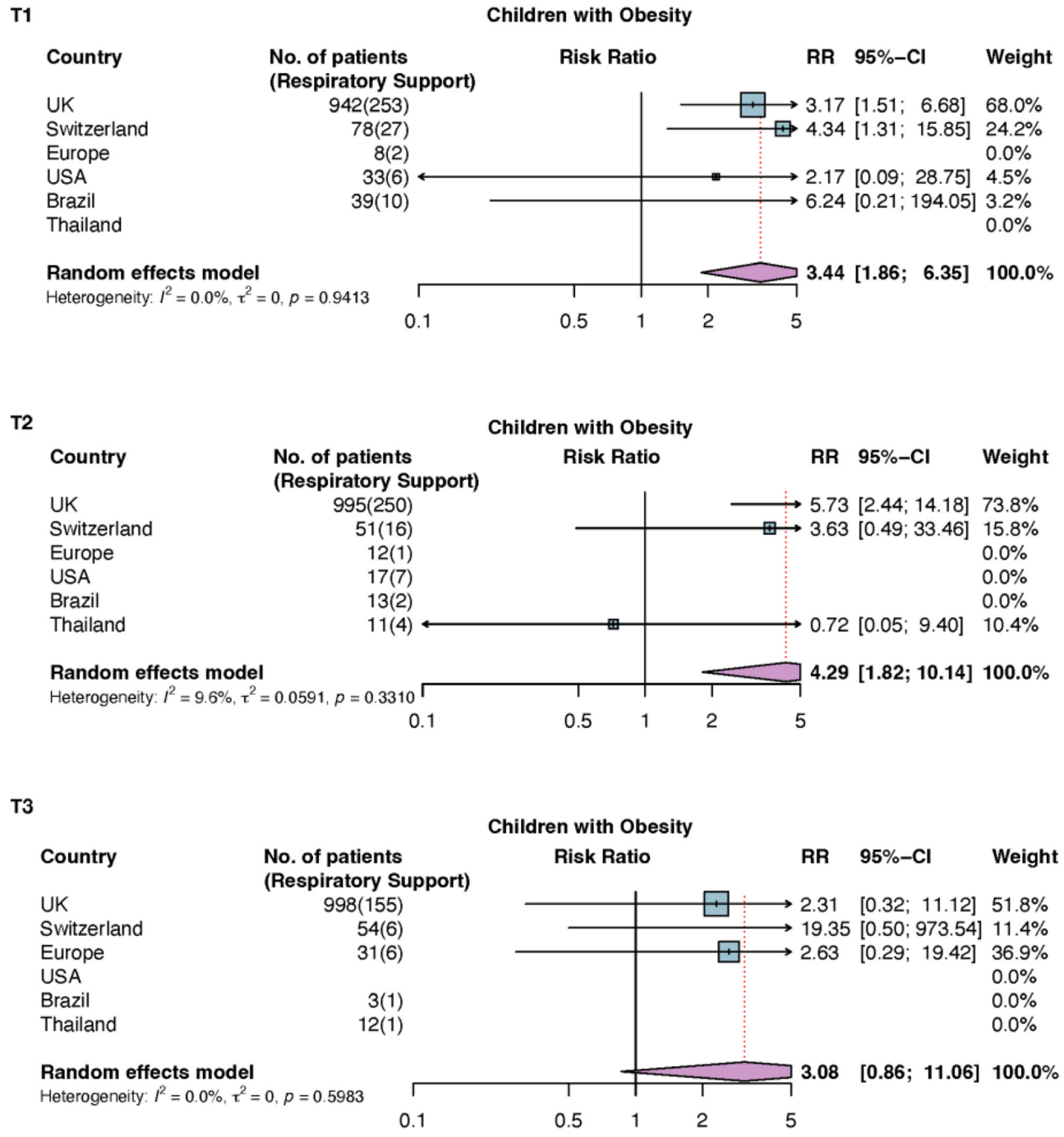

FIGURE 2. Obesity was not associated with increased need for respiratory support in children during the Omicron wave of the pandemic when using a randomly selected sample of 1100 hospitalized children per timeframe. Meta-analysis RRs for oxygen usage and/or ventilatory support among pediatric patients 2 to <18 years of age. Models were adjusted for age, sex (male/female), preexisting cardiovascular disease (yes/no), asthma (yes/no), neurological disorder (yes/no), childhood cancer (yes/no), immunological disease or immunosuppression (yes/no) and diabetes (yes/no) as appropriate.

DISCUSSION

Obesity is a known risk factor for severe COVID-19 in children.[5,6] However, these data are largely derived from the earlier stages of the pandemic where the ancestral, Beta or Alpha variants were dominant. Several single-site studies suggest that the association between obesity and severe COVID-19 in children was less apparent during the Omicron wave of the pandemic.[14,15] Consistent with these previous studies, the analysis performed herein noted a significant association between obesity and the need for respiratory support during the earlier stages of the pandemic but not during the Omicron wave.

These findings may be influenced by the fact that during the Omicron period, a greater proportion of children with

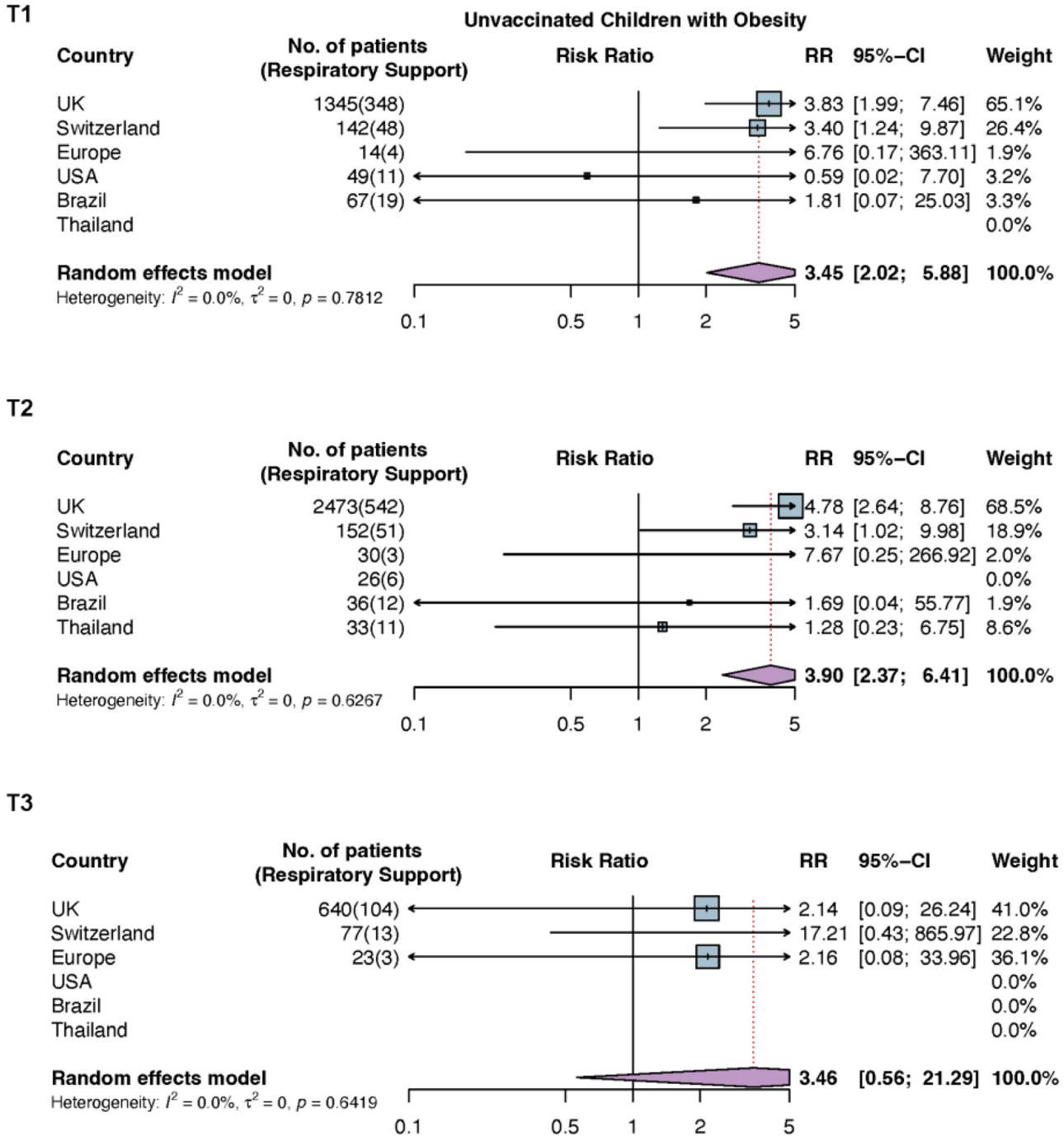

FIGURE 3. Obesity was not associated with increased need for respiratory support in unvaccinated children during the Omicron wave of the pandemic. Meta-analysis RRs for oxygen usage and/or ventilatory support among unvaccinated pediatric patients 2 to <18 years of age. Models were adjusted for age, sex (male/female), preexisting cardiovascular disease (yes/no), asthma (yes/no), neurological disorder (yes/no), childhood cancer (yes/no), immunological disease or immunosuppression (yes/no) and diabetes (yes/no) as appropriate.

obesity had the opportunity to receive SARS-CoV-2 vaccination, making them less vulnerable to severe disease.[14] However, our large dataset inclusive of children hospitalized in 8 countries does not support this. Namely, no association between obesity and respiratory support was observed during the Omicron wave when only unvaccinated children were included in the analysis. Moreover, should the associations in this wave of the pandemic be influenced by priority vaccination, then one would expect that children with other comorbidities would also no longer be at increased risk during the Omicron wave. In this study, preexisting neurological disease and asthma remained as risk factors for increased respiratory

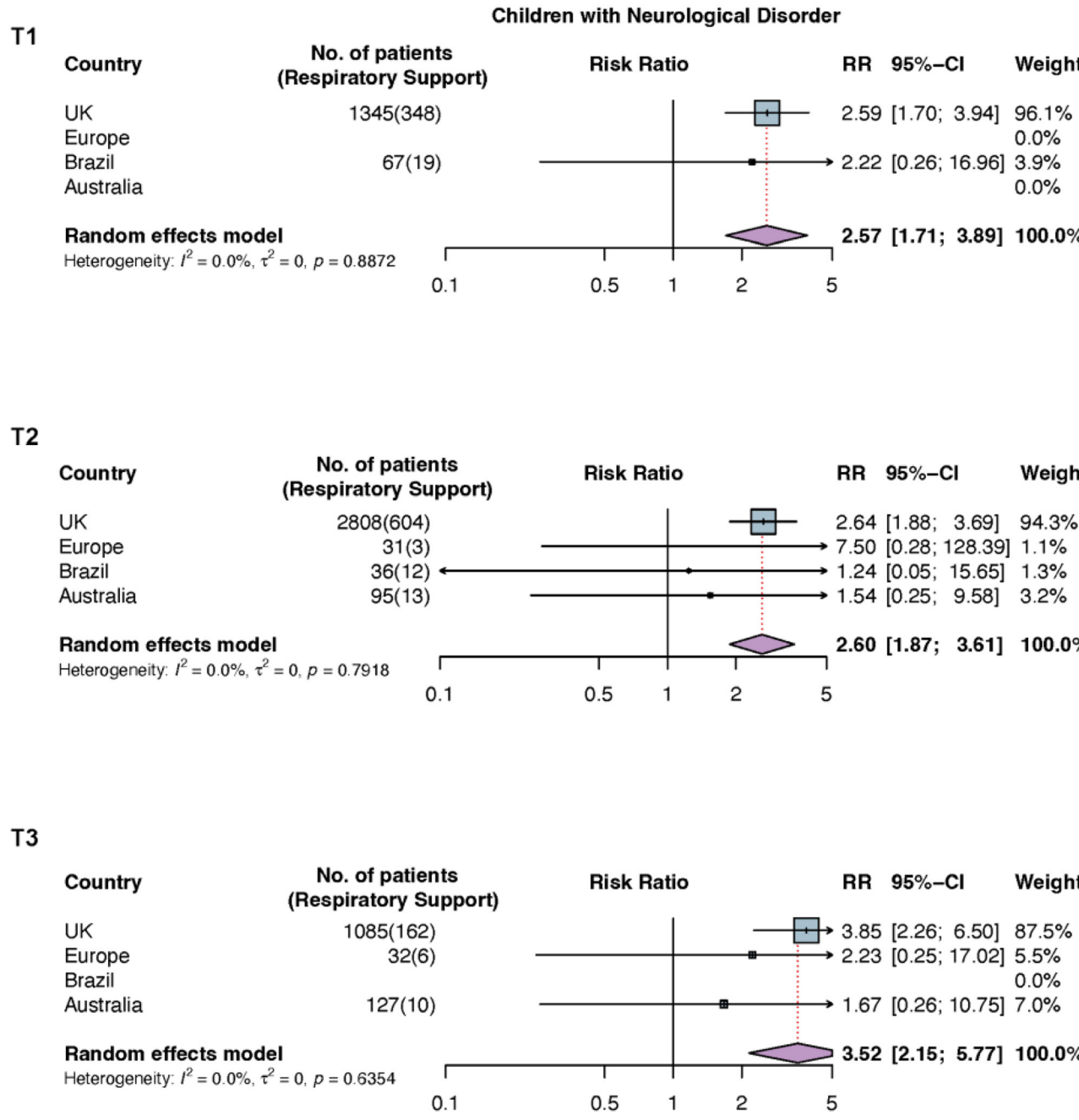

FIGURE 4. Neurological disease is associated with increased need for respiratory support in children during the Omicron wave of the pandemic. Meta-analysis RRs for oxygen usage and/or ventilatory support among unvaccinated pediatric patients 2 to <18 years of age. Models were adjusted for age, sex (male/female), preexisting cardiovascular disease (yes/no), asthma (yes/no), childhood cancer (yes/no), immunologic disease or immunosuppression (yes/no), diabetes (yes/no) and obesity (yes/no) as appropriate.

support during the Omicron wave. Indeed, these data are consistent with previous reports that children with neurological disease were still at increased risk of severe COVID-19 during the Omicron period[14] despite vaccination.

The question, therefore, remains why obesity was not a clear statistically significant risk factor for children during the Omicron wave of the pandemic. It is possible that these data reflect genetic changes in the Omicron variant that dramatically altered the pathogenesis of the virus. An alternative hypothesis is that these data reflect the protective effect of prior infection. Children with obesity may have had a higher risk of SARS-CoV-2 infection than other children, as has been suggested with other respiratory pathogens.[19,20] Thus, by the time the Omicron wave emerged, children with obesity had sufficient levels of prior immunity that the deleterious effect of obesity on COVID-19 outcomes was reduced. Despite being only a hypothesis, this theory is consistent with the

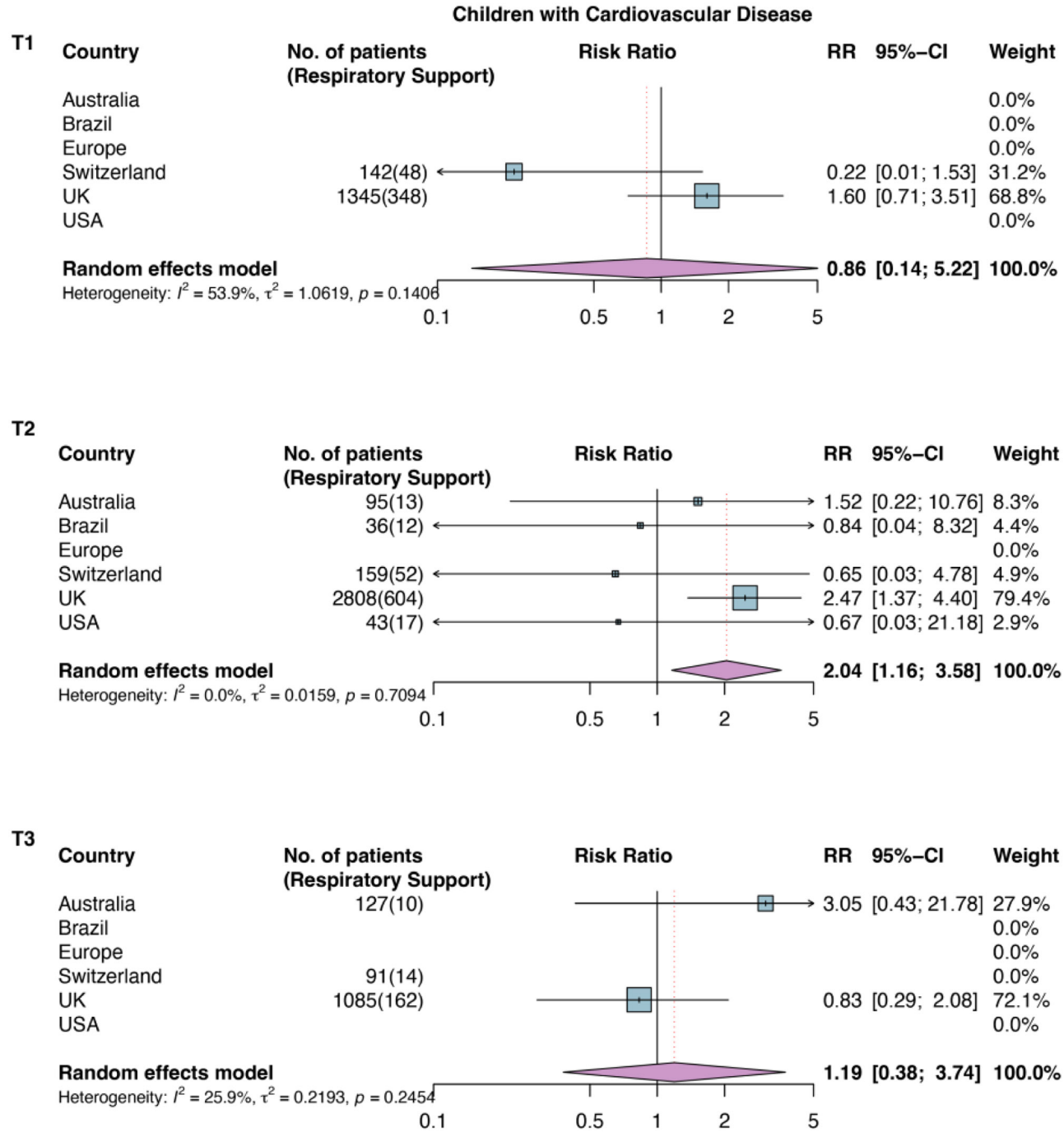

FIGURE 5. Cardiovascular disease is associated with increased need for respiratory support in children during T2. Meta-analysis RRs for oxygen usage and/or ventilatory support among unvaccinated pediatric patients 2 to <18 years of age. Models were adjusted for age, sex (male/female), neurologic disease (yes/no), asthma (yes/no), childhood cancer (yes/no), immunologic disease or immunosuppression (yes/no), diabetes (yes/no) and obesity (yes/no) as appropriate.

fact that obesity remained a risk factor for severe COVID-19 in children in China during the Omicron wave of the pandemic.[17] Due to strict quarantine and lockdown measures, there were limited SARS-CoV-2 infections in China prior to January 2023 when the country reopened borders (and was exposed to the Omicron variant). Accordingly, it is reasonable to assume that any increased risk that obesity provided for infection early in the pandemic would not have applied, and hence, children with obesity remained at a heightened risk of severe disease during the Omicron wave. Interestingly, while obesity was no longer significantly associated with respiratory support during the Omicron wave, both neurological disease and asthma were. Cardiovascular disease, in contrast, showed an association only during the pre-Omicron (T2) period. These results may reflect variant-specific effects, shifts in clinical

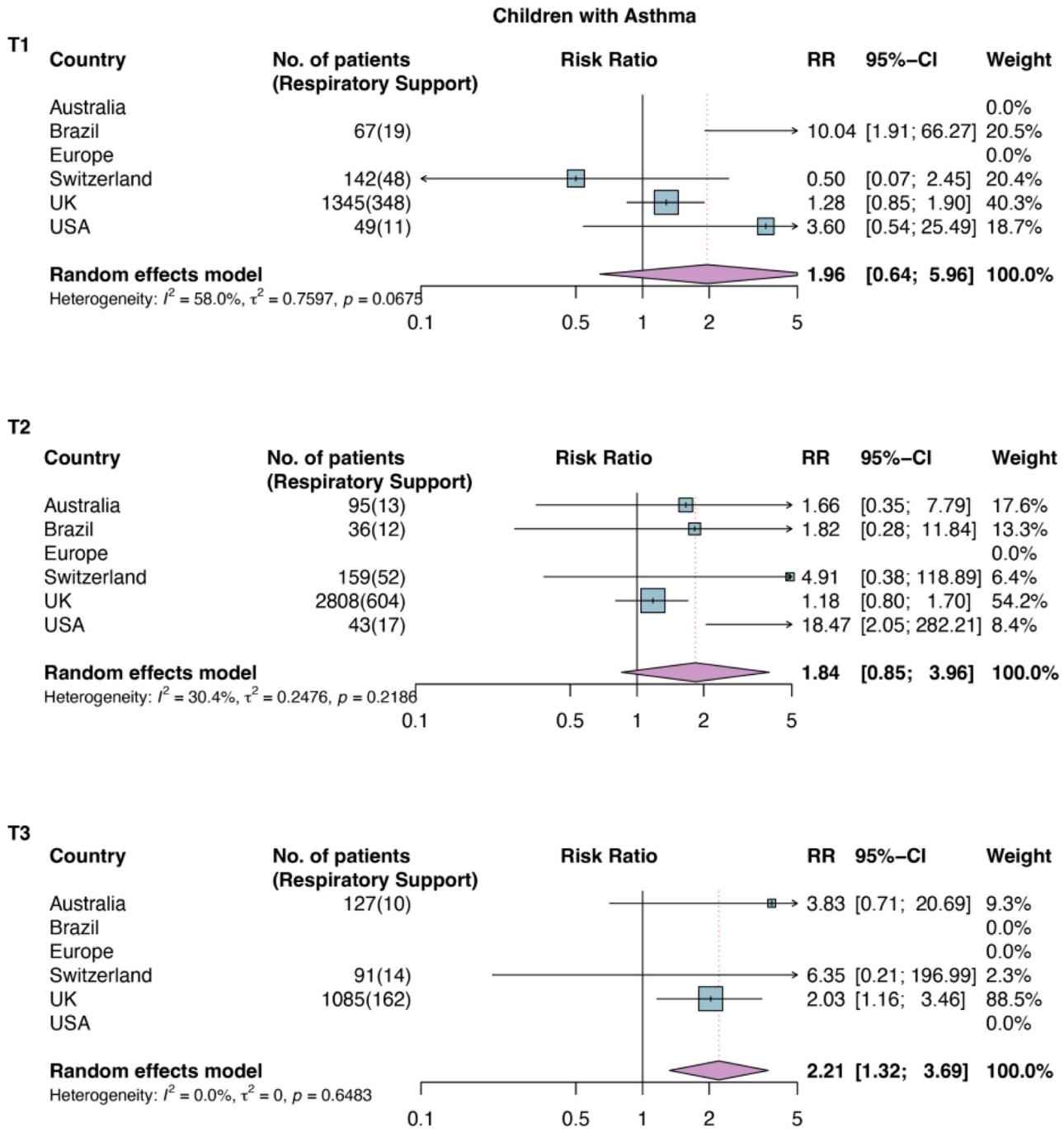

FIGURE 6. Asthma is associated with increased need for respiratory support in children during T3. Meta-analysis RRs for oxygen usage and/or ventilatory support among unvaccinated pediatric patients 2 to <18 years of age. Models were adjusted for age, sex (male/female), neurologic disease (yes/no), cardiovascular disease (yes/no), childhood cancer (yes/no), immunologic disease or immunosuppression (yes/no), diabetes (yes/no) and obesity (yes/no) as appropriate.

management practices or differential background immunity. Such changes highlight the dynamic nature of COVID-19 risk in children and reinforce the need to continuously reassess comorbidity-related vulnerability as the pandemic evolves.

This study was subject to several limitations. First, while this represents the first global analysis of obesity and disease severity across different pandemic waves, not all regions of the world were represented, and hence, regional disparities may have been overlooked. Similarly, while we hypothesize that these results were influenced by different levels of seropositivity in obese children with obesity during the Omicron wave, we were unable to specifically assess seropositivity. We also acknowledge that while it is important to stratify such studies according to different pediatric age groups (eg, pre-pubertal vs. post-pubertal), this was not possible in

this study due to a limited number. Indeed, BMI is often not routinely recorded, which dramatically reduced the number of children who could be analyzed compared with our prior publication.[10] It is also plausible that the lack of statistically significant association between obesity and respiratory support in T3 was related to lower case numbers at this timepoint. However, it is striking to note that when 1100 children were randomly selected from each timepoint for analysis, the same trend was observed. Moreover, an association with respiratory support was observed in T3 in children with neurological disease and asthma, despite the lower number for this timeframe. Although we performed these sensitivity analyses with matched sample sizes across time periods, we acknowledge that this approach does not fully account for potential differences in disease presentation, treatment practices or underlying risk across different variant waves. Despite these limitations, this study does suggest that risk factors for severe disease in children can change throughout the course of the pandemic. This emphasizes the need to constantly update clinical and resource prioritization guidelines around which populations are most at risk of severe disease as both the virus and population immunity evolve over the course of a pandemic.

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