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SYSTEMATIC REVIEW AND META-ANALYSIS

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Human Adenovirus 36 Infection Increased the Risk of Obesity

A Meta-Analysis Update

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Abstract: Human adenovirus 36 (HAdV-36), as the key pathogen, was supposed and discussed to be associated with obesity. We searched the references on the association between HAdV-36 infection and obesity with the different epidemiological methods, to explore the relationship with a larger sample size by meta-analysis and compare the differences of epidemiological methods and population subsets by the subgroup analyses.

We conducted literature search on the association between HAdV-36 infections and obesity in English or Chinese published up to July 1, 2015. The primary outcome was the HAdV-36 infection rate in the obese and lean groups; the secondary outcomes were the BMI level and BMI z-score in the HAdV-36 positive and negative groups. The pooled odds ratio (OR) was calculated for the primary outcome; the standardized mean differences (SMDs) were calculated for the secondary and third outcomes. Prediction interval (PI) was graphically presented in the forest plot of the random effect meta-analyses. Metaregression analysis and subgroup analysis were performed.

Finally 24 references with 10,191 study subjects were included in the meta-analysis. The obesity subjects were more likely to be infected with HAdV-36 compared to the lean controls (OR = 2.00; 95%CI: 1.46, 2.74; PI: 0.59, 6.76; $P < 0.001$) with a high heterogeneity ($I^2 = 80.1\%$; $P < 0.001$) estimated by the random effect model. Subgroup analysis demonstrated that the pooled OR of HAdV-36 infection for obesity were 1.77 (95%CI: 1.19, 2.63; PI: 0.44, 7.03; $P = 0.005$) and 2.26 (95%CI: 1.67, 3.07; PI: 1.45, 3.54; $P < 0.001$) in the adults and children, respectively. Compared to the HAdV-36 negative subjects, the SMD of BMI was 0.28 (95% CI: 0.08, 0.47; PI: −0.53, 1.08; $P = 0.006$) in the HAdV-36 positive subjects with a high heterogeneity ($I^2 = 86.5\%$; $P < 0.001$). The BMI z-score in the children with HAdV-36 infection was higher than those without HAdV-36 infection (SMD = 0.19; 95%CI: −0.31, 0.70; PI: −2.10, 2.49), which had no significantly statistical difference ($P = 0.453$).

HAdV-36 infection increased the risk of obesity. HAdV-36 also increased the risk of weight gain in adults, which was not observed in children.

(*Medicine* 94(51):e2357)

Abbreviations: BMI = body mass index, CI = confidence interval, ELISA = Enzyme linked immunosorbent assay, HAdV = human adenovirus, OR = odds ratio, PI = prediction interval, SMD = standardized mean differences, SNT = serum neutralization test.

INTRODUCTION

Obesity has become a public health problem with a global epidemic, leading to adverse metabolic effects on blood pressure, cholesterol, triglycerides, and so on,[1] and causing severe burden of diseases. According to the data from World Health Organization, 13% of adults aged ≥18 years old were obese in the year of 2014 (http://www.who.int/gho/ncd/risk_factors/overweight_text/en/). It is estimated that nearly more than half a billion adults worldwide are obese. Although the etiology of obesity is multifactorial, behavior that leads to overeating and underactivity is conventionally thought to be a major contributory factor, and certain infections are also under consideration.

Human adenovirus 36 (HAdV-36), as the key pathogen, was supposed and discussed to be associated with obesity. Previous study found that the adipogenic action of HAdV-36 was a direct effect on adipose tissue[2] and HAdV-36 upregulated the proliferation, adipogenic commitment, and differentiation of adult adipose tissue-derived stem cells and other adipogenic progenitors, leading to an increase in the number of fat cells in *vivo*/*vitro* and in the animal models.[1,3–5] Moreover, HAdV-36 infection seems to accumulate the triglycerides and reduce leptin expression and secretion,[6] induce the macrophages infiltration into adipocytes,[7] change norepinephrine levels in the paraventricular nucleus, and decrease corticosterone secretion, which plays a major role in fat metabolism,[5] thus increase the appetite and further increase the fat tissue. However, the results on the association between obesity and HAdV-36 were controversial in the population studies.[8–31]

Editor: Joshua Barzilay.
Received: July 10, 2015; revised and accepted: December 2, 2015.
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Supplemental Digital Content is available for this article.
The authors have no conflicts of interest to disclose.
M-YX and BC contributed equally to this study.
Funding: the study was supported by the Youth Innovation Funding (2014QN09) from Aerospace Center Hospital, the Youth Talent Support Program by School of Public Health, Peking University and the State Key Laboratory of Pathogen and Biosecurity (Academy of Military Medical Science, SKLPBS1442). The funding agents had no role in the design and conduct of the study; collection, management, analysis, interpretation of the data; preparation, review, or approval of the manuscript.
Author's contribution: Q-BL conceived and designed the experiments; M-YX, BC, and D-FW searched the references and collected data; M-YX, BC, and D-FW performed the statistical analysis; M-YX, Q-BL, and BC drafted the manuscript; JY, J-HG, K-LC, and MS contributed to the discussion. All authors have read and approved the final version of this article.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000002357

Among humans, 2 meta-analyses of cross-sectional data have been performed, showing that the infected individuals have a higher risk of obesity than uninfected individuals.[2] Metaregression also indicated that the association was stronger in children.[32] The association between HAdV-36 infection and obesity has become an advanced research hotspot. Several case-control and cohort studies were conducted to confirm the association continually.[8,14–16,19–21,24,25,29,30] As the 2 meta-analyses studies included the early references by the end of the year of 2012, it is necessary to perform a larger and newer meta-analysis to update the association between HAdV-36 infection and obesity.

Therefore, we searched the references on the association between HAdV-36 infection and obesity with the different epidemiological methods, to explore the relationship with a larger sample size by meta-analysis and to compare the differences of population subsets by the subgroup analysis.

METHOD

Ethical Review

Meta-analysis does not involve ethical review.

Search Strategy

We conducted literature search on the association between HAdV-36 infections and obesity in English or Chinese published up to July 1, 2015. PubMed, EMBASE, the Cochrane Databases, Chinese National Knowledge Infrastructure, China Biology Medical and Wanfang databases were searched by 2 researchers independently. The following terms were used: adenovirus 36, Ad36 in combination with obesity or obese. We evaluated potentially relevant publications by checking their titles and abstracts and then obtained the most relevant publications for a detailed examination. We also searched the reference lists of the retrieved articles and reviews for additional articles.

Selection Criteria

We performed initial screening of study titles or abstracts, whereas the second screening was based on the full-text review. The following criteria were used for the selection of reports for the meta-analysis: (1) the full text of report was published in English or Chinese; (2) the study was designed as a cohort study, case-control study, or cross-sectional study; (3) there were sufficient published data for estimating the mean and standard deviation (SD) of body mass index (BMI) or BMI z-score in the HAdV-36 positive and negative groups, and/or HAdV-36 frequencies of cases in the obese group and nonobese group.

Data Extraction

Data were extracted from the included studies using a standardized data extraction form by 2 reviewers independently, and any discrepancy was discussed and resolved by consensus with a third reviewer. The following information was obtained from each study: the first author, the publication year, country, study method, detection method of HAdV-36, population subset, sample size, mean and standard deviation (SD) of BMI or z-score in HAdV-36 positive and negative groups, HAdV-36 frequencies of cases with obesity and without obesity as well as the control group. The authors of the studies were contacted if necessary to obtain further details. The Newcastle–Ottawa Quality Assessment Scale was used to assess the quality of the studies included in the meta-analysis and performed by 2 reviewers with a third reviewer consulted in the case of discrepancy.

Outcome Measures

The primary outcome was the HAdV-36 infection rate in the obese and control groups; the secondary outcome was the BMI level and BMI z-score in the HAdV-36 positive and negative groups.

Statistical Analysis

Data were abstracted from all the studies that met our inclusion and exclusion criteria. The pooled odds ratio (OR) and 95% confidence interval (CI) were calculated for the primary outcome; the standardized mean difference (SMD) and 95%CI were calculated for the secondary outcomes. I^2 statistics were used to evaluate inter-study heterogeneity: $I^2 > 50\%$ indicates a large heterogeneity. Q-statistics was performed to further examine the heterogeneity, and $P < 0.10$ was considered significantly heterogeneous. If the data were homogeneous, the fixed effect model was applied to evaluate the HAdV-36 status of obesity. Otherwise, the random effect model was adopted. Prediction interval (PI) was graphically presented in the forest plot of the random effect meta-analyses.[33,34] Sensitivity analysis was performed to strengthen the result of the meta-analysis. Metaregression analysis and subgroup analysis were performed for the publication year (before 2011 and after 2011), geographic area (America, Europe, and Asia), detection method (serum neutralization test and ELISA), population subset (adult and children), study type (cross-sectional, case-control, and cohort study), and sample size ($\geq$500 and $<$500). The publication bias was tested using the funnel plot with Begg's test and Egger's test. $P < 0.05$ of variable was considered statistically significant. The meta-analysis data were analyzed by Stata 12.0 (Stata Corp LP, College Station, TX).

RESULTS

We identified 366 references focusing on the relationship between HAdV-36 and obesity with 90 duplicated references. After deleting the references which were not according to the inclusive criteria (n = 342), finally 24 references were included in the meta-analysis. The detailed flow diagram was shown in Figure 1.

Basic Information of the Included Studies

Table 1 showed the basic information of the included studies in the meta-analysis. Totally 10,191 study subjects were recruited in the study including 3383 (33.2%) children and 6808 (66.8%) adults. Among all studies, 66.7% (16/24) were published in the past 4 years (2012–2015). Different epidemiological methods were used in the studies, including 9 cross-sectional studies, 9 case-control studies, and 6 cohort studies. All studies received a score of $\geq$6, indicating good qualities.

Meta-Analysis on the Association Between HAdV-36 and Obesity

Altogether 17 studies were included to analyze the association between HAdV-36 and obesity. There were 3988 obesity cases and 2991 lean controls. The forest plot for the association between HAdV-36 and obesity was shown in Figure 2. The

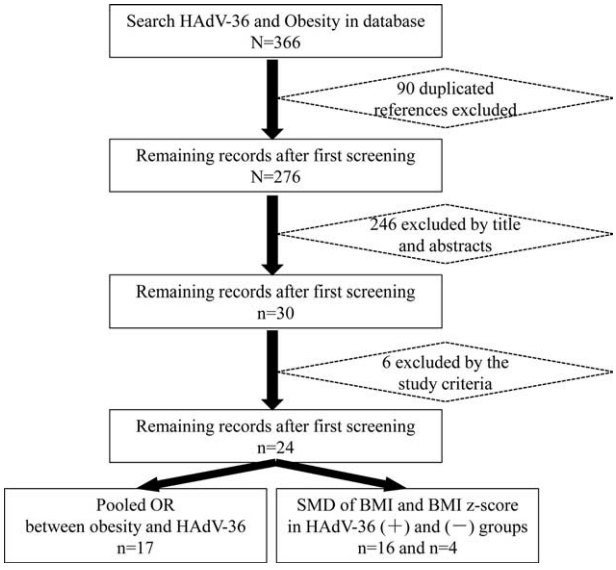

FIGURE 1. The flow diagram of the study selection for meta-analysis.

obesity subjects were more likely to be infected with HAdV-36 compared to the lean controls (OR = 2.00; 95%CI: 1.46, 2.74; PI: 0.59, 6.76; $P < 0.001$) with a high heterogeneity ($I^2 = 80.1\%$; $P < 0.001$) estimated by the random effect model (Fig. 2). Subgroup analyses demonstrated that the pooled ORs of HAdV-36 infection for obesity were 1.77 (95%CI: 1.19, 2.63; PI: 0.44, 7.03; $P = 0.005$) and 2.26 (95%CI: 1.67, 3.07; PI: 1.45, 3.54; $P < 0.001$) in the adults and children, respectively (Supplemental Figure 1A, http://links.lww.com/MD/A578). A high heterogeneity was detected in the adults ($I^2 = 84.8\%$; $P < 0.001$), but not in the children ($I^2 = 1.0\%$; $P = 0.410$). We did not observe the obvious decrease of the heterogeneity (Supplemental Figure 1B-F, http://links.lww.com/MD/A578).

A metaregression was further performed to explore the possible sources of the heterogeneity. We put the 6 variables in the subgroup analysis into the metaregression. As shown in Supplemental Table 1, http://links.lww.com/MD/A578, none of the 6 variables had any definite influence on the heterogeneity. The sensitivity analysis demonstrated stability and reliability of the meta-analysis results through consistency results (Supplemental Figure 2, http://links.lww.com/MD/A578). The plots shape, as well as the P value from Begg's regression and Egger's test ($P < 0.001$) showed there was publication bias (Supplemental Figure 3, http://links.lww.com/MD/A578).

Meta-Analysis on BMI Levels in the HAdV-36 Positive and Negative Groups

We analyzed the BMI levels in the HAdV-36 positive and negative groups using 16 studies. There were 5356 subjects, including 1390 HAdV-36 positive subjects and 3866 HAdV-36

TABLE 1. The Characteristics of the Included Studies in the Meta-Analysis

No.	First Author	Published Year	Country	Population	Study Method	Assay Method	Sample Size
1	Atkinson et al	2005	USA	Adult	Cohort	SNT	502
2	Wang et al	2008	China	Adults	Case-Control	SNT	300
3	Trovato et al	2009	Italy	Adults	Case-Control	SNT	203
4	Goossens et al	2009	Belgium	Adults	Cohort	SNT	509
5	Gabbert et al	2010	USA	Children	Cross-sectional	SNT	124
6	Broderick et al	2010	USA	Adults	Case-Control	ELISA	293
7	Atkinson et al	2010	Korea	Children	Cross-sectional	SNT	84
8	Na et al	2010	Korea	Children	Case-Control	SNT	318
9	Tosh et al	2012	USA	Adolescents	Cross-sectional	ELISA	13
10	Trovato et al	2012	Italy	Adults	Cohort	SNT	62
11	Na et al	2012	Korea	Adults	Case-Control	SNT	540
12	Almgren et al	2012	Sweden	Children	Case-Control	ELISA	387
12	Almgren et al	2012	Sweden	Adults	Case-Control	ELISA	1519
13	Laing et al	2013	USA	Adolescent	Cross-sectional	ELISA	115
14	Parra-Rojas et al	2013	Mexican	Children	Cross-sectional	ELISA	157
15	Wal et al	2013	USA	Adults	Cross-sectional	SNT	71
16	Lin et al	2013	USA	Adults	Cohort	SNT	1400
17	Voss et al	2014	USA	Adults	Cohort	ELISA	500
18	Cakmakliogullari et al	2014	Turkey	Children	Case-Control	SNT	120
19	Berger et al	2014	USA	Children	Cross-sectional	ELISA	291
20	Aldhoon-Hainerova et al	2014	Czech	Adolescents	Cohort	ELISA	1179
21	Chang et al	2015	China	Adults	Case-Control	SNT	232
22	Sabin, et al	2015	Finland	Children	Cross-sectional	ELISA	449
22	Sabin et al	2015	Finland	Adults	Cross-sectional	ELISA	449
23	Ergin et al	2015	Turkey	Adults	Case-control	SNT	98
24	Karamese et al	2015	Turkey	Children	Cross-sectional	ELISA	146
24	Karamese et al	2015	Turkey	Adults	Cross-sectional	ELISA	130

ELISA = Enzyme linked immunosorbent assay, SNT = serum neutralization test.

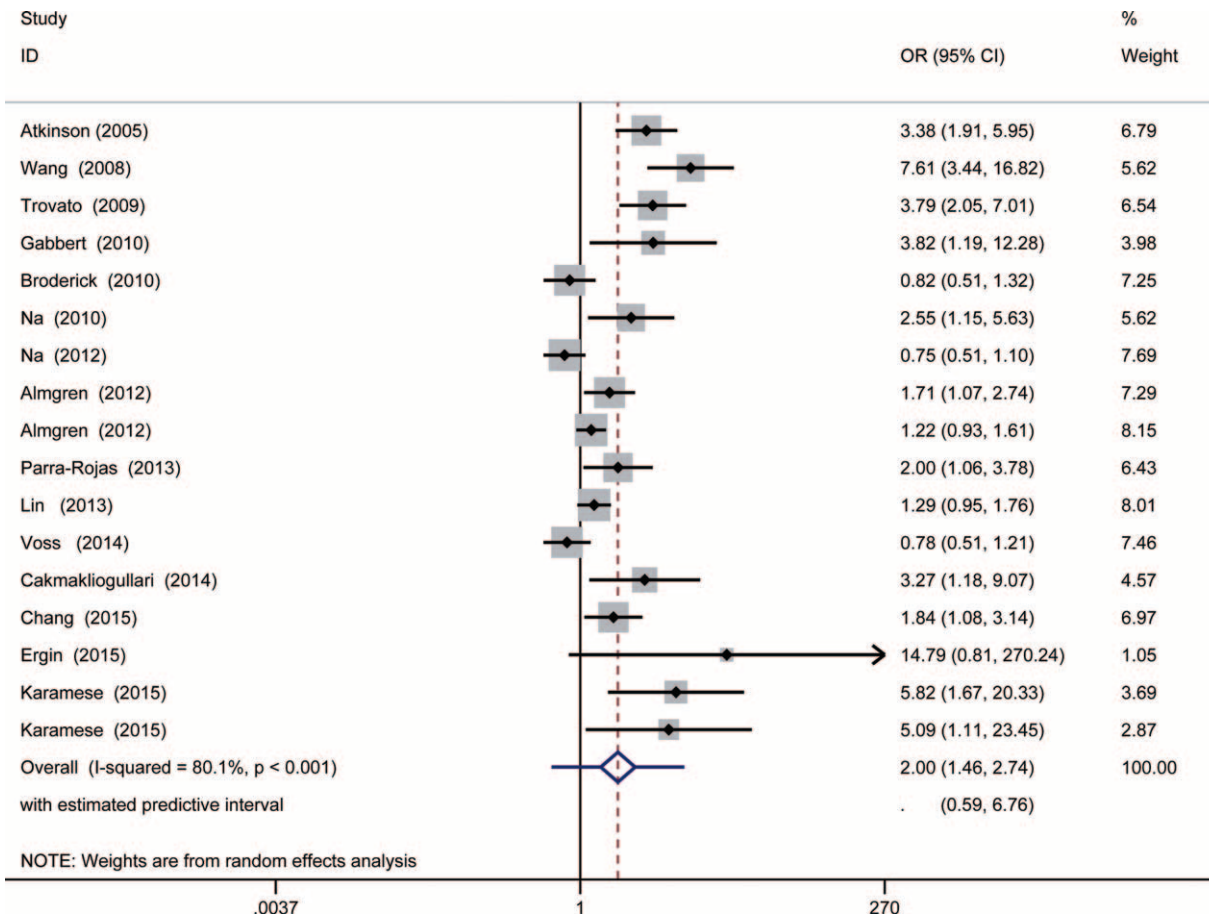

FIGURE 2. Forest plot of the studies comparing the association between HAdV-36 infection and obesity by meta-analysis with the random effects model. The pooled OR and 95%CI were calculated. CI = confidence interval, OR = odds ratio.

negative subjects. Compared to the HAdV-36 negative subjects, the SMD of BMI was 0.28 (95% CI: 0.08, 0.47; PI: −0.53, 1.08; $P = 0.006$) in the HAdV-36 positive subjects with a high heterogeneity ($I^2 = 86.5\%$; $P < 0.001$) presented in Figure 3. We did not find the source of heterogeneity by the metaregression (Supplemental Table 2, http://links.lww.com/MD/A578). In other words, HAdV-36 infection may be associated with an increasing risk of weight gain. This trend was also observed in the adults (SMD = 0.46; 95%CI: 0.08, 0.83; PI: −0.83, 1.74; $P = 0.016$), while not in the children (SMD = 0.14; 95%CI: −0.07, 0.35; PI: −0.54, 0.82; $P = 0.194$) (Supplemental Figure 4, http://links.lww.com/MD/A578). The sensitivity analysis revealed stability and reliability for the results (Supplemental Figure 5, http://links.lww.com/MD/A578). The plots shape, as well as the P value from Begg's regression and Egger's test ($P = 0.256$ and $P = 0.223$), did not show evidence of publication bias (Supplemental Figure 6, http://links.lww.com/MD/A578).

Meta-Analysis on BMI z-Score Levels in the HAdV-36 Positive and Negative Groups

Four studies were used to estimate the difference of BMI z-score in the children with/without the HAdV-36 infection. There were 570 children, including 182 ones with HAdV-36 infection and 388 ones without HAdV-36 infection. The BMI z-score in the children with HAdV-36 infection was higher than that without HAdV-36 infection (SMD = 0.19; 95%CI: −0.31, 0.70; PI: −2.10, 2.49), which was not significantly statistically different ($P = 0.453$) (Fig. 4).

DISCUSSION

This meta-analysis further confirmed the association between HAdV-36 infection and obesity with more studies than previous meta-analysis studies.[2,32] The HAdV-36 infection may contribute to the obesity development or the weight gain. We emphatically analyzed this relationship in the children population. Interestingly, the study showed HAdV-36 was associated with the status of obesity, but not with the weight gain through the analysis on the BMI or BMI z-score.

Numerous evidences have demonstrated the causative and correlative role of HAdV-36 in the obesity. The adipogenic effect of adenoviruses was first reported in the chicken by Dhurandhar et al,[35] and then HAdV-36, HAdV-5, and HAdV-37 were also found to increase adiposity in animals and human beings.[14,36] Subsequently many studies focused on the relationship between HAdV-36 and obesity. However, the findings were inconsistent with each other.[2,7–9,13–26,28–30,32,36] Due to geographical and age-group differences, it was difficult to compare the results. Especially, inadequate sample size and unrepresentative subjects may result in an untrusted conclusion. Above all, we performed the meta-analysis to summary the

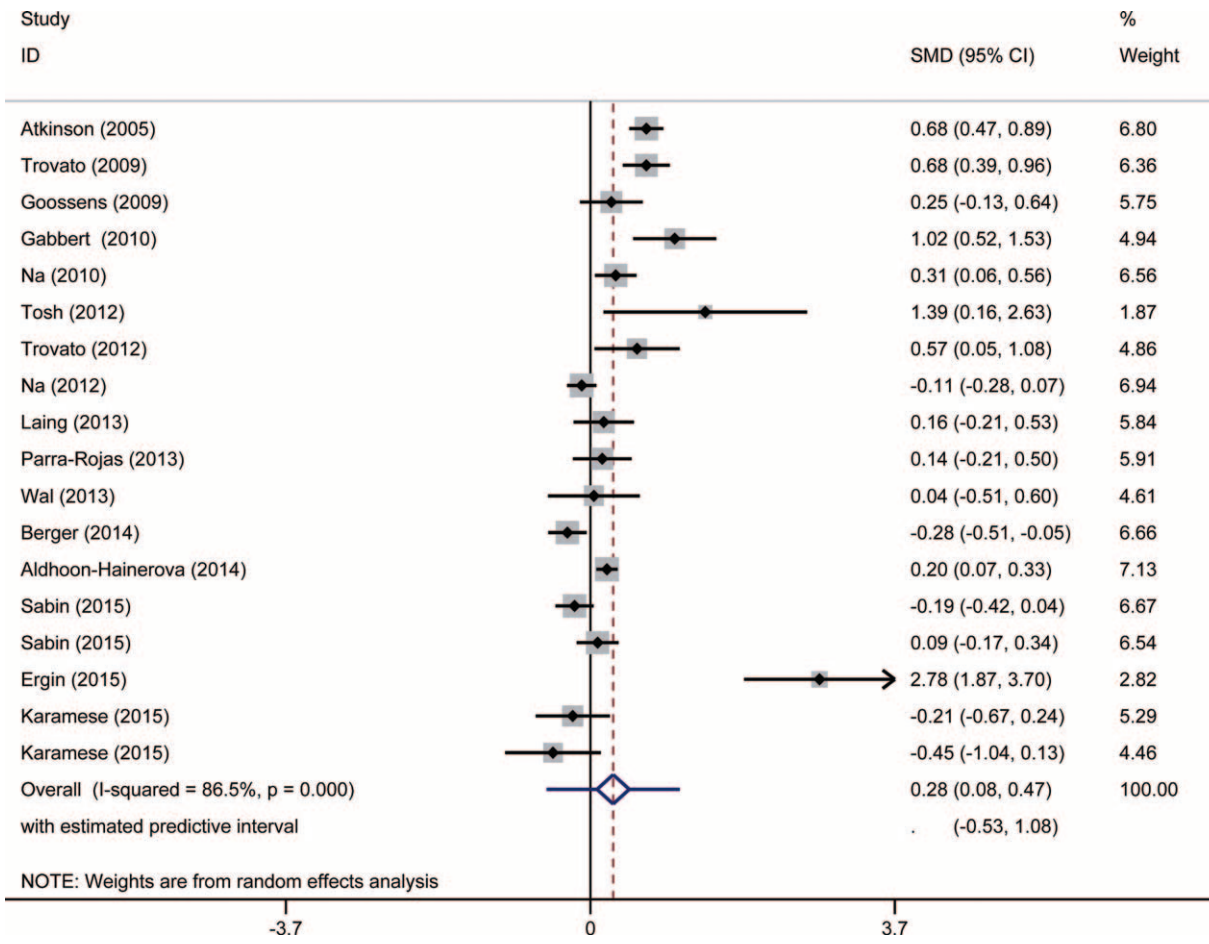

FIGURE 3. Forest plot of the studies comparing the BMI levels in the study subjects with/without HAdV-36 infection by meta-analysis with the random effects model. The SMD and 95%CI were calculated. BMI = body mass index, CI = confidence interval, SMD = standardized mean difference.

various results, which suggested that HAdV-36 infection might be associated with the human obesity.

By far, 3 meta-analyses were conducted on the association between HAdV-36 and obesity. Compared to the nonobese subjects, the pooled OR of HAdV-36 infection in the obese subjects was 1.90 (95%CI: 1.01, 3.56) by Yamada et al[2] and 1.60 (95%CI: 1.14, 2.25) by Shang et al.[32] In our study, we found the pooled OR was higher than both previous studies, as well as the pooled OR in the children. This result was more precise because of a large sample size. Overall, the results in the 3 meta-analyses were comparable to validate the relationship.

Waye et al thought that adenovirus might give rise to obesity via infliction of oxidative stress and strategies of reducing oxidative stress might also be useful for combating adenovirus-associated obesity and other related disabilities.[37] Many reports suggested that other microbes could contribute to human obesity. The interactions of HAdV-36 and other microbes should be considered on the effect of obesity risk. Dhurandhar et al has mentioned that it is important to determine whether the microbes exaggerate the effects of the abundance of food and decreased activity of recent years resulting in a widespread increase of obesity worldwide. Observed from our study, the effect of HAdV-36 on the weight gain was needed to be further confirmed as the wide PI across 1, although it showed to be significant evaluated by 95% CI.

We did not find the significant associations of HAdV-36 with the BMI or BMI z-score. The prevalence of obesity according to BMI in children has been leveling off.[38] So only using BMI to estimate obesity is not proper and has a bias on the association between HAdV-36 and obesity. For children, BMI-for-age percentile distribution (BMI z-score) was recommended. However, due to the limited studies with the data of BMI z-score, the result was needed to be confirmed in future.

There were some limitations in the meta-analysis. Owing to the failing to obtain the literature except for English and Chinese, the literatures were not comprehensive. We excluded some references included in our study from which we did not get the original value of the related data, leading to the reduced number of the studies for analysis.

However, this meta-analysis demonstrated that HAdV-36 infection increased the risk of obesity. HAdV-36 also increased the risk of weight gain in adults, which was not observed in children.

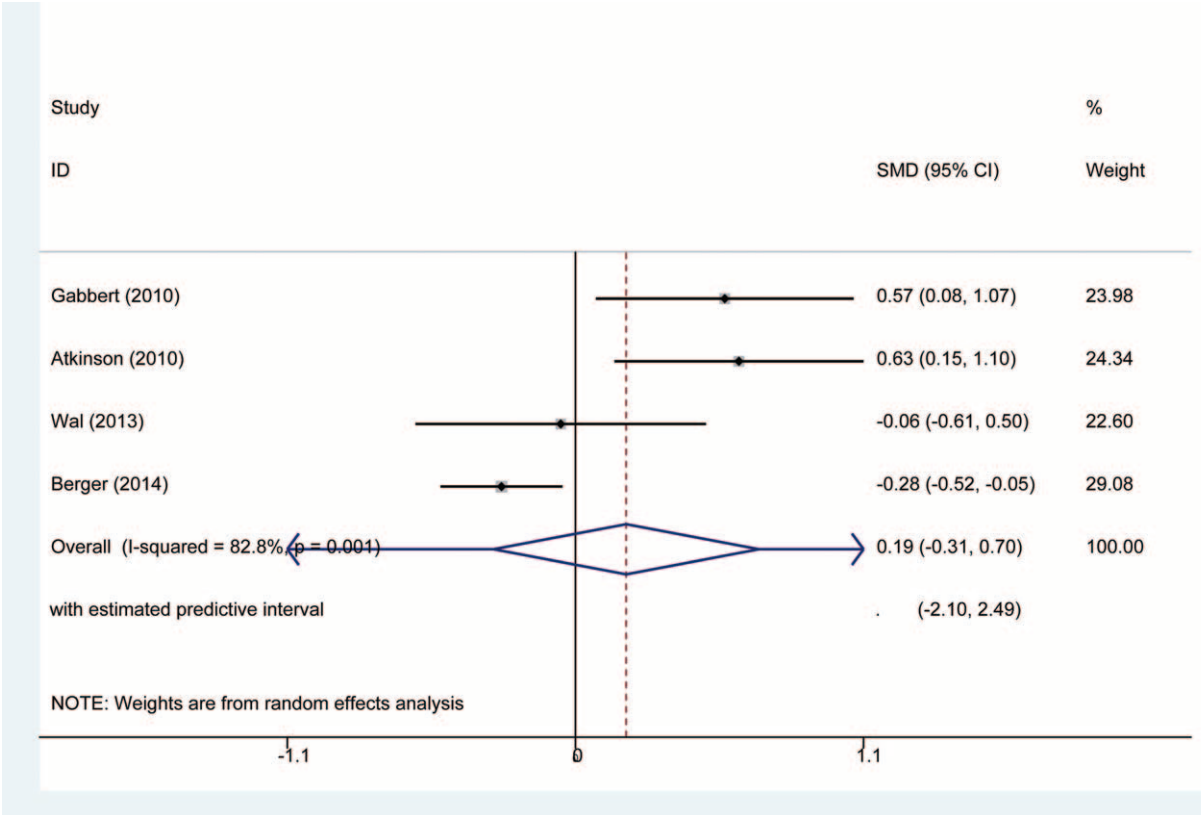

FIGURE 4. Forest plot of the studies comparing the BMI z-score levels in the study subjects with/without HAdV-36 infection and by meta-analysis with the random effects model. The SMD and 95%CI were calculated. CI = confidence interval, SMD = standardized mean difference.

ACKNOWLEDGMENTS

Thanks to the researchers of the original studies included in our meta-analysis. The authors alone are responsible for the content and writing of the paper. We thank team members for their supports and contributions to this study.

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