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Different body mass index grade on the risk of developing glioma: a meta-analysis

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Abstract

Background: Previous studies reported conflicting results about the risk of developing glioma and different body mass index. So we decided to execute a meta-analysis to solve the dispute.

Methods: Comprehensive literature retrieval was carried in PubMed, MEDLINE, and EMBASE up to September 15, 2014. Hand literature information retrieval was not carried. Six studies were fit for this meta-analysis. Pooled hazard ratio (HR) and 95 % confidence interval (CI) of different body mass index grade were performed by fixed/random-effects models, except for normal weight which was referent.

Results: Data of 3726 cases were included. Compared with normal weight (20 $kg.m^{-2}$ < body mass index (BMI) ≤ 24.9 $kg.m^{-2}$), the underweight (BMI ≤ 20 $kg.m^{-2}$) might have lower incidence on the risk of developing glioma (HR = 1.08, 95 % CI ranged 0.74 to 1.58, $P = 0.678$). While the overweight (25 $kg.m^{-2}$ < BMI ≤ 29.9 $kg.m^{-2}$) and obesity (BMI ≥ 30 $kg.m^{-2}$) were performed as a risk factor of developing glioma. The pooled HR of overweight group was 1.12 (95 % CI ranged 1.02 to 1.22, $P = 0.013$); the pooled HR of obesity was 1.14 (95 % CI ranged 1.02 to 1.27, $P = 0.017$). Sensitivity analysis approved that our results were stable. There was no publication bias of these studies.

Conclusions: Underweight could decrease the risk of developing glioma. Excess BMI was considered as a risk factor to develop glioma.

Keywords: Body mass index, Overweight, Obesity, Glioma, Meta-analysis

Background

According to the diagnostic criteria of Tumours of the Central Nervous System of 2007 version, gliomas are divided into grade I~IV; grade III and IV tumors are considered malignant gliomas [1], which account for 30 % primary CNS tumors [2]. Gliomas are considered as diffuse infiltration of white matter tracts [3]. Compared with common magnetic resonance (MR) sequences which is insensitivity for detecting the boundary of tumor [3, 4], MRS or/and DTI is/are effective methods to distinguish the infiltration area of glioma [5]. There is a great progress in surgical techniques and chemo-radiotherapy, but the median survival time of patients is 12–15 months [6]. The patients' 5-year survival rate of WHO grade III glioma is 18 % and it is <5 % for WHO grade IV tumors [7].

Body mass index (BMI ($kg.m^{-2}$)) was calculated as weight (kg) divided by height (cm) squared and categorized as underweight when BMI ≤ 20 $kg.m^{-2}$, normal weight when 20 $kg.m^{-2}$ < BMI ≤ 24.9 $kg.m^{-2}$, overweight when 25 $kg.m^{-2}$ < BMI ≤ 29.9 $kg.m^{-2}$ and obesity when BMI ≥ 30 $kg.m^{-2}$ [8]. Previous studies have shown overweight and obese contributed to increase the fatalities of endometrial cancer, colon cancer, and renal carcinoma [9]. But the relationships between developing glioma and BMI are uncertain. Several recent studies reported excess BMI was a predictor of glioma risk [10, 11], whereas other studies did not show the similar outcome [8, 12–14]. For solving this controversy, a meta-analysis was carried out.

Patients and methods

Literature retrieval and inclusive criteria

A literature search was executed in PubMed, MEDLINE, and EMBASE from inception to September 15, 2014.

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The search strategies used for each database were as follows: "body mass index", "overweight", "obesity" combined with "glioma" which was a MeSH and limited in "human". Two reviewers independently sorted out eligible trials according to the following inclusive criteria: (I) a clear diagnosis of glioma; (II) underweight, overweight, or obesity defined by BMI; (III) relative risk (RR) or hazard ratio (HR) with 95 % confidence interval (CI) of BMI was reported; (IV) we included the most recent and informative paper, if more than one article was found on the same trial; (V) we excluded those studies which were not fit for our inclusion criteria.

Data extraction and literature quality evaluation

Two reviewers (Z.F Dai and H.P Liu) independently sorted out eligible trials according to inclusive criteria. Data extraction was performed by two reviewers which included the first author, year of publication, study design, country of study, the number of male and female, median follow-up, median age, HR, and 95 % CI (Table 1). Any disagreements were resolved by discussion.

We used the Newcastle-Ottawa scale (NOS) to evaluate the quality of papers. The NOS is an evaluation standard of nonrandomized controlled trials composed with three major parts: selection of the study groups (0–4 stars), comparability of cases and controls (0–2 stars), or cohorts, and ascertainment of exposure/outcome (0–3 stars). A study was considered a high-quality research when its NOS were equal or greater than 6 stars [15].

Statistical analysis

The pooled HRs and 95 % CIs were assessed to know the correlation risk between glioma and underweight, overweight, or obesity. Greenland reported "if the outcome under study is rare in all populations and subgroups under review, one can generally ignore the distinctions among the various measures of relative risk (e.g., odds ratios, rate ratios, and risk ratios)" [16]. So we used this principle in the study of Benson et al.: RRs were accurate approximations of HRs [10]. Statistical heterogeneity was quantified with I^2 statistic and Cochran's Q with a significant level at $P < 0.1$ [17]. Fixed-effects model was executed for summary data, if heterogeneity was not significant ($I^2 < 50$ %). While if $I^2 > 50$ %, the random-effects model was selected [17]. When I^2 was less than 25 %, the heterogeneity was low; When I^2 was ranged 25 % from 50 %, the heterogeneity was moderate; and when I^2 was more than 50 %, the heterogeneity was high [18]. Sensitivity analysis was carried to evaluate the effect of each inclusive study on the results by excluding one study at a time. Sensitivity analysis was performed to evaluate the effect of each inclusive study on the results by excluding one study at a time. Begg's test was performed to examine publication bias at two-side test P value <0.05. All analyses were performed in STATA 12.0 version. All analyses were conducted in STATA 12.0 version. Screening article was based on preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement (Review Manager Version 5.2 (Revman, the Cochrane Collaboration, Oxford, England)) [19].

Results

Characteristics of included trials and patients

With our search strategy, 450 trials were satisfied, and Fig. 1 shows a flow diagram for the selection process. After reading the titles, 23 interesting articles were taken. After reading the abstracts, seven papers were needed to get full text. After reviewing the full-text, six trials met the inclusion criteria and were included in meta-analysis [8, 10–14]. Two studies were performed in the USA [11–13], and three trials in Europe [8, 10, 14]. Four studies

Table 1 Characteristics of the five trials included in meta-analysis

Author	Year	Design	Country	Male	Female	Median follow-up (months)	Median age (years)	NOS
Benson [10]	2008	Cohort study	UK	/	646	74.4	57 ± 4.5	******
Siegel [11]	2013	Case-control study	USA	506	347	12.4	57 ± 13.3	******
Wiedmann [8]	2013	Cohort study	Norway	83	65	282	48.1 (20–101)	******
Michaud [14]	2011	Cohort study	Cross-country[a]	167	173	100.8	/	*******
Jones [13]	2010	Cohort study	USA	832	427	40	58	******
Moore [12]	2009	Cohort study	USA	341	139	98.4	/	******

([a]Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom)

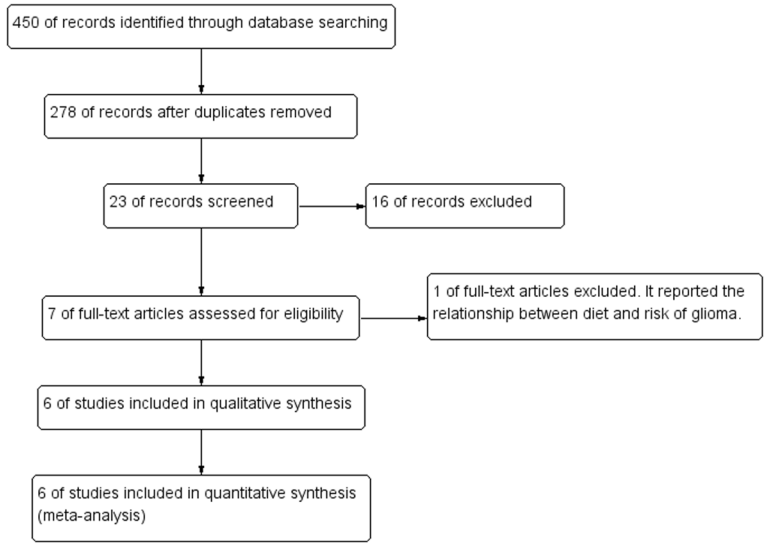

Fig. 1 The PRISMA statement of meta-analysis

included women and men [8, 11–14], and one study included women only [10]. All included studies were of high quality evaluated by NOS, which were equal to or more than six stars. Detailed characteristics and NOS score of the included studies are shown in Table 1.

Meta-analysis

Six studies [8, 10–14] which contained 3726 patients were included into meta-analysis. There was no significant heterogeneity between these studies ($I^2 = 0.0$ %, $P = 0.912$), so the fixed-effects model of analysis was performed. The

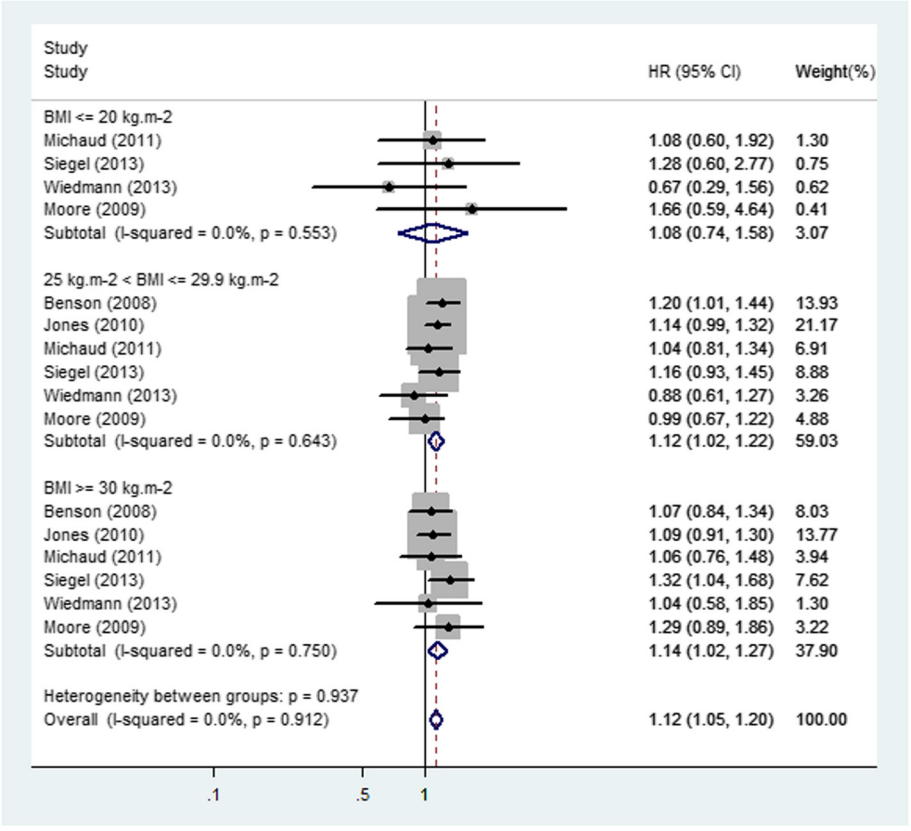

Fig. 2 Forest plots of meta-analysis results of underweight, overweight, and obesity, when normal weight was referent

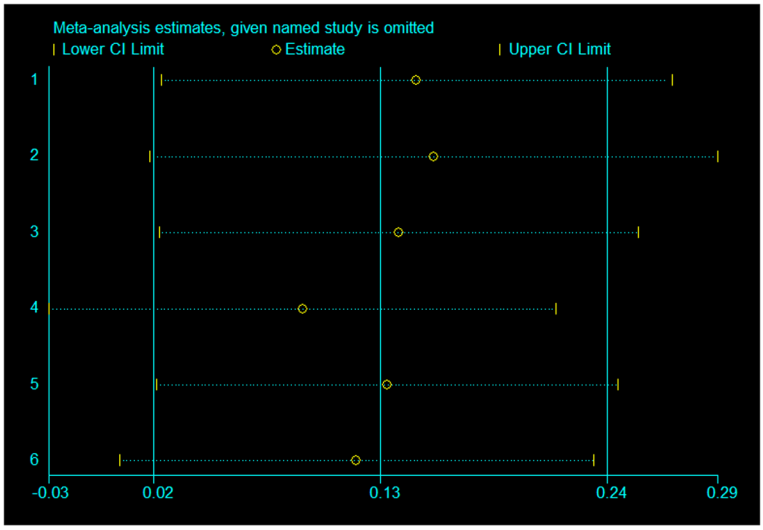

Fig. 3 Sensitivity analysis for obesity

pooled HR of all studies was 1.12 (95 % CI ranged 1.05 to 1.20, $P = 0.001$) (Fig. 2), which mean excess BMI was a risk factor to develop glioma.

Three studies [8, 11, 12, 14] provided the HR of underweight. The heterogeneity was significant in these studies ($I^2 = 0.0$ %, $P = 0.553$), so random-effects analysis was performed. The pooled HR of all studies was 1.08 (95 % CI ranged 0.74 to 1.58, $P = 0.678$) (Fig. 3), which mean underweight might decrease the risk of suffering from glioma.

Six studies [8, 10–14] provided the HR of overweight and obesity. There was no significant heterogeneity in two groups (all $I^2 = 0.0$ %), so fixed-effects analysis was performed. The pooled HR of overweight group was 1.12 (95 % CI ranged 1.02 to 1.22, $P = 0.013$); the pooled HR of obesity was 1.14 (95 % CI ranged 1.02 to 1.27, $P = 0.017$) (Fig. 2). Excess BMI was considered as a risk factor of developing glioma.

Sensitive analysis

Sensitivity analysis was carried by excluding one study at a time. There did not exist any one article that could significantly influence the overall result stability individually (Fig. 3).

Publication bias

The outcomes of Egger's test ($t = 0.17$, $P = 0.873$) and symmetric funnel plot showed that there was no publication bias from these outcomes (Fig. 4).

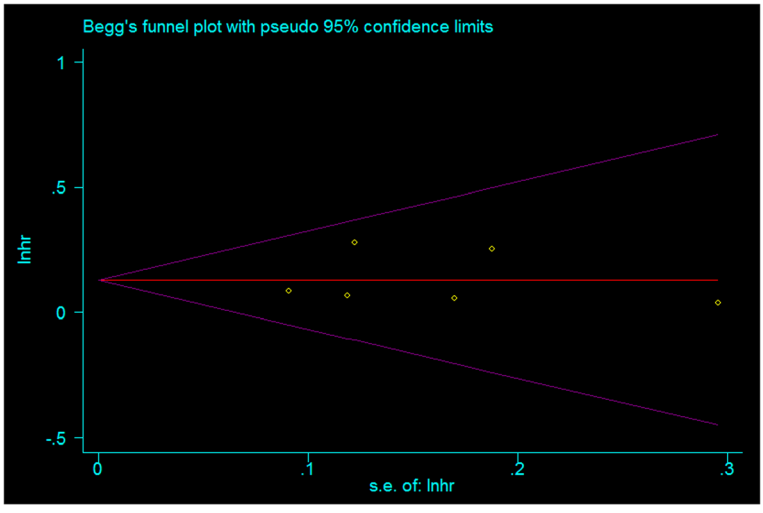

Fig. 4 Funnel plot for publication bias of obesity

Discussion

The meta-analysis showed the relationship of glioma with underweight, overweight, and obesity compared normal weight. Only three studies to date have analyzed the relationship between the risk of glioma and underweight, and pooled HR of three studies show underweight could decrease the risk of developing glioma [8, 11, 14]. Excess BMI (BMI ≥ 25 $kg.m^{-2}$) was significantly associated with a danger of developing glioma. Many studies reported the overweight and obesity were independent risk factors for poor outcome in patients with glioma [8, 11–14]. At present, several potential theories have been built to explain how obesity can influence the development of glioma. The most well-known mechanism is the insulin-like growth factor (IGF) hypothesis of obesity-related cancer, which has been implicated in glioma proliferation and progression in vitro [20–25]. A 22-case-control study showed a positive correlation between serum IGF-1 levels and glioma risk [26]. IGF-1 inhibitor was found effectively to suppress growth of glioblastoma cell and induced tumor regression in vitro [27]. There is a peak level of IGF during fetal brain development, and it decreases with age. But it reappears in nervous tissue of glioma cells [28]. Insulin resistance and hyperinsulinemia are very common among excess body mass especially obesity [29], which increase the level of free IGF. The free IGF can bind insulin-like growth factor binding protein 1 (IGFBP-1) and insulin-like growth factor binding protein 2 (IGFBP-2). Correspondence with a decrease of the binding protein, more and more higher circulating concentrations of free or bioactive insulin-like growth factor 1 (IGF-1), was detected [21, 30].

Basing on our findings, we thought weight loss is beneficial which may reduce insulin resistance in obese patients. In addition, nutrients and phytochemicals in fruit and vegetables might decrease glioma risk [31], while socioeconomic level, daily alcohol intake, smoking status, number of full-term pregnancies, age at first birth, and oral contraceptive use were not significantly associated with the incidence of glioma [10]. Moore et al. found no link between weight gain between ages 18 and 50 years and glioma risk [12].

As we know, this is the first meta-analysis illustrating the correlation of different BMI grades on the risk of glioma. There are some advantages of this meta-analysis. Firstly, meta-analysis can assess the consistency of result and find the origin of heterogeneity. Secondly, meta-analysis can evaluate and summarize results from different studies which can increase the statistical efficiency and accuracy. Thirdly, we could do detailed subgroup analysis to identify risk factors relative to glioma.

Several potential limitations of this meta-analysis should be noted. First, the number of included studies was small which might let us underestimate the true association. Second, as all included studies were observational, we cannot exclude all confounders like age, region, and race. Third, because of our strict inclusive criteria, many articles might exclude subject. Forth, the data were not stratified according to the WHO grade of tumors. Finally, unpublished negative results were needed to be considered.

Conclusion

Underweight could decrease the risk of developing glioma. Excess BMI was considered as a risk factor for developing glioma. But this outcome needs more prospective studies to further confirm the study.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

ZD and QH designed the research strategy; ZD and HL extracted and analyzed data; ZD wrote the main manuscript text. QH helped to correct the manuscript. All authors read and approved the final manuscript.

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