Body Mass Index as a Risk Factor for Diffuse Large B-Cell Lymphoma: A Systematic Review and Meta-Analysis

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Abstract: Introduction: Given the increasing prevalence of obesity, as measured by the Body Mass Index (BMI), and the significant impact of Diffuse Large B-cell lymphoma (DLBCL) on global health, it is crucial to update our understanding of the relationship between BMI and DLBCL.

Objective: to carry out a systematic review (SR) with meta-analysis to determine the association between DLBCL and BMI

Methods: This study is a systematic review and meta-analysis following the PRISMA guidelines. It searched PubMed/medline, SCOPUS, Web of Science, and EMBASE. The inclusion criteria were primary observational studies involving adults with DLBCL confirmed by biopsy. Exclusions were non-peer-reviewed materials and studies without inferential statistics. The findings of the study are presented as association measures such as relative risks (RR), accompanied by their corresponding 95% confidence intervals (95% CI).

Results: From 451 articles, 13 met the criteria for inclusion. The included studies, conducted between 2002 and 2013 in various countries, showed varied follow-up periods and sample sizes. The meta-analysis revealed that individuals with high BMI have a 1.31 times higher risk of developing DLBCL than those with lower BMI (RR: 1.31; 95% CI 1.07, 1.61). The heterogeneity among studies was moderate.

Conclusions: The study confirms an association between higher BMI and the increased risk of developing DLBCL. This finding underscores the need to explore further how obesity, chronic inflammation, and the development and progression of DLBCL are interconnected. Understanding this area could significantly reduce DLBCL incidence and improve patient outcomes.

Keywords: Lymphoma, B-cell, Body Weights and Measures, Body Mass Index, Systematic Review (Source: MeSH NLM).

INTRODUCTION

A variety of non-Hodgkin lymphoma called Diffuse Large B-cell lymphoma (DLBCL) results from malignant changes that arise within B-lymphocytes, whereby these cancerous B-cells multiply unchecked as they spread chaotically throughout the lymphatic system. This most widespread non-Hodgkin lymphoma subtype, accounting for 30 to 60% of documented instances, comprises the most significant share of its kinds described [1]. DLBCL is a significant public health concern because it is invasive and recurrent. The steady rise in the incidence of DLBCL across recent decades has been well documented, with references pointing to its growing prevalence over the past few decades [2].

In 2018, the rate at which diffuse large B-cell lymphoma occurred was estimated to be 7.0 for every 100,000 individuals globally, accounting for roughly 400,000 novel instances of the disease globally [3]. Between 2013 and 2017, within America’s boundaries, available data notes around 28,000 fresh occurrences annually [4], which tallies to a rate of almost 8.3 out of every 100,000 persons [5]. While reports on the frequency across Latin America vary considerably, projections anticipate fluctuations in the rate of 6 to 8 such happenings per 100,000 residents. Unfortunately, the absence of robust cancer registries across the region poses challenges for generating precise estimates of incidence frequencies [6].

While various investigations have assessed body mass index (BMI) as a possible hazard for diffuse large B-cell lymphoma, the outcomes have lacked uniformity. While specific studies have found an elevated likelihood of developing DLBCL for those who are overweight or obese [7, 8], other investigations have not established a comparable connection [9, 10]. Further research is needed to determine whether BMI is a definitive risk factor for DLBCL.
Due to the increasing frequency of obesity worldwide coupled with the considerable effects of DLBCL on public health globally, updating our comprehension of the link between BMI and DLBCL is imperative. A systematic review of recent literature addressing this association could offer a more thorough and contemporary perspective on the current state of research within this domain. Such an update could help guide clinical decision-making and public health initiatives to prevent and treat DLBCL.

METHODS

A systematic review (SR) with meta-analysis of observational studies. The framework of this document is informed by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [11].

Search Strategy

The execution of this study involved applying a search strategy across four different databases: PubMed/Medline, SCOPUS, Web of Science, and EMBASE. The key terms: "Lymphoma, Large B-cell, Diffuse, "obesity," Body Mass Index," and "risk" were used. The search strategy for each database is available in supplementary material 1.

Selection Criteria

We utilized the following criteria for inclusion: 1) Primary observational studies released in peer-reviewed journals that utilized a cross-sectional design, cases, and control or cohort; 2) Studies on human participants who were 18 years old or older; 3) Studies that investigated the link between DLBCL and BMI; and 4) DLBCL diagnosis confirmed by biopsy. Any studies that fulfilled any of the following were excluded: 1) Letters to the editor, conference proceedings' abstracts, protocols, and review studies; 2) Articles that failed to provide inferential statistics or measures of association; 3) Articles that were not available in full text or abstract form in either Spanish or English.

Selection of Studies

The software Rayyan (https://rayyan.qcri.org) catalogs the articles discovered in each searched database. Three researchers independently undertook the task of scrutinizing the manuscript titles and abstracts. A manuscript was included if they all concurred. Otherwise, it was excluded. If there were any disagreements, the co-authors convened to reach a consensus on the manuscript.

Next, a thorough review of the entire text of each included article was conducted. A record was kept in an Excel spreadsheet, indicating whether or not the study should be incorporated. This procedure mirrored the method applied in the initial selection process.

Data Extraction and Qualitative Analysis

The remaining articles proceeded to data extraction, utilizing a file in Microsoft Excel 2022. The following details were gleaned from each article chosen: First Author, year, country, follow-up time (mean or median), sample, population (selection criteria), sex (% female), age, BMI cut-off point, BMI ascertainment, incidence of DLBCL (%), DLBCL ascertainment, association measure and adjustment variables.

Risk of Bias Assessment

Three authors independently evaluated the risk of bias in each included study and deliberated their findings until a consensus was reached. This was facilitated using the modified New Castle Ottawa (NCO) risk of bias instrument for cohort investigations [12]. Fundamentally, the NCO gauges the risk profile of a manuscript via three core domains: 1) Selection, which encompasses four facets and assigns one star for each; 2) Comparability, which is one facet that can garner up to two stars; and 3) Exposure/Outcome, which contains three facets, each of which can secure one star. The NCO for cohort studies scrutinizes the manuscript's risk level based on three key domains: selection of study groups, comparability of groups, and ascertainment of exposure or outcome. Any scoring differences were addressed and reconciled through discussions among the reviewers, leading to the awarding of a final, agreed-upon score to every study.

Quantitative Analysis

The computations were executed using RevMan 5.3, and the variables of interest were dichotomized. DLBCL served as the outcome variable, while obesity was the predictor variable. Measures of association were conveyed as odds ratios (OR) or relative risks (RR) alongside their corresponding 95% confidence intervals (95% CI).

We combined the Odds Ratios (OR) with the Relative Risks (RR). This approach was taken due to the extremely low incidence of DLBCL. Because of this
low incidence, the value of the OR closely approximates the RR, making this combination a logical step for our analysis.

Because most of the reviewed studies presented Body Mass Index (BMI) data in terms of tertiles, quartiles, and quintiles, a meta-analysis was conducted using only those studies that met the following conditions: 1) BMI was objectively measured rather than self-reported by the subjects, to ensure the accuracy of the data; and 2) The highest value of BMI was compared in the analysis, a value which is consistent with the definition of obesity, against the reference value. This selection criterion was used to focus the analysis on the potential health implications of obesity, as defined by BMI, rather than a broader range of BMI categories. The reference value, typically the lowest category in the tertile, quartile, or quintile division, was the control group in these analyses.

We applied Cochrane's Q test and calculated the I² statistic to scrutinize heterogeneity among the incorporated cohort studies [13]. Heterogeneity was evaluated using the I² index. The values of the I² index were divided according to the upper limit into mild if it was up to 25%, moderate if it was up to 50%, and if it was higher, it corresponded to severe heterogeneity [14].

Owing to the observed heterogeneity, we reported outcomes utilizing random effects models per DerSimonian and Laird's method. Publication bias was not assessed because fewer than ten studies were included in the meta-analysis.

**Ethical Considerations**

This research is a secondary analysis of data derived from primary studies previously published in scholarly journals, implying the risks posed to the original study participants are negligible.

**RESULTS**

**Eligible Studies**

In the initial search, 451 articles were identified. Upon removal of 351 duplicate entries, 100 studies were scrutinized based on their title and abstracts. This led to the exclusion of 49 papers, leaving 51 full-text articles identified in the search formula:

- Scopus: 115 articles
- Embase: 164 articles
- PubMed: 74 articles
- Web of Science: 98 articles

After removing 351 duplicate articles, 100 records were reviewed, and 49 excluded items were identified. 51 articles were evaluated for eligibility, and 38 excluded items were identified:

- Not assessing the intended aim
- Missing a defined measure of association
- Composed in an unsuitable language
- Constitutes an abstract from a conference proceeding
- Is a review

13 articles included in the systematic review.

**Figure 1: Flowchart.**
articles for further evaluation. After strict adherence to the selection criteria, 13 articles were included in the final review [15–27]. See Figure 1.

**Study Characteristics**

The manuscripts were conducted between 2002 and 2013 [15–27]. These were primarily driven in seven countries: the USA [15–18, 21, 23, 24], Austria, Norway [20, 25], Sweden [20, 25, 27], Denmark [27], Netherlands [19], and the United Kingdom [26], and the follow-up period ranged from 4.2 to 32 years. The number of participants varied from 3509 to 1249897. The average age ranged from 44 to 64 years.

The cut-off points used for BMI varied across studies, employing tertiles [25, 26], quartiles [15–18, 21, 22, 24, 27], and quintiles [19, 23]. However, the research conducted by Lim *et al.* [16], Troy *et al.* [24], Kabat *et al.* [21], Murphy *et al.* [26], and Patel *et al.* [25] segmented BMI based on the traditional criteria defined by the World Health Organization (WHO) [28]. Regarding BMI measurement methods, eight studies relied on self-reporting [15–19, 21, 24, 26], while five utilized anthropometric criteria [20, 22, 23, 25, 27].

**Risk of Bias Assessment**

The level of bias varied among the studies, ranging from 6 to 9 points. The reasons for this included eight studies measuring BMI through self-reporting [15–19, 21, 24, 26], Cerhan *et al.*’s work had inadequate control for age and sex [15], and the survey by Pylypchuk *et al.* did not control for other confounding factors [19]. Four investigations did not have an adequate follow-up level [16, 22, 24, 27]. Only three studies scored nine points [20, 23, 25]. See Table 2.

**Meta-Analysis of the Association between Obesity and Prediabetes**

For the meta-analysis, all studies that met the criteria outlined in the methodology section were combined [20, 22, 23, 25, 27]. The survey by Bertrand *et al.* [23] was entered twice, as they assessed both men and women separately. In this way, it was found that those with a high BMI had a 1.31 times higher risk of developing DLBCL in the long term than those with a low BMI (RR: 1.31; 95% CI 1.07, 1.61). The level of heterogeneity was moderate, with an I² of 47%. See Figure 2.

**DISCUSSION**

Through meticulous, systematic analysis and aggregation of available research, crucial understandings have been gained regarding the relationship between increasing weight, as quantified by the BMI index, and the likelihood of developing DLBCL, an aggressive cancer of the lymphatic system. Our findings indicate that individuals with a higher BMI are at an increased long-term risk of developing DLBCL, supporting the hypotheses proposed by the authors.

These results align with those of previous joint research by Castillo *et al.* [7, 8] yet differ from the findings of Hidayat *et al.*’s systematic review [9, 10]. However, this review presented differences compared to previous ones. The meta-analysis exclusively incorporated investigations utilizing suitable BMI quantification, evading amalgamating self-reported BMI figures [9, 10]; it solely regarded cohort research [7, 8], and we selected BMI as our principal signpost for this assessment rather than depending on an assortment of markers [9, 10]. A variety of considerations contributed to the formulation of this determination. While BMI is a commonly applied and utilized metric for evaluating weight and adiposity status among adults, permitting comparability and consistency across diverse studies and populations, its widespread usage overlooks meaningful individual factors. Additionally, in categorizing individuals into groups of underweight, average weight, overweight, and obesity using the traditional BMI classification approach rather than...
<table>
<thead>
<tr>
<th>First Author, year, Country</th>
<th>Follow up time (mean or median)</th>
<th>Sample</th>
<th>Population (selection criteria)</th>
<th>Sex (% female)</th>
<th>Age</th>
<th>BMI cut-off point</th>
<th>BMI ascertainment</th>
<th>Incidence of DLBCL (%)</th>
<th>DLBCL ascertainment</th>
<th>Association measures</th>
<th>Adjustment variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerhan, 2002, USA</td>
<td>13 years</td>
<td>37093</td>
<td>Women with self-reported history of cancer or cancer chemotherapy on the baseline questionnaire were excluded.</td>
<td>100.00%</td>
<td>61.7</td>
<td>Q1: &lt; 22.5</td>
<td>Q2: 23.5 - 26.1</td>
<td>Q3: 26.2-29.9</td>
<td>Q4: ≥ 29.8</td>
<td>Self-reported</td>
<td>261/3973</td>
</tr>
<tr>
<td>Chang, 2005, Denmark and Sweden</td>
<td>4.2 years</td>
<td>3509</td>
<td>All residents between 18 and 74 years of age in Denmark and in Sweden, and to have no history of organ transplantation, of a positive test for HIV, or of prior hematopoietic malignancy were included.</td>
<td>49.64%</td>
<td>Control: 56.1</td>
<td>DLBCL: 57.4</td>
<td>Q1: &lt; 22.8</td>
<td>Q2: 22.8 - 24.9</td>
<td>Q3: 25-27.5</td>
<td>Q4: ≥ 27.6</td>
<td>Measured</td>
</tr>
<tr>
<td>Lim, 2007, USA</td>
<td>5.5 years</td>
<td>473984</td>
<td>We excluded one withdrawal, duplicates, 55 persons who had died or moved out of the study area before study entry, persons with a history of cancer by self-report and registry data, persons with a diagnosis at death without histology information, proxy respondents persons with extreme caloric, and persons with BMI values that were missing, cutters, or less than 15.5</td>
<td>Q1: 50%</td>
<td>Q2: 31%</td>
<td>Q3: 37%</td>
<td>Q4: 55%</td>
<td>62 years</td>
<td>Q1: 18.5 - 24.9</td>
<td>Q2: 25 - 29.9</td>
<td>Q3: 30 - 34.9</td>
</tr>
<tr>
<td>Britton, 2008, Europe</td>
<td>9 years</td>
<td>371883</td>
<td>All residents between 25 and 74 years of age. Were excluded persons with prevalent cancer cases</td>
<td>61.99%</td>
<td>51 years</td>
<td>Q1: &lt; 24</td>
<td>Q2: 24 - 26.1</td>
<td>Q3: 26.2-28.69</td>
<td>Q4: ≥ 28.7</td>
<td>Measured</td>
<td>144/371883</td>
</tr>
<tr>
<td>Maskarinec, 2008, USA</td>
<td>10 years</td>
<td>193051</td>
<td>We excluded individuals because they did not belong to one of the five main ethnic groups, subjects because their dietary information was deemed invalid, and patients who were diagnosed with NHL, chronic lymphocytic leukemia (CLL) before entry into the cohort. Subjects with missing values for BMI at cohort entry or BMI at age 21</td>
<td>54.89%</td>
<td>60 years</td>
<td>Q1: &lt;22.5</td>
<td>Q2: 22.5 - 24.9</td>
<td>Q3: 25.0 - 29.9</td>
<td>Q4: ≥ 30</td>
<td>Self-reported</td>
<td>264/193051</td>
</tr>
<tr>
<td>First Author, year</td>
<td>Country</td>
<td>Follow up time (mean or median)</td>
<td>Sample</td>
<td>Population (selection criteria)</td>
<td>Sex (% female)</td>
<td>Age</td>
<td>BMI cut-off point</td>
<td>BMI ascertainment</td>
<td>Incidence of DLBCL (%)</td>
<td>DLBCL ascertainment</td>
<td>Association measurement</td>
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<tr>
<td>Lu, 2009</td>
<td>USA</td>
<td>11 years</td>
<td>121216</td>
<td>We excluded women who were not California residents, were aged 15 years or older at cohort entry, who had limited their participation in breast cancer research, who had a prior history of a hematopoietic malignancy, or whose history of cancer was unknown</td>
<td>100.00%</td>
<td>62</td>
<td>Q1: &lt; 20</td>
<td>Self-reported</td>
<td>155/121216</td>
<td>Cancerregistry</td>
<td>Risk Ratio Q1: 1.42 (0.83 - 2.45) Q2: Referente Q3: 1.07 (0.72 - 1.59) Q4: 1.37 (0.86 - 2.16)</td>
</tr>
<tr>
<td>Pylypchuk, 2009</td>
<td>Netherlands</td>
<td>13.3 years</td>
<td>120852</td>
<td>Subjects with missing data or body mass index at baseline and on height were excluded</td>
<td>51.80%</td>
<td>62</td>
<td>Q1: &lt; 20</td>
<td>Self-reported</td>
<td>224/120852</td>
<td>Cancerregistry</td>
<td>Q1: 0.96 (0.61 - 1.50) Q2: Reference Q3: 0.99 (0.64 - 1.54) Q4: 1.35 (0.88 - 2.10) Q5: 1.29 (0.71 - 2.33)</td>
</tr>
<tr>
<td>Troy, 2010</td>
<td>USA</td>
<td>9 years</td>
<td>142982</td>
<td>Subjects with aged 55–74 years with no prior history of the cancer</td>
<td>49.60%</td>
<td>61</td>
<td>Q1: &lt; 18.5</td>
<td>Self-reported</td>
<td>215/142982</td>
<td>Cancerregistry</td>
<td>Q1: NA Q2: Reference Q4: 1.07 (0.76 - 1.50) Q4: 1.58 (1.10 - 2.27)</td>
</tr>
<tr>
<td>Nagel, 2012</td>
<td>Austria, Norway and Sweden</td>
<td>11 - 13 years</td>
<td>575386</td>
<td>Exclusion of subjects with unrealistic or missing baseline data or prevalent cancer 20 diagnosis</td>
<td>48.89%</td>
<td>44</td>
<td>Q1 - Q5</td>
<td>Measured</td>
<td>195/575386</td>
<td>Cancerregistry</td>
<td>Q1: Reference Q2: 1.02 (0.47 - 2.24) Q3: 1.12 (0.92 - 1.39) Q4: 1.24 (0.89 - 1.47) Q5: 1.05 (0.83 - 1.32)</td>
</tr>
<tr>
<td>Kabat, 2012</td>
<td>USA</td>
<td>11 years</td>
<td>158975</td>
<td>Women between the ages of 56 and 79. Were excluded women who reported a history of lymphoma or leukemia at recruitment, women with missing bmis or extreme values for baseline body mass index (&lt;15 kg/m2 and &gt;50 kg/m2), and women who were missing MET/hw</td>
<td>100%</td>
<td>84</td>
<td>Q1: &lt; 25</td>
<td>Self-reported</td>
<td>302/158975</td>
<td>Cancerregistry</td>
<td>Q1: Reference Q2: 1.11 (0.89 - 1.42) Q3: 1.13 (0.86 - 1.42) Q4: 0.94 (0.86 - 1.22)</td>
</tr>
<tr>
<td>Murphy, 2013</td>
<td>UK</td>
<td>10 years</td>
<td>124989</td>
<td>We were excluded women who reported a history of cancer</td>
<td>100%</td>
<td>56.6</td>
<td>Q1: &lt; 25</td>
<td>Self-reported</td>
<td>4165/1249897</td>
<td>Cancerregistry</td>
<td>Q1: Reference Q2: 1.18 (1.03 - 1.35) Q3: 1.37 (1.17 - 1.62)</td>
</tr>
<tr>
<td>Patel, 2013</td>
<td>Austria, Norway and Sweden</td>
<td>11 - 13 years</td>
<td>152423</td>
<td>We excluded from this analysis 6251 men and women who were lost to follow-up who reported prevalent cancer (except non-melanoma skin cancer) at baseline, or whose lymphoid cancer could not be verified through medical or cancer registry records. Finally, we excluded individuals with missing or extreme BMI</td>
<td>52.54%</td>
<td>63</td>
<td>Q1: &lt; 25</td>
<td>Measured</td>
<td>195/152423</td>
<td>Cancerregistry</td>
<td>Q1: Reference Q2: 1.29 (1.04 - 1.61) Q3: 1.64 (1.25 - 2.16)</td>
</tr>
</tbody>
</table>
### Table 1: Continued.

<table>
<thead>
<tr>
<th>First Author, year</th>
<th>Country</th>
<th>Follow up time (mean or median)</th>
<th>Sample</th>
<th>Population (selection criteria)</th>
<th>Sex (% female)</th>
<th>Age</th>
<th>BMI cut-off point</th>
<th>BMI ascertainment</th>
<th>Incidence of DLBCL (%)</th>
<th>DLBCL ascertainment</th>
<th>Association measures</th>
<th>Adjustment variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bertrand, 2013</td>
<td>USA</td>
<td>22–32 years</td>
<td>163364</td>
<td>Men and women diagnosed with cancer (except non-melanoma skin cancer) before baseline were excluded.</td>
<td>28.39%</td>
<td>54 years</td>
<td>Q1: 15-22.9 Q2: 23 - 24.9 Q3: 25 - 26.9 Q4: 27 - 20.9 Q5: 30 - 45</td>
<td>Measured</td>
<td>83/163364</td>
<td>Cancer registry</td>
<td>Men Q1: Reference Q2: 1.57 (0.75, 3.23) Q3: 1.56 (0.75, 3.34) Q4: 1.65 (0.75, 3.64) Q5: 2.16 (0.88, 5.43) Women Q1: Reference Q2: 0.97 (0.64, 1.43) Q3: 1.06 (0.69, 1.65) Q4: 0.85 (0.52, 1.33) Q5: 1.36 (0.88, 2.13)</td>
<td>age, height (continuous inches), smoking, physical activity, race</td>
</tr>
</tbody>
</table>

### Table 2: Assessment of the Quality of the Included Studies using the Newcastle-Ottawa Scale

<table>
<thead>
<tr>
<th>Authors, year</th>
<th>Representativeness of the exposed cohort</th>
<th>Selection of the non-exposed cohort</th>
<th>Exposure Ascertainment</th>
<th>Outcome not present at the start of the study</th>
<th>Study controls for sex and age</th>
<th>Study controls for any additional important factor</th>
<th>Outcome Assessment of outcome</th>
<th>Length of follow-up</th>
<th>Adequacy of follow up</th>
<th>Score</th>
<th>Overall Judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerhan, 2002</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>6</td>
<td>High risk</td>
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<tr>
<td>Chang, 2005</td>
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<td>*</td>
<td>*</td>
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<td>*</td>
<td>8</td>
<td>Low risk</td>
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<tr>
<td>Lim, 2007</td>
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<td>?</td>
<td>Low risk</td>
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<td>Britton, 2008</td>
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<td>*</td>
<td>8</td>
<td>Low risk</td>
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<td>Maskarinec, 2008</td>
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<td>8</td>
<td>Low risk</td>
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<td>Lu, 2009</td>
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<td>8</td>
<td>Low risk</td>
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<td>Plypchuk, 2009</td>
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<td>7</td>
<td>Low risk</td>
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<td>Troy, 2010</td>
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<td>8</td>
<td>Low risk</td>
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<td>Nagel 2012</td>
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<td>Low risk</td>
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<td>Kabat, 2012</td>
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analyzing increments per 10 kg/m² or alternative categorization techniques, we determined that was the preferable path. This traditional approach allows for a more intuitive and accessible interpretation of the results.

Despite consistency with existing studies, it's essential to acknowledge the moderate heterogeneity observed in the results. An I² of 47% indicates significant variability in individual studies [14]. This heterogeneity could be attributed to diversity in methodology and BMI measurement criteria, including 1) BMI cut-off points, 2) different adjustment variables, and 3) varying populations [20, 22, 23, 25, 27].

The systematic review in question considered investigations that were predominantly led within seven countries, specifically the United States of America, the Republic of Austria, the Kingdom of Norway, the Kingdom of Sweden, the Kingdom of Denmark, the Kingdom of the Netherlands, and the United Kingdom of Great Britain and Northern Ireland. Including diverse geographical locations is relevant as it lends more generalization to the findings. Notably, studies from the United States constituted the most significant proportion of the sample [15–27]. Although this review included studies from various countries, many regions worldwide have not extensively researched the association between BMI and DLBCL. Differences in genetics, diet, lifestyle, healthcare systems, and socioeconomic conditions may influence the relationship between obesity and DLBCL, highlighting the importance of understanding how this association may vary across contexts [2]. By expanding research internationally to incorporate populations from additional low and middle-income nations, current understanding may be enhanced by perspectives that have been historically overlooked yet offer valuable insights regarding representation across diverse demographic profiles. This could help identify whether there are differences in the association between BMI and DLBCL in these contexts and show a more comprehensive global picture of this relationship.

The association between obesity and DLBCL could be due to several mechanisms. Chronic inflammation, often associated with obesity, can promote B-cell proliferation, leading to the development of DLBCL. Though adipose cells are understood to discharge pro-inflammatory cytokines like IL-6 and TNF-α at heightened levels in individuals with obesity, contributing to the ongoing mild systemic swelling usually related to excess fatty tissue, these cells are thought in addition to contribute to the chronic mild systemic swelling commonly connected with surplus adiposity. These substances promote the survival and proliferation of B-cells, which could trigger malignant transformation [29, 30].

Unfortunately, as obesity frequently induces insulin resistance, this tends to concurrently elicit amplified levels of both insulin and IGF-1 throughout the body. Both hormones stimulate cell growth and are implicated in oncogenesis. B-cells in obese individuals might also undergo metabolic changes, such as lipid and glucose metabolism dysfunctions, potentially influencing DLBCL progression. Obesity potentially undermines immune function in a manner that could hinder the body’s natural defenses against the emergence of cancerous growths. Together, these effects create an environment conducive to B-cell proliferation and the associated malignant transformation in DLBCL [29, 30].

Limitations and Strengths

While several limitations merit consideration, the preponderance of observational studies hindered definitively establishing a causal linkage between BMI and DLBCL given randomized controlled trials' infeasibility and lack of ethics in this context, necessitating well-designed prospective research to corroborate the findings. BMI remains an imperfect obesity metric since disregarding fat versus muscle mass composition, optimally discerning adiposity and risk would necessitate body fat percentage as the gold standard. In contrast, varied high versus low BMI cut-offs across studies potentially introduced inconsistencies to the meta-analysis results as duration and degree of confounding factor adjustments differed among studies, risking biased conclusions. Moreover, molecular subtypes of DLBCL were unexamined in this review. The association with obesity may become more robust for specific B-cell subtypes; 6) potential effect modifiers like age, sex, diet, and exercise that could influence the relationship between BMI and DLBCL were not explored.

This exhaustive review employed a comprehensive search strategy to identify every pertinent study on the topic, limiting the possibility of overlooking significant information, performed a more rigorous appraisal of potential bias in the incorporated research, unveiling divergent outcomes from other analyses, including equivalent variables, and combined investigations from an assortment of nations, consequently expanding the
extent to which its results can be applied more generally. While the outcomes appear generalizable beyond a single community, encompassing a broader range of individuals, the effect seen, with a relative risk of 1.31 consistent with prior work, supports the legitimacy of this finding.

CONCLUSIONS

There is an association between BMI and the development of DLBCL. The meta-analysis underscores the necessity of additional scrutiny into the intricate interconnections linking excess weight, obesity, prolonged inflammation, and the origination and advancement of DLBCL, emphasizing where supplementary understanding is still anticipated. Advancements within this domain conceivably promise momentous repercussions concerning potentially diminishing the frequency of such lymphoma while enhancing the prognoses of those experiencing such a condition.

It’s recommended to conduct more prospective studies on a global scale to establish causality between the variables more accurately. Additionally, future reviews should include analyses of molecular subtypes of DLBCL and the biological mechanisms linking them to obesity, including inflammatory markers and metabolic factors, to provide a deeper understanding of how BMI could affect different populations from various geographical regions, particularly in low- and middle-income areas. Finally, it is also recommended that future studies use standardized tools to assess the quality and bias of the studies.

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This study is self-financed.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

INFORMED CONSENT

It was not necessary to obtain informed consent in this Study

DATA AVAILABILITY

Data are available upon request to the corresponding author.

AUTHORS’ CONTRIBUTION

Víctor Juan Vera-Ponce: Conceptualization, Investigation, Methodology, Resources, Project administration, Writing - Original Draft, Writing - Review & Editing.

Joan A. Loayza-Castro: Software, Data Curation, Formal analysis, Writing - Review & Editing.

Luisa Erika Milagros Vásquez Romero: Validation, Visualization, Writing - Original Draft, Writing - Review & Editing.

Fiorella E. Zuzunaga-Montoya: Methodology, Supervision, Funding acquisition, Writing - Review & Editing.

SUPPLEMENTARY FILE

The supplementary file can be downloaded from the journal website along with the article.

REFERENCES


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