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

Víctor Juan Vera-Ponce[1,2,*], Joan A. Loayza-Castro[1,2], Luisa Erika Milagros Vásquez-Romero[1,2] and Fiorella Elvira Zuzunaga-Montoya[1,2]

[1]*Instituto de Investigación de Enfermedades Tropicales, Universidad Nacional Toribio Rodríguez de Mendoza de Amazonas (UNTRM), Amazonas, Perú*

[2]*Facultad de Medicina (FAMED), Universidad Nacional Toribio Rodríguez de Mendoza de Amazonas (UNTRM), Amazonas, Perú*

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.

Address correspondence to this author at the Universidad Tecnológica del Perú, Lima, Peru; E-mail: vicvepo@gmail.com

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

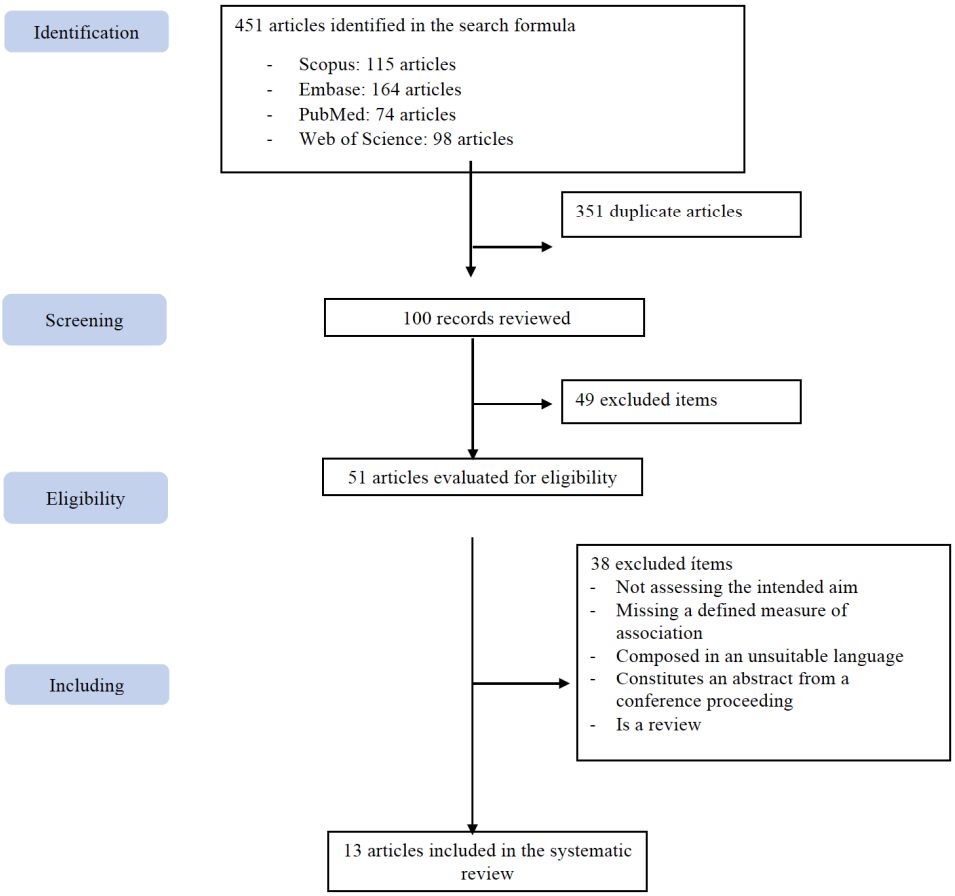

Figure 1: Flowchart.

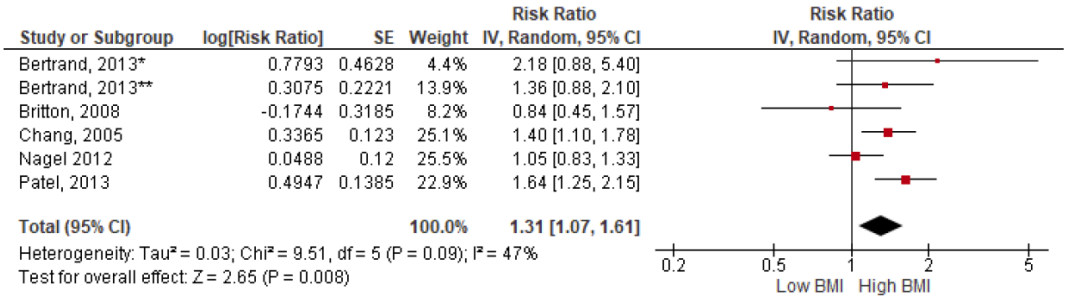

Figure 2: Forest plot of the association between obesity according to BMI and DLBCL in cohort studies.

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 1: Characteristics of the Studies

First Author, year	Country	Follow up time (mean or median)	Sample	Population (selectioncriteria)	Sex (% female)	Age	BMI cut-off point	BMI ascertainment	Incidence of DLBCL (%)	DLBCL ascertainment	Associationmeasure	Adjustment variables
Cerhan, 2002	USA	13 years	37931	Women with a self- reported history of cancer or cancer chemotherapy on the baseline questionnaire were excluyed	100.00%	61.7	Q1: < 23.5 Q2: 23.5 - 26.1 Q3: 26.2-29-9 Q4: ≥ 29.8	Self-reported	261/39731	Cancerregistry	Risk Ratio Q1: Reference Q2: 1.0 (0.5 - 2-2) Q3: 1.4 (0.7 - 2.8) Q4: 1.3 (0.6 - 2.6)	Age
Chang, 2005	Denmark and Sweden	4.2 years	3509	Al 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.	49.64%	Control: 56.1 DLBCL: 57.4	Q1: < 22.8 Q2: 22.8- 24.9 Q3: 25-27.5 Q4: ≥ 27.6	Measured	Q1: 160/794 Q2: 192/783 Q3: 207/791 Q4: 236/790	Cancerregistry	Odds ratio Q1: Reference Q2: 1.1 (0.9 - 1.5) Q3: 1.2 (0.9 - 1.5) Q4: 1.4 (1.1 - 1.7)	age, sex, and country
Lim, 2007	USA	5.5 years	473984	We excluded one withdrawal, duplicates, 582 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 calories, and persons with BMI values that were missing, outliers, or less than 18.5	Q1: 50% Q2: 31% Q3: 37% Q4: 56%	62 years	Q1: 18.5 - 24.9 Q2: 25 - 29.9 Q3: 30 - 34.9 Q4: ≥ 35	Self-reported	346/473984	Cancerregistry	Risk Ratio Q1: Reference Q2: 0.92 (0.72 - 1.18) Q3: 1.10 (0.81 - 1.51) Q4: 1.17 (0.73 - 1.88)	Age, sex, ethnicity, alcohol intake, ´hysical activity
Britton, 2008	Europe	9 years	371883	Al residents between 25 and 70 years of age. Were excluyed persons with prevalent cancer cases	61.99%	51 years	Q1: < 24 Q2: 24 - 26.1 Q3: 26.2-28.69 Q4: ≥ 28.7	Measured	144/371883	Cancerregistry	BMI Q1: Reference Q2: 0.44 (0.21 - 0.92) Q3: 0.62 (0.32 - 1.19) Q4: 0.84 (0.45 - 1.56)	Age.study center
Maskarinec, 2008	USA	10 years	193051	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, BMI at age 21, height, weight at cohort entry or weight at age 21	54.89%	60 years	Q1: <22.5 Q2: 22.5 - 24.9 Q3: 25.0 - 29.9 Q4: ≥ 30	Self-reported	284/193051	Cancerregistry	Hazard ratio Women Q1: 1.41 (0.66-3.00) Q2: Reference Q3: 1.06 (0.58-1.96) Q4: 1.45 (0.75-2.82) Men Q1: 0.65 (0.35-1.21) Q2: Reference Q3: 0.90 (0.56-1.43 Q4: 0.78 (0.40-1.52)	Age at cohort entry, ethnicity, education, and alcohol intake.

(Table 1). Continued.

First Author, year	Country	Follow up time (mean or median)	Sample	Population (selectioncriteria)	Sex (% female)	Age	BMI cut-off point	BMI ascertainment	Incidence of DLBCL (%)	DLBCL ascertainment	Associationmeasure	Adjustment variables
Lu, 2009	USA	11 years	121216	we excluded women who were not California residents, were aged 85 years or older at cohort entry, who had limited their participation to breast cancer research, who had a prior history of a hematopoietic malignancy, or whose history of cancer was unknown	100.00%	62 years	Q1: < 20 Q2: 20- 24.9 Q3: 25-29.9 Q4: ≥ 30	Self-reported	155/121216	Cancerregistry	Risk Ratio Q1: 1.42 (0.83 - 2.42) Q2: Referente Q3: 1.07 (0.72 - 1.59) Q4: 1.37 (0.86 - 2.16)	Age, ethnicity, alcoholintake
Pylypchuk, 2009	Netherlands	13.3 years	120852	Subjects with missing data on body mass index at baseline and on height were excluded	51.80%	62 years	Q1: < 20 Q2: 20 - < 21.5 Q3:21.5 - < 23.0 Q4: 23.0 - < 25.0 Q5: ≥ 25	Self-reported	224/120852	Cancerregistry	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 - 2.35)	Age, sex
Troy, 2010	USA	9 years	142982	Subjects with aged 55–74 years with no prior history of the cancer	49.60%	61 years	Q1: < 18.5 Q2: 18.5 - 24.9 Q4: ≥ 25 - 29.9 Q4: ≥ 30	Self-reported	215/142982	Cancerregistry	Q1: NA Q2: Reference Q4: 1.07 (0.76 - 1.50) Q4: 1.58 (1.10 - 2.27)	Age, sex, ethnicity, education
Nagel 2012	Austria, Norway and Sweden	11 - 13 years	575386	exclusion of subjects with unrealistic or missing baseline data or prevalent cancer 20 diagnosis	48.89%	44 years	Q1 - Q5	Measured	195/575386	Cancerregistry	Q1: Reference Q2: 1.02 (0.47 - 2.24) Q3: 1.12 (0.92 - 1.39) Q4: 1.12 (0.89 - 1.41) Q5: 1.05 (0.83 - 1.32)	Age, sex, smoking history
Kabat, 2012	USA	11 years	158975	Women between the ages of 50 and 79. Were excluded women who reported a history of lymphoma or leukemia at recruitment, women with missing or extreme values for baseline body mass index (<15 kg/m2 and >50 kg/m2), and women who were missing MET- h/wk	100%	64 years	Q1: < 25 Q2: 25- < 30 Q3: 30 - < 35 Q4: ≥ 35	Self-reported	302/158975	Self-reported with centralized verification of medical records and pathology reports	Q1: Reference Q2: 1.11 (0.89 - 1.25) Q3: 1.13 (0.86 - 1.21) Q4: 0.94 (0.86 - 1.22)	Age, alcohol history, smoking history, education, caloric intake, ethnicity
Murphy, 2013	UK	10 years	1249897	Were excluded women who reported a history of cancer	100%	56.6 years	Q1: < 25 Q2: 25- < 30 Q3: 30 - < 35	Self-reported	4165/1249897	Cancerregistry	Q1: Referemce Q2: 1.18 (1.03 - 1.35) Q3: 1.37 (1.17 - 1.62)	Age, alcohol consumption, smoking, and socioeconomic status
Patel, 2013	Austria, Norway and Sweden	11 - 13 years	152423	We excluded from this analysis 6261 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 individualswithmissingor extreme BMI	52.54%	63 years	Q1: < 25 Q2: 25- < 30 Q3: 30 - < 35	Measured	195/152423	Cancerregistry	Q1: Referemce Q2: 1.29 (1.04 - 1.61) Q3: 1.64 (1.25 - 2.16)	Age, sex, smoking history

(Table 1). Continued.

First Author, year	Country	Follow up time (mean or median)	Sample	Population (selectioncriteria)	Sex (% female)	Age	BMI cut-off point	BMI ascertainment	Incidence of DLBCL (%)	DLBCL ascertainment	Associationmeasure	Adjustment variables
Bertrand, 2013	USA	22–32 years	163364	Men and women diagnosed with cancer (except non-melanoma skin cancer) before baseline were excluded.	28.39%	54 years	Q1: 15-22.9 Q2: 23 - 24.9 Q3: 25 - 26.9 Q4: 27 - 29.9 Q5: 30 - 45	Measured	83/163364	Cancerregistry	Men Q1: Reference Q2: 1.57 (0.75, 3.28) Q3: 1.58 (0.75, 3.34) Q4: 1.65 (0.75, 3.64) Q5: 2.18 (0.88, 5.40) Women Q1: Reference Q2: 0.97 (0.64, 1.46) Q3: 1.06 (0.69, 1.65) Q4: 0.85 (0.52, 1.38) Q5: 1.36 (0.88, 2.10)	age, height (continuous inches), smoking, physical activity, race

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

Authors, year	Selection				Comparatibility		Outcome				
	Representativenes of the exposed cohort	Selection of the non-exposed cohort	Exposure Ascertainment	Outcome not present at the start of the study	Study controls for sex and age	Study controls for any additional important factor	Assement of outcome	Length of follow-up	Adequacy of follow up	Score	Overall Judgement
Cerhan, 2002	*	*		*			*	*	*	6	High risk
Chang, 2005	*	*	*	*	*	*	*	*		8	Low risk
Lim, 2007	*	*		*	*	*	*	*		7	Low risk
Britton, 2008	*	*	*	*	*	*	*	*		8	Low risk
Maskarinec, 2008	*	*		*	*	*	*	*	*	8	Low risk
Lu, 2009	*	*		*	*	*	*	*	*	8	Low risk
Pylypchuk, 2009	*	*		*	*		*	*	*	7	Low risk
Troy, 2010	*	*		*	*	*	*	*		7	Low risk
Nagel 2012	*	*	*	*	*	*	*	*	*	9	Low risk
Kabat, 2012	*	*		*	*	*	*	*	*	8	Low risk
Murphy, 2013	*	*		*	*	*	*	*	*	8	Low risk
Patel, 2013	*	*	*	*	*	*	*	*	*	9	Low risk
Bertrand, 2013	*	*	*	*	*	*	*	*	*	9	Low risk

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 bemore 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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FINANCIAL DISCLOSURE

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.

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