Is there an association between a high dietary glycemic index/glycemic load and the risk of developing gynecological cancer in women?

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***Abstract*—** This study aimed to investigate the correlation between a carbohydrate-rich diet, measured by the glycemic index (GI) and glycemic load (GL), and the risk of developing gynecological cancers (GC) such as cervical, endometrial, and ovarian cancer. The study involved a comprehensive literature review to gather existing data on the relevant biological mechanisms observed. Data from epidemiological studies, including case-control and cohort studies, was collected from a variety of research journals to ensure the robustness and reliability of the findings. A random-effects meta-analysis model using multiple statistical techniques was then performed to calculate the pooled risk (odds ratio) of a diet high in carbohydrates on GC incidence, which was diagrammatically represented using forest plots. High dietary GI and GL resulted in a pooled effect size of 1.19 (95% confidence interval between 1.04 and 1.35) and 1.17 (95% confidence interval between 1.02-1.35) respectively, suggesting a positive association. No publication bias was found, and moderate heterogeneity was present among the studies that were included in the analysis. As many of the existing studies have inconclusive results and are relatively outdated, this project is crucial in shedding light on lifestyle choices that women can make to reduce their risk, potentially informing future prevention strategies and public health recommendations (Figure 1).

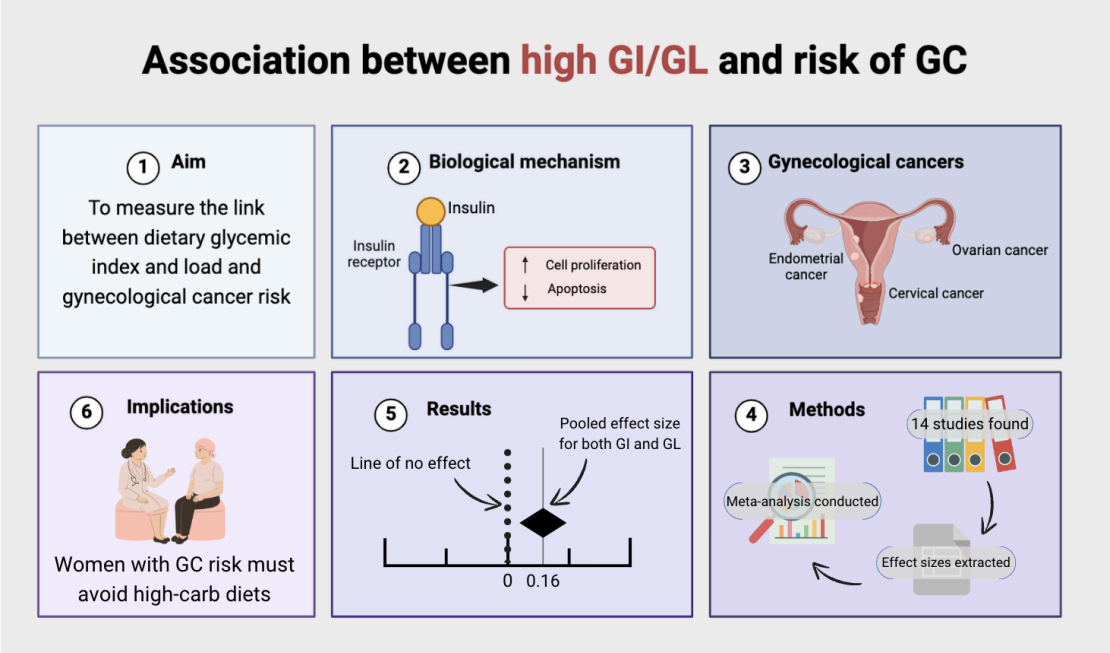

Figure 1. Graphical abstract, created with BioRender.com.

I. INTRODUCTION

High-carbohydrate diets are associated with a number of health risks like obesity and type 2 diabetes. A diet is considered high-carb when more than 60% of its calories come from carbohydrates. This happens because, over time, the body becomes more resistant to insulin,

leading to consistently high blood sugar levels after meals. To compensate, the pancreas produces extra insulin to restore normal blood sugar levels. It is also associated with tumorigenesis as chronic hyperinsulinemia is more likely to promote cell proliferation via insulin receptor signaling pathways (Figure 2). While insulin is not carcinogenic, it acts as a mitogen by inducing cell proliferation and inhibiting apoptosis, thereby functioning as a growth factor. When insulin binds to an insulin receptor (IR) at the cell membrane, tyrosine kinases phosphorylate the amino acid tyrosine present in the receptor subunit, triggering 2 separate signal transduction pathways. The phosphoinositide 3-kinase (PI3K) pathway is responsible for the metabolic effects of insulin on the cell, such as the uptake of glucose by fat and muscle cells through GLUT- 4 (glucose-transporter type 4) channels. On another hand, the mitogen-activated protein kinase (MAPK) pathway involves a cascade of activated proteins that ultimately affect cell proliferation/survival, as well as cell migration/adhesion.[4] Similarly, such a diet increases IGF-I (insulin- like growth factor type 1) levels, which are polypeptide chains that bind to IGF-IR (IGF-1 receptors). The MAPK and PI3K pathways are activated again here, with insulin also able to bind to this receptor, albeit with lower affinity. Furthermore, increased insulin levels can lead to an increase in IGF-I production.[3] For example, Insulin can, directly or indirectly, affect the activity of IGFBPs (IGF binding proteins) – six proteins that can either enhance or suppress the expression, the binding affinities, and activities of IGFs.[2] Incidentally, when cells become insulin-resistant, the PI3K pathway is suppressed; however, the MAPK pathway signals continue to transduce normally. Thus, when the pancreas increases production of insulin in an effort to maintain glucose homeostasis, the MAPK pathway is upregulated, enhancing its mitogenic responses.[4] This overactivation, along with other IGF-I mediated activities like the activation of glycolytic enzymes, further increases the occurrence of the Warburg effect, a cancer hallmark where cancer cells predominantly acquire energy from aerobic glycolysis. This increases the risk of tumor development, because the cells are now in a metabolic state that is favorable for tumor growth.[5]

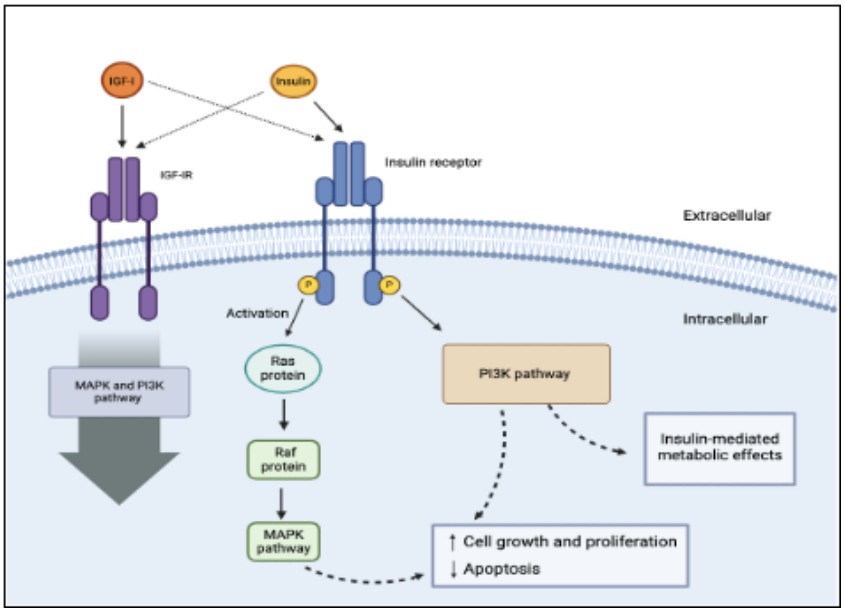

Figure 2. Illustration of the key signaling pathways involved in tumorigenesis. The binding of Insulin/IGF-1 onto IGF-IR/IR triggers a cascade of proteins involved in the MAPK and PI3K pathway. Created with BioRender.com.

Gynecological cancers (GCs) are defined as cancers that start in the female reproductive organs, located within the pelvis (Figure 3). In the context of GCs that are sex-hormone dependent, like ovarian and uterine, hyperinsulinemia plays an additional role by decreasing sex-hormone binding globulin levels and increasing the synthesis of sex-hormones. This indirectly results in free, unbound sex hormones like estrogen (a human carcinogen) to increase the rate of cell division in the gonads.[6]

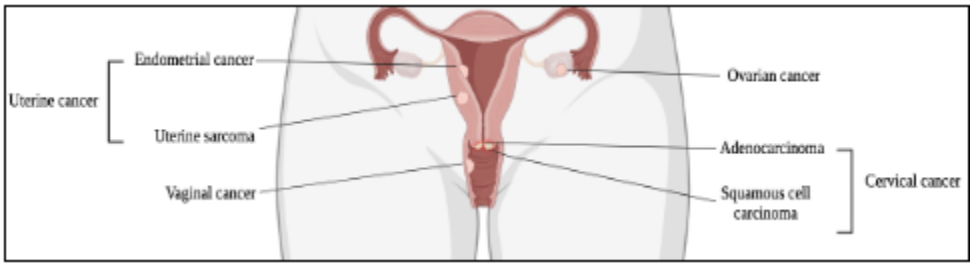

Figure 3. Illustration of the primary types of GCs, including ovarian, uterine, vaginal, and cervical cancer. Created with BioRender.com.

Type of GC	Cervical	Ovarian	Uterine	Vaginal
Symptoms	Vaginal bleeding and pain, heavier periods and pungent vaginal discharges, painful bowel movements and urination.	Similar to that cervical, along with pain in the abdominal organs, increase in the frequency of urination, gastrointestinal issues such as constipation and bloating, lack of appetite, and a lump in the pelvic region.	Similar to that of cervical cancer, with the addition of a lump in the vagina and weight loss.	Similar to that of uterine cancer.
Risk factors	HPV, HIV, immunosuppressant drugs, prolonged use of oral contraceptives, obesity, smoking.	Aging, obesity, fertility drugs, endometriosis on the ovaries, family history of ovarian, breast and prostate cancer.	Obesity, type 2 diabetes, aging, history with either ovarian or breast cancer, estrogen dominance due to PCOS or hormone replacement therapy, radiation therapy in the pelvic area, Tamoxifen, never being pregnant, history of retinoblastoma, family history of endometrial cancer, and endometrial hyperplasia.	Aging, HPV and HIV infection, history of cervical cancer, and irritation in the vagina.
Preventions	HPV vaccine, by screening for high-risk HPV infections and regular Pap tests, lifestyle changes.	Surgically removing the ovaries, using birth control pills, genetic testing, lifestyle changes.	Use of hormonal contraceptive and lifestyle changes.	HPV vaccine, lifestyle changes.
Treatments	Surgery, Radiation therapy, chemotherapy, targeted therapy, immunotherapy.	Surgery, chemotherapy, targeted therapy.	Surgery, radiation therapy, chemotherapy, hormone therapy, targeted therapy, immunotherapy.	Surgery, radiation therapy, topical chemotherapy.

Table 1. Symptoms, risk factors, preventions and treatments for the primary types of GCs. Data was collected from references 7-9.

A meta-analysis is the quantitative synthesis of studies that share a similar research question. It can help reconcile conflicting studies while increasing the sample size and statistical power of a study. With respect to the current study, a meta-analysis will help determine whether such a diet truly acts as a risk factor for GCs as some epidemiological studies support this conclusion, while others do not. In this meta-analysis, high-carbohydrate diets will be quantified by measuring the average dietary glycemic index (GI) and glycemic load (GL). GI is the measure of how quickly a

food can make one's blood glucose levels rise. It is a number ranging from 0 to 100, where 100 is the value assigned to pure glucose/white bread. GL rates food based on not only the glycemic index, but also the mass of carbohydrates per serving, giving a more accurate idea of the effect of a particular food on blood sugar levels. Frequent consumption of foods with high GI/GL is positively correlated to the concentration of insulin in the blood. Hence, the exposures are defined as the GI and GL while the outcome is the incidence of GC in women. This is a pertinent research topic given the recent rise in global cancer cases and their correlation with the prevalence of processed, fast-food culture. Dietary choices, among other environmental factors, undoubtedly play a key role in the development of certain cancers. Here, studies encompassing any type of gynecological cancer (GC) will be included in the analysis to holistically assess the risk of such a diet on women's health. Furthermore, there are multiple similarities among the GCs, suggesting similar biological mechanisms (Table 1). Therefore, previously conducted case-control and cohort studies will be compiled to test the hypothesis that the risk of developing gynecological cancer (GC) is positively associated with high glycemic index (GI) and glycemic load (GL), as formulated based on the background information described earlier.

II. METHODS

Literature search

A search strategy involving multiple databases (Google Scholar, PubMed, EMBASE, MDPI and Cochrane Library) and the keywords used were recorded. Screening of papers was done by reading the abstracts of studies with the most relevant titles and classifying the papers as either case-control or prospective cohort studies. Duplicate studies found from two or more different databases were removed. References from existing reviews and meta-analysis papers were also explored. Following this, relevant information, like the effect sizes, from the full texts was extracted and stored on an excel spreadsheet based on whether it met the inclusion and exclusion criteria, as seen in Table 2 and 3. These criteria required a quantitative measure of the effect of GI/GL on the risk of developing any of the four GCs highlighted in Table 1, without specifying ethnicity, age, or the publication date.

Data collection

The effect sizes were taken in the form of the odds ratio (OR) from each study. The ratio suggests the odds of an outcome (GCs) occurring given a specific exposure (GI/GL), as opposed to the odds of it not occurring given the lack of that exposure. The ratio should be either greater than 1 (suggesting that it is a risk factor) or less than 1 (suggesting that it is a protective factor) if the exposure is indeed related to the outcome. The 95% confidence intervals (CI), a range of values in which the estimate for the OR in a sample is 95% likely to fall in if the test was repeated, was also logged since if CI spans 1, it is likely that the association is not statistically significant. Studies that used other effect sizes like HR (hazard's ratio) and RR (risk ratio) had their OR estimated from those ratios. Since the outcome studied here occurs in less than 10% of the unexposed population, the OR provides a reasonable approximation of the HR and RR. The OR values were taken from each study's comparison between the lowest (control) and highest quantile or quintile of GI and GL. Potential confounding factors were noted based on the "Risk factors" row in Table 1. The factors each study adjusted for were also recorded in the spreadsheet. Notably, all the studies included adjusted for age and total energy intake per day, while one study (Folsom et al.) collected data from only post-menopausal women. The form

of data collection in most of the epidemiological studies collected were questionnaires concerning a woman's diet and lifestyle.

Keywords	Study	Exposure	Outcome	Confounding factors	OR	CI	Cases	Controls
"Glycemic and endometrial cancer" in google scholar, 12th result	Silvera et al. (2005)	GI	Endometrial cancer	Adjusted for age, BMI, menopausal status, smoking, alcohol, use of hormone replacement therapy, use of oral contraceptives, parity, age at menarche, participation in vigorous physical activity, intake of energy, study centre and treatment allocation.	1.47	0.90-2.41	110	1,41,333
		GL			1.36	1.01-1.84	112	1,40,438
"Glycemic and ovarian cancer" in google scholar, 4th result	Silvera et al. (2007)	GI	Ovarian cancer	Adjusted for age, BMI, alcohol, use of hormone replacement therapy, use of oral contraceptives, parity, age at menarche, menopausal status at baseline, total energy intake, participation in vigorous physical activity, energy-adjusted total fibre intake, study centre and treatment allocation.	1.27	0.65-2.47	58	2,00,641
		GL			1.72	1.13-2.62	68	1,99,385
"Glycemic and endometrial cancer" in google scholar, 3rd result	Folsom et al. (2003)	GI	Endometrial cancer	Adjusted for age, energy, BMI, waist–hip ratio, diabetes, hypertension, alcohol, age at menarche, age at menopause, hormone replacement, smoking.	1.05	0.77-1.43	93	Not mentioned
		GL			1.24	0.9-1.72	91	Not mentioned
"Glycemic and endometrial cancer" in google scholar, 5th result	Cust et al. (2007)	GI	Endometrial cancer	Adjusted for age, center, total energy intake (residual method), body mass index, height, physical activity level, and smoking status.	1.04	0.84-1.28	175	4,72,341
		GL			1.15	0.94-1.41	200	4,74,813
"Glycemic and endometrial cancer" in google scholar, 6th result	Coleman et al. (2013)	GI	Endometrial cancer	Adjusted for age at completion of the Diet History Questionnaire (years), BMI, age at menarche, age at menopause, race/ethnicity, oral contraceptive use, and energy intake.	0.94	0.70-1.26	89	8939
		GL			0.63	0.46-0.84	73	8955
"Glycemic and endometrial cancer" in google scholar, 7th result	Larson et al (2006)	GI	Endometrial cancer	Adjusted for age and total energy instake.*	1	0.77-1.30	123	1,88,999
		GL			1.15	0.88-1.51	144	1,86,821

Table 2. Data extracted from the cohort studies, involving the keywords used, study name, exposure, outcome, confounding variables, OR, CI, cases and controls. Data was collected from references 15-28.

Conducting the meta-analysis

The statistical analysis was performed using JASP (JASP Team, 2023)[10], a user-friendly software part of an open-source project supported by the University of Amsterdam. It features various meta-analytic tests relevant to this paper while providing graphical representations of the results like forest and funnel plots. The data from Tables 3 and 4 were imported into the software's dataset after further processing of the extracted data. This included taking the natural logarithm of the OR values, along with calculating the standard errors (SE) for each study by substituting the 95% confidence intervals into the formula below:[11]

$$SE = \frac{\ln(Upper\ CI) - \ln(Lower\ CI)}{2 \times 1.96}$$

These transformations were done to ensure the data was compatible with JASP's classical Meta-Analysis module. As a result, the vertical line of no effect is now shifted to 0 instead of 1 on the x-axis.

Keywords	Study	Exposure	Outcome	Confounding factors	OR	CI	Cases	Controls
"Glycemic and endometrial cancer" in pubmed, 4th result	Brenner et al. (2015)	GL	Endometrial cancer	Adjusted for age at reference, parity, hormone therapy and menopausal status, rural residential status (vs. urban), weight at reference, waist circumference, co-morbidities (Type II diabetes, hypertension, thrombosis, pulmonary embolism, myocardial infarction, angina pectoris, stroke, high cholesterol), fiber intake and total caloric intake.	0.87	0.52-1.46	129	245
"Glycemic and endometrial cancer" in pubmed, 5th result	Nagle et al. (2012)	GI	Endometrial cancer	Adjusted for age (years), age at menarche, educational level, BMI last year, smoking status, parity, OC use, hormone replacement therapy (HRT) use, menopausal status, history of diabetes, physical activity level and energy (kJ/day).	1.43	1.11-1.83	348	349
		GL			1.15	0.90-1.48	332	351
"Glycemic and gynecological cancer" in google scholar, 4th result	Galeone et al. (2013)	GI	Endometrial cancer	Adjusted for year at interview, years of education, menopausal status and age at menopause, age at menarche, parity, OC and HRT use, history of hypertension and diabetes, noncarbohydrate energy intake, alcohol consumption, smoking habit, BMI, and occupational physical activity	1.03	0.67-1.58	85	181
		GL			1.01	0.64-1.61	105	182
"Glycemic and gynecological cancer" in google scholar, 2nd result	Augustin et al. (2003)	GI	Endometrial cancer	Adjusted for age, study centre, education, BMI, history of diabetes and hypertension, HRT and total energy intake.	1.9	1.25-2.91	108	149
		GL			1.1	0.6–2.03	122	149
"Glycemic and gynecological cancer" in google scholar, 9th result	Nagle et al. (2010)	GI	Ovarian cancer	Adjusted for age (years), parity, OC use, level of postschool education, energy intake, menopausal status, and BMI.	1.09	0.87-1.36	350	345
		GL			1.24	1.00-1.55	362	333
"Glycemic and gynecological cancer" in google scholar, 10th result	Augustin et al. (2003)	GI	Ovarian cancer	Adjusted for quinquennia of age, study center, years of education, occupational physical activity, history of diabetes, oral contraceptive use, parity, menopausal status, number of daily meals, intakes of fiber, alcohol and total energy intake.	1.65	1.30-2.09	1031	2411
		GL			1.65	1.30-2.09	1031	2411
"Glycemic and gynecological cancers" in google scholar, 15th result	Sreeja et al. (2020)	GI	Cervical cancer	Adjusted for age (years), energy intake (kcal/day), marital status, education level, physical activity, smoking status, history of pregnancy, oral contraceptive use, hospitals and family history of cervical cancer.	0.74	0.21-2.66	33	133
		GL			0.67	0.20-2.33	28	133
"Glycemic and ovarian cancer" in google scholar, 17th result	Qin et al. (2015)	GI	Ovarian cancer	Adjusted for age, education, region, total energy intake, parity, oral contraceptive use, menopause status, tubal ligation, and family history of breast/ovarian cancer.	1.03	0.70-1.50	406	609
		GL			1.35	0.93-1.97	406	609

Table 3. Data extracted from the case-control studies, involving the keywords used, study name, exposure, outcome, confounding variables, OR, CI, cases and controls. Data was collected from references 15-28.

Additionally, a random effects (RE) model using the restricted maximum likelihood method was adopted to calculate the pooled effect size and CI. In comparison to the fixed effects model, the RE model allows the results to be generalized to a larger population as it also considers the effect of heterogeneity on the differences observed between each study's OR, despite making it a test of lower power. Moreover, the Wald test is used to determine whether the exposure has a statistically significant effect on the outcome based on the p-value. If it is less than 0.05, then the null hypothesis stating that the OR is 1 (there is no effect) is rejected. This is necessary as a positive pooled OR alone does not confirm the association.[12] To measure the heterogeneity between all the studies, that is, the proportion of genuine variability in the OR that is due to the differences in sample groups, methodologies, or other such parameters that does not include chance, the Cochrane Q test is used. This test is based on the chi-squared statistic and produces an I^2 statistic that indicates the magnitude of heterogeneity. If this value is greater than 75%, then further sub-group analysis will be done. Lastly, the tendency to publish only significant results – publication bias – will be tested using visual inspection of a funnel plot and Egger's test. The null hypothesis for this test is that there is likely no publication bias, and if the p-value is less than 0.05, the null hypothesis is rejected.[13-14]

III. RESULTS

The results of the tests mentioned above were generated as tables in JASP. The forest plots and funnel plots were displayed separately for GI and GL, with the cases and controls from both case-control and cohort studies grouped together. There was no publication bias as the p-values from the Egger's test for GI and GL were 0.951 and 0.345 respectively, with the funnel plot being mostly symmetrical. The I^2 statistic for GI and GL were 49.1% and 62.5% respectively, suggesting moderate heterogeneity among all the studies used in the analysis.

The summarized results of the meta-analysis can be observed in Figures 4 and 5. The square for each study represents its effect size, and the size of each square is proportional to that study's weight. A larger square suggests that the study has more weight due its narrow CI and hence higher precision and consistency in results. This is usually due to a large sample size. The line of no effect is a vertical line in the plot that represents the value at which there is no difference between the case group and the non-cases/control group, implying that there is no association between the exposure and the outcome. As the effect size in the plots is represented by logOR, the vertical line stands at 0. The diamond represents the overall effect size, in this case the OR, and the pooled 95% CI.

The estimated pooled odds ratio for the effect of glycemic index on GC risk from both case-control and cohort studies was 1.19, with the upper bound of the 95% confidence interval being 1.04 and the lower bound being 1.35 (Figure 4). The Wald test revealed a p-value of 0.009, further rejecting the null hypothesis and supporting the fact that the pooled OR is not 1. The estimated pooled odds ratio for the effect of glycemic load on GC risk from both case-control and cohort studies was 1.17, with the upper bound of the 95% confidence interval being 1.02 and the lower bound being 1.35 (Figure 5). The p-value from the Wald test was 0.029, rejecting the null hypothesis.

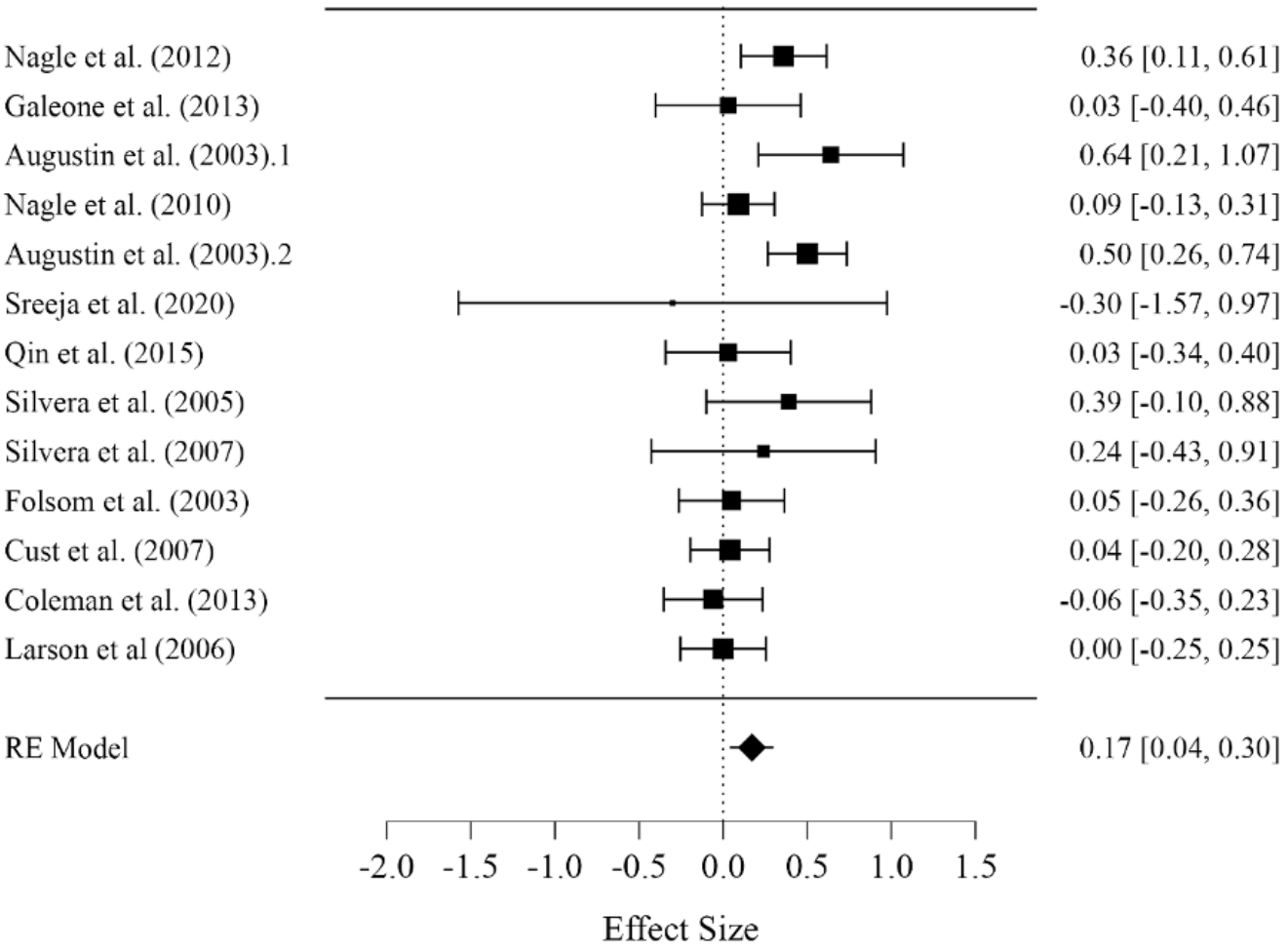

Figure 4. Forest plot with the effect sizes and confidence interval of each study investigating the effect of glycemic index on gynecological cancer risk, along with the pooled odds ratio. The effect size scale is based on the logarithm of the odds ratio.

Thus, the alternate hypothesis, stating that there is a statistically significant association between dietary GI/GL and gynecological cancer risk has been supported. It can be concluded that since the pooled odds ratios and confidence intervals for both exposure variables do not include the value 1, and the p-values are less than 0.05, a zero difference in GC risk between those who consume excessive carbohydrates and those with a standard carbohydrate intake is unlikely. Furthermore, the diamond in the forest plot lies on the right-hand side of the line of no effect, suggesting high GI/GL is a risk factor for the development of GCs.

IV. DISCUSSION

The results of the meta-analysis suggest that there is a positive association between dietary GI/GL and the risk of developing gynecological cancer in women. The explanation for this links back to the mechanisms explained in the introduction, wherein high blood sugar levels lead to

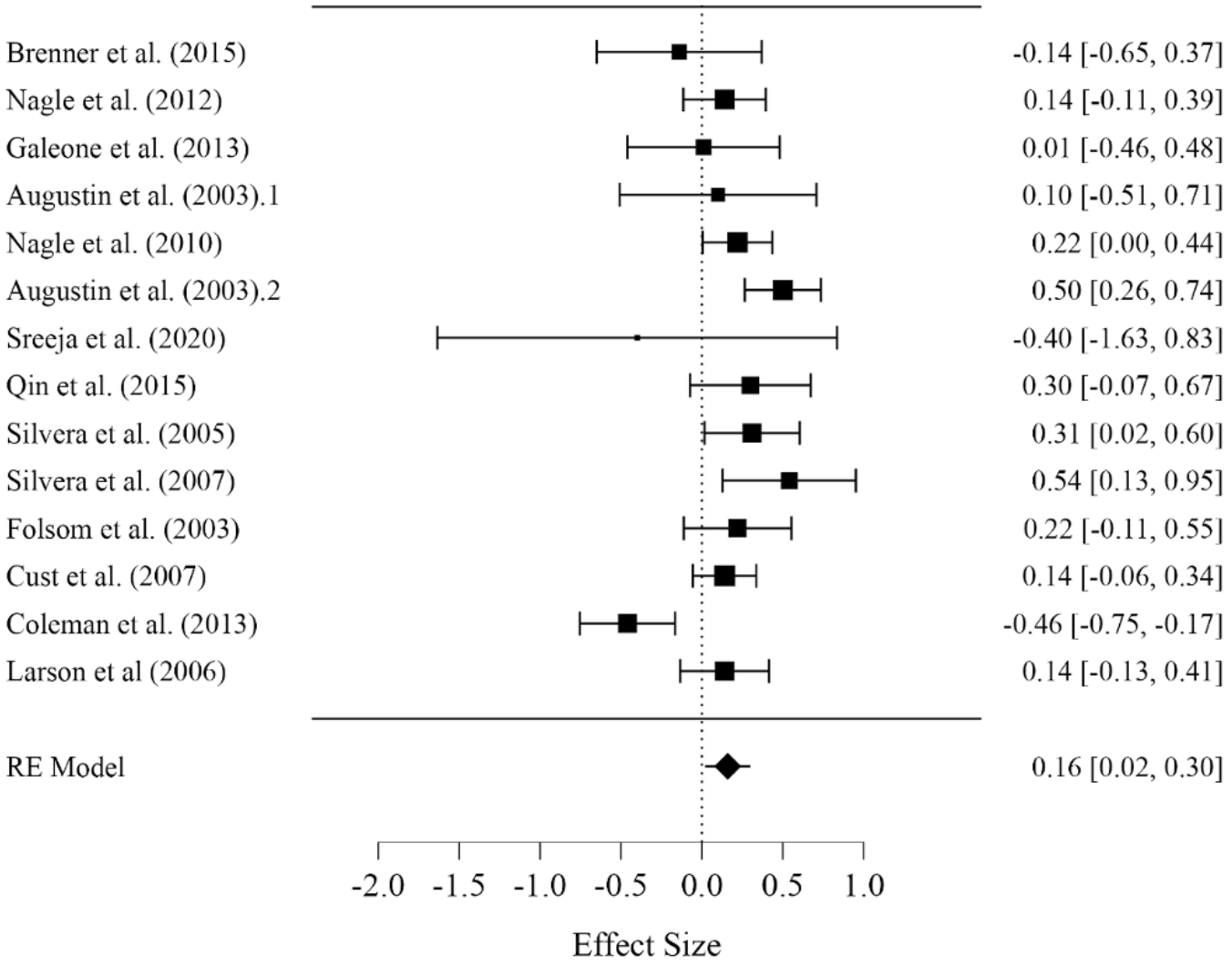

Figure 5. Forest plot with the effect sizes and confidence interval of each study investigating the effect of glycemic load on gynecological cancer risk, along with the pooled odds ratio. The effect size scale is based on the logarithm of the odds ratio.

hyperinsulinemia, which upregulated cell growth and division, and downregulated cell apoptosis, while increasing the bioavailability of free sex hormones. This excess estrogen may, in turn, activate the E6 and E7 oncogenes, promoting cervical cancer[29], or result in the formation of endometrial hyperplasia, as estrogen is responsible for building the endometrial lining by interacting with estrogen receptors. It should be noted that these cellular and molecular explanations are still being studied for further clarity, and that they represent only a few of the ways in which GI/GL may affect GC risk.

These results are partially consistent with those from other meta-analysis studies. For example, the Mulholland et al. study reported positive association between high GL, but not high GI, and endometrial cancer risk.[30] This was also concluded in the Turati et al. study, which, at the same time, reported weak associations between high GI/GL and ovarian cancer risk.[31] The preference

for GL over GI arises from the importance of carbohydrate proportion sizes in each dish in affecting blood glucose levels. Interestingly, this disconnection was not reflected in the meta-analysis conducted for this paper, where GI showed a marginally stronger association than GL. Despite this, consuming foods with a lower glycemic index and higher fiber content is still recommended. To elaborate, total dietary fiber intake was found to be negatively associated with endometrial cancer risk in the Chen et al. study, potentially making it a protective factor that counteracts the effects of overconsumption of carbohydrates.[32]

One of the primary strengths of this investigation was the high sample size, resulting from the larger number of studies included in the meta-analysis compared to other studies. This enhanced reliability is reinforced by the high statistical power inherent in each meta-analysis, establishing it as the strongest research design in terms of scientific evidence within the hierarchy of epidemiological studies. Another strength is the lack of publication bias, rendering it unlikely that the effect sizes stated in this paper are overestimated. Lastly, the heterogeneity among the studies included in the analysis was moderate, indicating that it was appropriate to conduct a meta-analysis by grouping them together, as the differences between studies were not substantial enough to prevent meaningful comparison.

On the other hand, the conclusions presented in this paper must be interpreted with caution due to certain limitations, like the dichotomous nature of the exposure variables. The effect sizes extracted from each study included data only from the highest and lowest categories of GI/GL, excluding the effect sizes for moderate dietary GI/GL values. Thus, a more comprehensive conclusion could be reached if a dose-response meta-analysis were conducted to track the trendline between exposure dose (by taking increments of GI/GL values) and gynecological cancer risk, and to mitigate selection bias. The large weightage given to the case-control studies in this paper is also a weakness due to the retrospective nature of this study design. Recall bias is a major limitation in case-control studies, where it becomes a systematic error when participants omit relevant details in their responses or misremember them. Since prospective cohort studies are preferred for their accuracy, a more valid interpretation could be achieved by analyzing the pooled effect sizes separately for case-control and cohort studies. This subgroup analyses could also be conducted for participants with and without obesity, as hyperinsulinemia is more pronounced in those with significant insulin resistance, potentially increasing the effect size for women with obesity. This phenomenon is explored in more detail in the Nagle et al. (2012) study on endometrial cancer.[16] Lastly, the pooled OR values obtained have confidence intervals that are extremely close to the line of no effect. This weakens the association by making it more likely to fail sensitivity checks, which are tests conducted to determine whether the results change significantly when one or more studies are removed.

To conclude, studies like this one play a pertinent role in evidence-based medicine by producing conclusions that are more generalizable and accurate than individual trials. Clinicians may therefore feel comfortable suggesting that their patients at high risk of gynecological cancers revise their dietary lifestyle and monitor their carbohydrate intake. Simultaneously, questions about the effect of high GI/GL on some of the rarer gynecological cancers, such as vaginal and vulvar cancer, should be addressed within the scientific community through further case-control and cohort studies investigating this issue.

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