Effects of Caloric Restriction on Sleep Quality Across Gender in Adult

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1. Introduction

Caloric restriction (CR) has been extensively studied for its potential to promote healthy weight, longevity, and age-related health improvements, though its effects on human sleep quality remain unclear (Hu et al., 2019). Poor sleep affects millions globally, contributing to metabolic problems, heart disease, and cognitive decline (Cappuccio et al., 2010; Grandner et al., 2016). To systematically assess and understand these sleep-related challenges, researchers have developed measurement tools, with the Pittsburgh Sleep Quality Index (PSQI), introduced by Buysse et al. (1989), emerging as a comprehensive and widely-used instrument for examining sleep quality. Therefore, we employed the PSQI as our outcome index to comprehensively assess and quantify sleep quality in this project.

The CALERIE™ (Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy) clinical trial was the first study to focus on the effects of sustained CR in humans (Ravussin et al., 2015). This study revealed that participants successfully maintained a 12% reduction in caloric intake, resulting in a sustained 10% weight loss over two years (Kraus et al., 2019). While the CALERIE trials have provided insights into the physiological and metabolic effects of CR (Redman et al., 2018), further research is needed to specifically address how CR influences sleep quality in different genders.

The purpose of the present research was to examine the effects of a 25% caloric restriction (CR) intervention on sleep quality over a two-year period using data from the CALERIE™ Phase 2 randomized controlled trial. Several hypotheses regarding this association were tested: (1) it was hypothesized that CR would have a significant effect on sleep quality, as measured by the PSQI; (2) gender differences with time were expected, with men and women potentially experiencing different magnitudes of improvement in sleep quality; (3) weight loss was hypothesized to mediate the association between CR and sleep quality. This research aimed to clarify the mechanisms linking CR to sleep patterns and contribute to a better understanding of the broader health implications of structured CR interventions. As shown in Figure 1, we hypothesize that CR impacts sleep quality both directly (Path c) and indirectly via weight change, with weight loss serving as a mediator (Paths A and B).

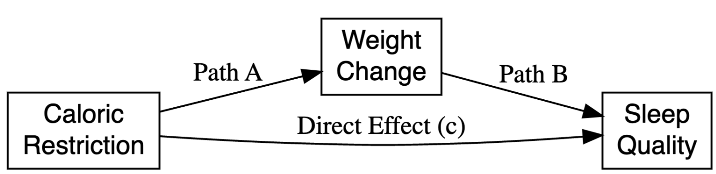

Figure 1. DAG of CR, PSQI and weight change

2. Data Description

The analysis used publicly available CALERIE™ Phase 2 data, a collection of datasets from a two-year randomized clinical trial designed to investigate the effects of caloric restriction (CR) on various physiological and psychological outcomes in humans. This trial involved 220 healthy volunteers randomized in a 2:1 ratio to either a 25% caloric restriction (CR) group or an ad libitum (AL) diet group. To address the research questions, multiple datasets were merged using subject ID to ensure a comprehensive view of the variables of interest. Key datasets included: PSQI.CSV, which provides Global PSQI Scores for sleep quality across three timepoints (baseline, 12 months, and 24 months); SUBJECT1.CSV, which includes demographic and baseline variables such as gender, age, and BMI; IVRSRAND.CSV, which details treatment group allocation; and CLWTVIS.CSV, which reports changes in weight over time.

The outcome is the global PSQI score, which quantifies sleep quality and ranges from 0 to 21, with lower scores indicating better sleep quality. The exposure is the treatment group (CR vs. AL). Outcome and exposure are the same for all three research questions. Additional covariates include gender (male/female), age (continuous, 20–50 years), BMI (categorized as 22–24.9 or 25–27.9), and weight change (kg, continuous). Since this dataset has rich longitudinal design and robust measurement of physiological and psychological variables, is highly appropriate for addressing the research question on the impact of caloric restriction on sleep quality over time, while also considering the influence of key demographic and physiological covariates.

3. Methods

To address these three research questions, we used a variety of statistical methods to address the longitudinal and mediation characteristics of the dataset. The analysis was conducted in three stages, with each stage focusing on a specific research question. A descriptive table was first created to show the distribution of all variables in the dataset we merged, followed by primary analyses using longitudinal (GEE) and traditional mediation analysis.

3.1 Descriptive Analysis

We created a descriptive table to summarize the demographic and clinical characteristics of participants stratified by treatment group (CR vs. AL) and three time points. Key variables included gender, BMI categories, age, Global PSQI scores, and weight changes. The table (Table 1) shows that this study population was well-balanced at baseline across treatment groups, with similar distributions for gender, BMI categories, and age. Randomization at beginning, effectively minimized potential confounding from demographic factors. Therefore, these factors are unlikely to significantly influence our subsequent analyses.

Descriptive Statistics Stratified by Time and Treatment

	0		12		24		Overall	
	Caloric Restriction (N=143)	Control (N=72)	Caloric Restriction (N=128)	Control (N=67)	Caloric Restriction (N=119)	Control (N=67)	Caloric Restriction (N=390)	Control (N=206)
Gender								
Female	99 (69.2%)	51 (70.8%)	89 (69.5%)	47 (70.1%)	82 (68.9%)	48 (71.6%)	270 (69.2%)	146 (70.9%)
Male	44 (30.8%)	21 (29.2%)	39 (30.5%)	20 (29.9%)	37 (31.1%)	19 (28.4%)	120 (30.8%)	60 (29.1%)
BMI								
22-24.9	68 (47.6%)	36 (50.0%)	60 (46.9%)	32 (47.8%)	56 (47.1%)	34 (50.7%)	184 (47.2%)	102 (49.5%)
25-27.9	75 (52.4%)	36 (50.0%)	68 (53.1%)	35 (52.2%)	63 (52.9%)	33 (49.3%)	206 (52.8%)	104 (50.5%)
Age (years)								
Mean (SD)	38.0 (7.34)	37.8 (6.93)	38.3 (7.23)	37.9 (6.99)	38.5 (7.32)	38.1 (7.02)	38.2 (7.28)	37.9 (6.95)
Median [Min, Max]	40.1 [20.7, 50.8]	38.0 [23.0, 50.6]	40.6 [20.7, 50.8]	38.1 [23.0, 50.6]	40.8 [20.7, 50.8]	38.7 [23.0, 50.6]	40.6 [20.7, 50.8]	38.2 [23.0, 50.6]
Global PSQI score								
Mean (SD)	3.85 (2.67)	3.44 (2.23)	3.89 (2.56)	4.34 (3.03)	4.07 (2.19)	4.33 (2.93)	3.93 (2.49)	4.02 (2.76)
Median [Min, Max]	3.00 [0, 14.0]	3.00 [0, 11.0]	3.00 [0, 14.0]	4.00 [0, 12.0]	4.00 [0, 11.0]	3.00 [0, 15.0]	3.00 [0, 14.0]	3.00 [0, 15.0]
Change in Weight (kg)								
Mean (SD)	0.0558 (0.326)	-0.0324 (0.334)	-8.31 (3.11)	-0.424 (2.95)	-7.54 (3.47)	0.444 (4.20)	-5.01 (4.67)	-0.00464 (2.94)
Median [Min, Max]	0.0571 [-0.942, 1.41]	-0.00417 [-0.867, 0.824]	-8.44 [-17.6, -0.252]	0.158 [-9.77, 5.93]	-7.65 [-17.1, 2.34]	0.683 [-8.42, 10.4]	-5.74 [-17.6, 2.34]	0.0250 [-9.77, 10.4]

Table 1. Descriptive table for variables and covariables

3.2 Stage 1: Main Effects of Caloric Restriction on Sleep Quality over The Two-year Period

We used the Generalized Estimating Equations (GEE) model with an exchangeable correlation structure to evaluate the main effect of caloric restriction (CR) on sleep quality over the two-year period. The Global PSQI score was used as the dependent variable, while treatment group (CR vs. AL) and time were included as independent variables. An interaction term between treatment group and time was added to determine whether the effect of CR on sleep quality changed over time. We intentionally designed a concise model with an interaction term between treatment group and time so that we could assess whether the effect of caloric restriction on sleep quality changed dynamically over study time. Given the robustness of the baseline randomization, we intentionally omitted additional covariates to allow for a more direct and accurate test of the relationship between caloric restriction and sleep quality. In addition, the GEE model was chosen since it accounts for the correlation between repeated measures within individuals over time for individual participants. This approach allowed us to capture the time-varying effects of caloric restriction on sleep quality, thereby providing insight into potential longitudinal changes.

3.3 Stage 2: Gender as a Modifier

To investigate whether gender modified the effect of CR on sleep quality, we extended the GEE model from stage 1 by including interaction terms between treatment group, time, and gender. While the initial randomization process minimizes potential gender-related confounding, we remain interested in understanding whether gender might influence the CR effect on sleep quality over time.

We want to use different interaction term:

treatment_group × gender: To evaluate whether the overall effect of CR differs between men and women.

treatment_group × time × gender: To assess whether the direction of CR's effects on sleep quality changes over time for men and women.

We chose to continue using the GEE model as a natural extension of our previous analyses in order to comprehensively investigate the potential moderating role of gender between caloric restriction and sleep quality.

3.4 Stage 3: Traditional Mediation Analysis with Weight Change as Mediator

Traditional mediation analysis and the Sobel test were applied to evaluate the indirect effects of CR on sleep quality via weight change. Additionally, the effects for males and females to explore potential gender-specific differences in the mediation process are also analyzed.

Baron and Kenny Three-Step Method: This approach examines the relationship between CR, weight change, and sleep quality through five pathways. Path A evaluates the effect of CR on weight change, hypothesizing significant reductions in weight; Path B assesses the impact of weight change on sleep quality; and Path C measures the total effect of CR on sleep quality without considering weight change. The direct effect represents CR's impact on sleep quality independent of weight, while the indirect effect, calculated as the product of Paths A and B, quantifies the portion mediated by weight change.

Sobel Test: To formally test the statistical significance of the indirect path, the Sobel test is implied.

$$Z = \frac{a \cdot b}{\sqrt{b^2 \cdot SE(a)^2 + a^2 \cdot SE(b)^2}}$$

Where a and b are the coefficients for Paths A and B, SE(a) and SE(b) are the standard errors for the respective coefficients. A significant Sobel test indicates that weight change mediates the relationship between CR and sleep quality.

Gender-Stratified Mediation Analysis: To explore gender-specific mediation effects, we conducted separate analyses for males and females, estimating Path A, Path B, and the Sobel test for each group. This allowed us to evaluate whether the pathways linking CR, weight change, and sleep quality are modified by gender.

4. Results

As shown in Table 2, the coefficient for the interaction term between time and treatment group (CR) is -0.027 with a standard error of 0.016. This negative coefficient indicates that the improvement in sleep quality (lower PSQI score) over time was slightly larger in the caloric restriction (CR) group compared to the ad libitum (AL) group. However, there is not significant evidence ($p=0.084>0.05$) to suggest that the CR group experienced a greater improvement in sleep quality over time compared to the AL group. Therefore, we fail to reject the null hypothesis that caloric restriction (CR) has no effect on the change in sleep quality over the two-year intervention period compared to the ad libitum (AL) group.

Summary of GEE Model Results

Term	Estimate	Std. Error	Wald Statistic	p−value
Intercept	3.596	0.271	175.94	0.000
Treatment = AL	0.238	0.340	0.49	0.484
Time	0.036	0.013	7.03	0.008
Treatment = AL:Time	−0.027	0.016	2.98	0.084

Table 2: Result for Question 1

As shown in Table 3, The coefficient for the interaction between CR and male gender ($\beta = 1.095$) indicates that males in the CR group had slightly higher PSQI scores (worse sleep quality) at baseline compared to females in the CR group, However, with a p-value of $0.118 > 0.05$, this difference is not statistically significant. The coefficient for the three-way interaction term ($\beta = -0.022$) suggests that the effect of caloric restriction (CR) on changes in sleep quality over time results in a slightly smaller reduction in PSQI scores for males compared to females. However, with a p-value of $0.470>0.05$, this difference is not statistically significant. Based on these results, we fail to reject the null hypothesis that gender does not modify the effect of caloric restriction on sleep quality over time. These findings suggest that the relationship between CR, time, and sleep quality (as measured by PSQI scores) is not meaningfully different for males and females.

Summary of GEE Model Coefficients

Term	Estimate	Standard Error	Wald Statistic	P−Value
Baseline Sleep Quality (AL, BMI (22−25))	3.781	0.345	120.423	0.000
Effect of CR (Baseline, Female)	−0.088	0.416	0.045	0.832
Effect of Time (AL Group)	0.036	0.018	4.085	0.043
Effect of Male Gender (AL Group)	−0.639	0.518	1.520	0.218
Interaction: CR × Time	−0.020	0.020	1.031	0.310
Interaction: CR × Male Gender	1.095	0.701	2.441	0.118
Interaction: Time × Male Gender	−0.003	0.023	0.015	0.904
Interaction: CR × Time × Male Gender	−0.022	0.030	0.522	0.470

Table 3 : Result for Question 2

The mediation analysis explored the relationship between caloric restriction (CR), weight change, and sleep quality, with results summarized in Table 1 and illustrated in Figures 2–4. The total effect of CR on sleep quality (Path C) was not significant ($\beta = -0.095$, $p = 0.670$), indicating that CR alone does not directly improve sleep quality without accounting for weight change. However, CR had a highly significant effect on weight reduction ($\beta = -5.048$, $p < 0.001$), demonstrating its effectiveness in inducing weight loss over the study period (Path A). Weight change was significantly associated with improved sleep quality (β = 0.070, p = 0.032), suggesting that greater weight loss correlated with lower PSQI scores (Path B).

The Sobel test confirmed a significant indirect effect of CR on sleep quality mediated by weight change (Z = -2.13, p = 0.033), underscoring weight loss as the primary pathway linking CR to improved sleep quality. Gender-stratified analysis revealed notable differences between males and females. In females, the mediation effect was significant (Z = -2.28, p = 0.023), indicating that weight change is a key mechanism linking CR to improved sleep quality in this group. In contrast, in males, the mediation effect was not significant (Z = -0.376, p = 0.707), suggesting that other factors may influence the relationship between CR and sleep quality in this group.

Overall, the mediation analysis revealed that weight change significantly mediated the relationship between caloric restriction (CR) and sleep quality in females, suggesting that CR improves sleep quality primarily through weight reduction. The negative association between weight loss and PSQI scores indicates that as body weight decreases, sleep quality improves. However, this mediation effect was not observed in males, implying that other mechanisms may be responsible for the relationship between CR and sleep quality in this group. These findings highlight the importance of weight change as a key mediator in females, while pointing to potential gender-specific differences in how CR impacts sleep quality.

Effect	Estimate	Std. Error	p-value	Significance
Total Effect	3.1618	0.6077	0.466	Not Significant
Path A	-7.007	0.3826	<2e-16	Highly Significant
Path B	0.0576	0.0239	0.0163	Significant
Sobel Test (Overall)	-2.39		0.0169	Significant
Sobel Test (Female)	-2.34		0.019	Significant
Sobel Test (Male)	-0.587		0.557	Not Significant

Table 4. Mediation Analysis Summary

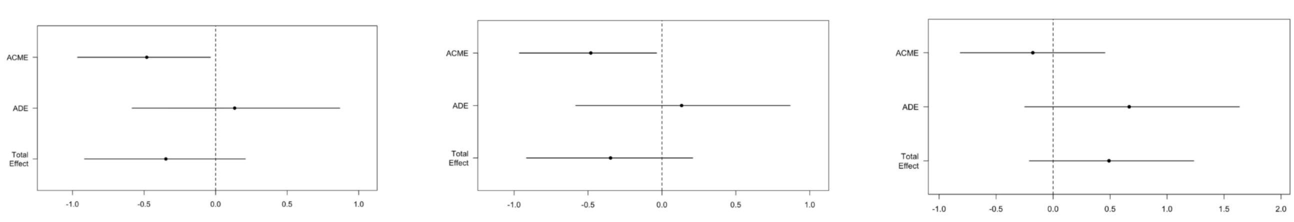

Figure 2. Mediation Analysis: Overall (left), Female (middle), and Male (right)

5. Discussion

This study investigated the effects of caloric restriction (CR) on sleep quality, gender as a potential modifier, and the mediating role of weight change. We found that there was no statistically significant direct effect of CR on sleep quality, as measured by PSQI scores, over the two-year intervention period and gender also did not significantly modify the relationship between CR and sleep quality. However, mediation analysis revealed that weight change significantly mediated the relationship between CR and sleep quality in women, while no such effect was observed in men.

Some previous studies have reported associations between CR and sleep quality. For example, Cao, Clark, and Aggarwal (2022) mentioned that "most research to date indicates that caloric restriction improves sleep outcomes, including sleep quality." and These findings are not fully concordant with ours, which may be due to differences in focus. Unlike prior studies, our analysis specifically examined time-varying effects, which were not addressed in earlier research. In addition, Spaeth et al. (2014) demonstrated that men and women exhibit distinct caloric intake responses to sleep restriction, with men showing a greater increase in caloric consumption, particularly during late-night hours. This difference may contribute to gender-specific outcomes in weight-related health interventions. Our study aligns with these findings in observing differential gender responses to weight change but contrasts in failing to find a significant modification by gender in the CR-sleep quality relationship. The male subgroup's limited mediation effect could reflect behavioral or metabolic differences highlighted by Spaeth et al., such as variances in late-night caloric intake or hormonal influences.

The longitudinal design and mediation analyses strengthen the persuasiveness of this study but it also has some limitations. First, self-reported sleep quality (PSQI) may have some subjective bias compared to objective measures since it relies on participants' perceptions. Second, the sample sizes for gender-stratified analyses were relatively small, especially for the male subgroup. This may limit statistical power and thus may mask subtle gender-specific mediating effects. Third, unmeasured confounders such as stress, physical activity, and diet may affect the results, thus limiting the precision of causality. Fourth, the results of the study were only available for healthy adults aged 20-50 years, which reduces the generalizability to older populations or those with comorbidities. Lastly, the mediation analysis assumes linearity, which may oversimplify complex biological and behavioral interactions between caloric restriction, weight change, and sleep quality. Therefore, Future studies could incorporate objective measures of sleep and include more diverse populations. Additionally, accounting for potential confounding factors, such as stress, physical activity, and diet, could provide a clearer understanding of the mechanisms linking CR and sleep quality.

References

Andersen, I. G., Holm, J. C., & Homøe, P. (2016). Obstructive sleep apnea in children: the role of tonsil and adenoid treatment. International journal of pediatrics, 2016.

Araghi, M. H., Jagielski, A., Neira, I., Brown, A., Higgs, S., Thomas, G. N., & Taheri, S. (2013). The complex associations among sleep quality, anxiety-depression, and quality of life in patients with extreme obesity. Sleep, 36(12), 1859-1865.

Ballinger, G. A. (2004). Using generalized estimating equations for longitudinal data analysis. Organizational research methods, 7(2), 127-150.

Buysse, D. J., Reynolds, C. F., Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry research, 28(2), 193-213.

Cao, V., Clark, A., & Aggarwal, B. (2022). Dieting Behavior Characterized by Caloric Restriction and Relation to Sleep: A Brief Contemporary Review. International journal of environmental research and public health, 20(1), 276. https://doi.org/10.3390/ijerph20010276.

Cappuccio, F. P., D'Elia, L., Strazzullo, P., & Miller, M. A. (2010). Sleep duration and all-cause mortality: a systematic review and meta-analysis of prospective studies. *Sleep*, *33*(5), 585–592. https://doi.org/10.1093/sleep/33.5.585

Grandner, M. A., Alfonso-Miller, P., Fernandez-Mendoza, J., Shetty, S., Shenoy, S., & Combs, D. (2016). Sleep: important considerations for the prevention of cardiovascular disease. *Current opinion in cardiology*, *31*(5), 551–565. https://doi.org/10.1097/HCO.0000000000000324

Harvie, M. N., Pegington, M., Mattson, M. P., Frystyk, J., Dillon, B., Evans, G., ... & Howell, A. (2011). The effects of intermittent or continuous energy restriction on weight loss and metabolic disease risk markers: a randomized trial in young overweight women. International journal of obesity, 35(5), 714-727.

Hu F. B. (2019). Calorie restriction in an obesogenic environment: reality or fiction?. *The lancet. Diabetes & endocrinology*, *7*(9), 658–659. https://doi.org/10.1016/S2213-8587(19)30196-2

Kraus, W. E., Bhapkar, M., Huffman, K. M., Pieper, C. F., Krupa Das, S., Redman, L. M., Villareal, D. T., Rochon, J., Roberts, S. B., Ravussin, E., Holloszy, J. O., Fontana, L., & CALERIE Investigators (2019). 2 years of calorie restriction and cardiometabolic risk (CALERIE): exploratory outcomes of a multicentre, phase 2, randomised controlled trial. *The lancet. Diabetes & endocrinology*, *7*(9), 673–683. https://doi.org/10.1016/S2213-8587(19)30151-2

Little, R. J., & Rubin, D. B. (2019). Statistical analysis with missing data (Vol. 793). John Wiley & Sons.

Ravussin, E., Redman, L. M., Rochon, J., Das, S. K., Fontana, L., Kraus, W. E., Romashkan, S., Williamson, D. A., Meydani, S. N., Villareal, D. T., Smith, S. R., Stein, R. I., Scott, T. M., Stewart, T. M., Saltzman, E., Klein, S., Bhapkar, M., Martin, C. K., Gilhooly, C. H., Holloszy, J. O., … CALERIE Study Group (2015). A 2-Year Randomized Controlled Trial of Human Caloric Restriction: Feasibility and Effects on Predictors of Health Span and Longevity. *The journals of gerontology. Series A, Biological sciences and medical sciences*, *70*(9), 1097–1104. https://doi.org/10.1093/gerona/glv057

Redman, L. M., Smith, S. R., Burton, J. H., Martin, C. K., Il'yasova, D., & Ravussin, E. (2018). Metabolic Slowing and Reduced Oxidative Damage with Sustained Caloric Restriction Support the Rate of Living and Oxidative Damage Theories of Aging. *Cell metabolism*, *27*(4), 805–815.e4. https://doi.org/10.1016/j.cmet.2018.02.019

Rubin, D. B. (1976). Inference and missing data. Biometrika, 63(3), 581-592.

Spaeth, A. M., Dinges, D. F., & Goel, N. (2014). Sex and race differences in caloric intake during sleep restriction in healthy adults. *The American journal of clinical nutrition*, *100*(2), 559–566. https://doi.org/10.3945/ajcn.114.086579

Tasali, E., Leproult, R., Ehrmann, D. A., & Van Cauter, E. (2008). Slow-wave sleep and the risk of type 2 diabetes in humans. Proceedings of the National Academy of Sciences, 105(3), 1044-1049.

Theorell-Haglöw, J., & Lindberg, E. (2016). Sleep duration and obesity in adults: what are the connections?. Current obesity reports, 5(3), 333-343.

Van Cauter, E., & Knutson, K. L. (2008). Sleep and the epidemic of obesity in children and adults. European journal of endocrinology, 159(suppl 1), S59-S66.

Appendix

The R code and results of the analyzed data are displayed in the following html file.