REVIEW   **OPEN ACCESS**

The Effect of Exercise on Leptin and Adiposity: A Systematic Review

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Abstract
Introduction: Leptin has been characterized as an important regulator of metabolic homeostasis, functioning in the inhibition of food intake and promotion of energy expenditure. Leptin resistance has been implicated in the development of cardiovascular diseases and obesity, and as exercise programs are used as a therapeutic measure for these disorders, it is hypothesized that exercise will decrease concentrations of leptin in the blood.
Methods: A comprehensive literature search of MedLine was conducted from inception to September 2020. Relevant search terms include: Leptin, Obesity, Exercise, Physical activity, BMI, and Adiposity. Eligible randomized control trials (RCTs) include RCTs reporting on the effects of low, moderate or high intensive exercise on leptin concentration. We followed the search strategy based on PRISMA to report our systematic review, and assessed the studies independently and in duplicate for their risk of bias (ROB) using the Cochrane ROB2 tool. Statistical analysis was performed to compare ROB (categorized as "high" or "low/some") in relation to impact factor, number of citations, and number of authors.
Results: Forty-eight studies involving the relationship between physical exercise and leptin met the inclusion criteria. After completing the ROB, the relationships between ROB and impact factor (0.2775, p > 0.6405), citation number (2.059, p > 0.0962), and the number of authors (-5.235, p > 0.5551) were determined.
Discussion: The leptin pathway involves an overactivation of mTOR contributing to the development of obesity, with this pathway being inhibited by physical activity. This corresponds to the findings that thirty-nine studies reported that physical exercise resulted in a statistically significant decrease in leptin levels as compared to the control group. However, the overall evidence was insufficient to suggest a statistically significant relationship between ROB and impact factor, citation number, and the number of authors.
Conclusion: This systematic review indicated an inverse relationship between physical exercise and leptin However, further research is needed to address the varying effects of physical activity on leptin and to define a more concrete relationship between risk of bias and the characteristics of studies in this field.

Keywords: leptin; physical exercise; obesity

Introduction

There is increasing evidence that leptin plays a vital role in the modulation of physiological processes related to individuals struggling with obesity and body weight. As a chemical messenger, leptin is released by adipocytes, and is stored proportionally to the individual's fat levels [1]. Leptin hormones signal the hypothalamus, which is involved in energy maintenance and other metabolic activities in order to facilitate the long-term regulation of food intake, energy, and overall body weight [2]. Leptin inhibits feelings of hunger, therefore earning the title of the "satiety hormone", and ultimately helping to maintain metabolic homeostasis [1].

The relationship between leptin and weight has been readily documented in literature. First, It has been hypothesized that individuals with obesity have excess levels of leptin within their bloodstream, and in turn, become desensitized to leptin, thus developing *leptin resistance* [3]. This resistance causes an insatiable hunger drive, prompting excess eating, thus increasing weight and leptin levels. On the other hand, dieting assists individuals with weight loss, therefore resulting in a reduction in fat tissue and leptin levels [4,5]. This, however, leads to increased appetite as a result, creating barriers to further dieting and weight loss. Occasionally, some individuals may have congenital leptin deficiency, which consequently leads to severe hunger [6].

This would encourage leptin-deficient individuals to incessantly ingest food, serving as a catalyst to obesity.

The effect of physical activity on leptin levels is controversial. Previous research has reported that exercise may reduce leptin levels, or it may have no effect at all [7-9]. As aforementioned, leptin levels and weight are positively correlated, therefore weight loss through exercise may consequently reduce leptin levels. However, there is opposing research suggesting that other modulators of the leptin system, such as cortisol, upregulate leptin in response to stimulators such as exercise [10].

The objective of this study is to first conduct a narrative review to evaluate the effect of physical activity on leptin levels in randomized controlled trials, with change in leptin levels as the primary outcome. Leptin is an important factor in understanding the variability of physical activity interventions. Uncovering the impact of exercise on the leptin system will help inform future clinical decision-making and allow us to better advise individuals struggling with weight loss. This study has additionally completed a systematic review of the quality of studies evaluating the effects of physical activity on leptin. By determining which factors increase bias in randomized control trials of physical activity and leptin, these findings can be used by policy makers and clinicians when deciding which study findings should be implemented into clinical practice.

Methods
Search Strategy

A comprehensive literature search was conducted in the Medline database from inception to September 2020. The search was restricted to the English language. According to the specific syntax of the Medline database, the following search terms were applied: leptin AND obesity AND (exercise OR physical activity), as well as BMI and adiposity. Studies that were not randomized control trials (observational studies, narrative studies, systematic reviews, cohort studies, case reports etc.) were excluded. Further, the references of relevant articles identified by the search were scanned to reveal any other relevant studies. The COVIDENCE tool was then used to compile the studies obtained from the manual search and database, manually removing duplicates in the process. Independently and in duplicate, two authors (R. T. and Z. E.) reviewed all abstracts and titles for inclusion or exclusion. Conflicts were resolved with the help of two third parties (S. F. and H. T.).

Selection Criteria

The following inclusion criteria was used in the article selection process: (1) participants in the intervention and control groups must have their leptin measures recorded at baseline and post-intervention; (2) must include a physical activity intervention (any physical activity intervention which exceeded levels of a sedentary control, ranging from light to vigorous physical activity); (3) must be a randomized

control trial. Studies were similarly excluded if they were: (1) non-human studies (cadaver or animal); (2) non-English studies.

Data Extraction

After completing the full-text review, the two authors (R. T. and Z. E.) independently and in duplicate extracted the following data from the studies: general study characteristics (year of publication, first author name, and journal name), most recent available journal impact factor, number of citations as indicated by Google Scholar, number of authors, dichotomous conflict of interest statement (Y/N), and changes in leptin level (statistically significant decrease/no change/increase). After completion of the extracted forms, a third party (S. F. and H. T.) was once again recruited to resolve any conflicts. All data was extracted using Microsoft Excel.

Risk of Bias

Following data extraction, studies were further assessed by two authors (R. T. and Z. E.) independently and in duplicate for their risk of bias, using the Cochrane ROB2 tool. The following bias domains were examined: (1) bias arising from the randomization process, (2) bias due to deviations from the intended intervention, (3) bias due to missing outcome data, (4) bias in measurement of the outcome, and (5) bias in selection of the reported result. Each bias domain received a score of low risk of bias, some concerns or high risk of bias. Each study was then further given an overall risk of bias score using this same scale. Two third parties (S. F. and H. T.) were consulted when conflicts arose between the two authors. The ROBVIS software was used to visualize these scores.

Statistical Analysis

Statistical analysis regarding the quality of the studies were conducted by comparing overall risk of bias scores in relation to impact factor, number of citations, and number of authors. In order to obtain an adequate sample size for each of the groups, the 48 included studies were divided into two groups, high risk of bias and low/some risk of bias. Comparisons were conducted using two-tailed paired t-tests with a 95% confidence interval via GraphPad PRISM.

Results
Study Selection and Characteristics

Results of the search strategy and selection were summarized in the following PRISMA flow chart seen in figure 1. After duplicates were identified, the search strategy presented 997 articles which contained this systematic review's keywords of interest (leptin, physical activity, obesity etc.) This was further narrowed to 116 articles for full-text analysis, of which forty-eight were identified for extraction and risk of bias analysis. All forty-eight studies examined changes in leptin measures in response to some

form of physical activity intervention, and thus all forty-eight studies were included in the analysis [11-58].

Figure 1. PRISMA flow diagram

Extracted information of the selected studies has been presented in Table 1. As none of the forty-eight studies identified any conflict of interests which may have otherwise interfered with the study quality, this dichotomous outcome was unimportant to the systematic review. Other characteristics, including impact factor, author number and citation number as identified by google scholar largely varied between the different studies and were thus a source of analysis. The primary outcome of changes in leptin levels was measured as a dichotomous variable, with "yes" representing a statistically decrease in leptin levels in the physical activity group as compared to the control, whereas a "no" represented either an increase or no change in leptin levels between groups.

Table 1. Characteristics of the studies included in the systematic review

Study	Impact Factor	Number of Authors	Citations on Google Scholar	Conflict of Interest (Y/N)	Was there a significant decrease in Leptin between the groups?
#912 - Balducci 2010	3.7	12	138	N	Yes
#143 - Sturgeon 2016	5.057	11	5	N	Yes
#921 - AsleMohammadiZadeh 2018	0.693	4	1	N	No
#833 - Cohen 2018	3.67	5	3	N	Yes
#835 - Clarson 2014	1.14	11	4	N	No
#773 - Dundar 2019	1.73	3	2	N	Yes
#803 - deOliveira 2010	2.45	3	0	N	Yes
#200 - SantaMina 2013	1.419	8	12	N	No
#828 - Cooper 2012	6.513	10	7	N	Yes
#678 - McNeil 2015	6.31	6	6	N	Yes
#494 - Gonseth 2014	2.69	7	2	N	Yes
#645 - Morell-Azanza 2019	2.083	7	2	N	Yes
#167 - Sjögren 2012	3.004	10	5	N	Yes
#799 - DekkerNitert 2015	1.644	6	37	N	No
#859 - Brown 2018	3.671	11	8	N	Yes
#238 - Rogers 2013	2.657	10	96	N	Yes
#99 - Tremblay 2019	3.455	14	9	N	Yes
#700 - Markofski 2014	5.236	7	50	N	Yes
#226 - Rosety-Rodriguez 2013	0.566	8	21	N	Yes
#348 - Kim 2019	2.849	4	5	N	Yes
#94 - Turner 2010	6.766	4	29	N	Yes
#353 - Khosravi 2018	1.326	7	0	N	Yes
#81 - vanPoppel 2019	7.518	25	8	N	Yes
#795 - Demark-Wahnefried 2017	5.791	12	6	N	Yes
#907 - Bartlett 2017	5.163	7	13	N	Yes
#257 - Loria-Kohen 2013	6.77	6	5	N	Yes
#995 - Ackel-D'Elia 2014	2.16	9	10	N	Yes
#908 - Barbeau 2003	2.95	8	7	N	No
#672 - Mendham 2014	3.02	4	6	N	Yes
#135 - Swisher 2015	2.86	8	30	N	Yes
#451 - Henning 2018	4.311	12	4	N	No
#914 - Balagopal 2010	3.742	7	14	N	Yes
#941 - Chen 2018	4.32	4	1	N	Yes
#927 - Arikawa 2018	1.76	4	3	N	Yes
#401 - Ihalainen 2018	3.255	8	5	N	Yes
#411 - Huang 2015	3.47	6	5	N	Yes
#664 - Miller 2014	1.94	9	5	N	Yes
#406 - Hvid 2016	2.34	8	10	N	No
#393 - Janjgava 2014	1.826	5	7	N	No
#413 - Hossain 2018	1.734	6	2	N	Yes
#777 - Dorling 2019	4.21	8	0	N	Yes
#727 - Friedenreich 2011	4.8	15	33	N	Yes
#235 - Rokling-Andersen 2007	6.66	8	38	N	Yes
#901 - Beavers 2013	4.19	4	26	N	Yes
#207 - Salas-Salvadó 2019	16.019	36	26	N	Yes
#794 - Demark-Wahnefried 2020	5.145	13	0	N	Yes
#776 - Douglas 2015	3.76	8	10	N	No
#537 - Reseland 2001	6.66	7	26	N	Yes

Study	Impact Factor	Number of Authors	Citations on Google Scholar	Conflict of Interest (Y/N)	Was there a significant decrease in Leptin between the groups?
#912 - Balducci 2010	3.70	12	138	N	Yes
#143 - Sturgeon 2016	5.06	11	5	N	Yes
#921 - AsleMohammadiZadeh 2018	0.69	4	1	N	No
#833 - Cohen 2018	3.67	5	3	N	Yes
#835 - Clarson 2014	1.14	11	4	N	No
#773 - Dundar 2019	1.73	3	2	N	Yes
#803 - deOliveira 2010	2.45	3	0	N	Yes
#200 - SantaMina 2013	1.42	8	12	N	No
#828 - Cooper 2012	6.51	10	7	N	Yes
#678 - McNeil 2015	6.31	6	6	N	Yes
#494 - Gonseth 2014	2.69	7	2	N	Yes
#645 - Morell-Azanza 2019	2.08	7	2	N	Yes
#167 - Sjögren 2012	3.00	10	5	N	Yes
#799 - DekkerNitert 2015	1.64	6	37	N	No
#859 - Brown 2018	3.67	11	8	N	Yes
#238 - Rogers 2013	2.66	10	96	N	Yes
#99 - Tremblay 2019	3.46	14	9	N	Yes
#700 - Markofski 2014	5.24	7	50	N	Yes
#226 - Rosety-Rodriguez 2013	0.57	8	21	N	Yes
#348 - Kim 2019	2.84	4	5	N	Yes
#94 - Turner 2010	6.77	4	29	N	Yes
#353 - Khosravi 2018	1.33	7	0	N	Yes
#81 - vanPoppel 2019	7.52	25	8	N	Yes
#795 - Demark-Wahnefried 2017	5.79	12	6	N	Yes
#907 - Bartlett 2017	5.16	7	13	N	Yes
#257 - Loria-Kohen 2013	6.77	6	5	N	Yes
#995 - Ackel-D'Elia 2014	2.16	9	10	N	Yes
#908 - Barbeau 2003	2.95	8	7	N	No
#672 - Mendham 2014	3.02	4	6	N	Yes
#135 - Swisher 2015	2.86	8	30	N	Yes
#451 - Henning 2018	4.31	12	4	N	No
#914 - Balagopal 2010	3.74	7	14	N	Yes
#941 - Chen 2018	4.32	4	1	N	Yes
#927 - Arikawa 2018	1.76	4	3	N	Yes
#401 - Ihalainen 2018	3.26	8	5	N	Yes
#411 - Huang 2015	3.47	6	5	N	Yes
#664 - Miller 2014	1.94	9	5	N	Yes
#406 - Hvid 2016	2.34	8	10	N	No
#393 - Janjgava 2014	1.83	5	7	N	No
#413 - Hossain 2018	1.73	6	2	N	Yes
#777 - Dorling 2019	4.21	8	0	N	Yes
#727 - Friedenreich 2011	4.80	15	33	N	Yes
#235 - Rokling-Andersen 2007	6.66	8	38	N	Yes
#901 - Beavers 2013	4.19	4	26	N	Yes
#207 - Salas-Salvadó 2019	16.02	36	26	N	Yes
#794 - Demark-Wahnefried 2020	5.14	13	0	N	Yes
#776 - Douglas 2015	3.76	8	10	N	No
#537 - Reseland 2001	6.66	7	26	N	Yes

Risk of Bias

The following bias domains were examined: (1) bias arising from the randomization process, (2) bias due to deviations from the intended intervention, (3) bias due to missing outcome data, (4) bias in measurement of the outcome, and (5) bias in selection of the reported result. There were no concerns of bias with regards to allocation concealment and the randomization process of the 48 included studies. Furthermore, little reporting bias was noted among the included studies, as studies reported all statistics based on protocols and as per hypothesis. With regards to bias arising from deviations from the intended intervention, some studies resulted in moderate to high bias due to a lack of blinding participants, personnel and/or outcome assessors. For instance, in a study assigning participants to a physical intervention group with a regimented exercise schedule versus the control group, the physical intervention group could be more motivated to exercise and result in more exaggerated outcomes beyond the intended measurement. Furthermore, several studies had significant issues with

attrition. Thus, bias was present in the domains of: bias due to deviations from the intended intervention, bias due to missing outcome data, and bias in measurement of the outcome. The ROBVIS software (Figure 2) was used to visualize these scores.
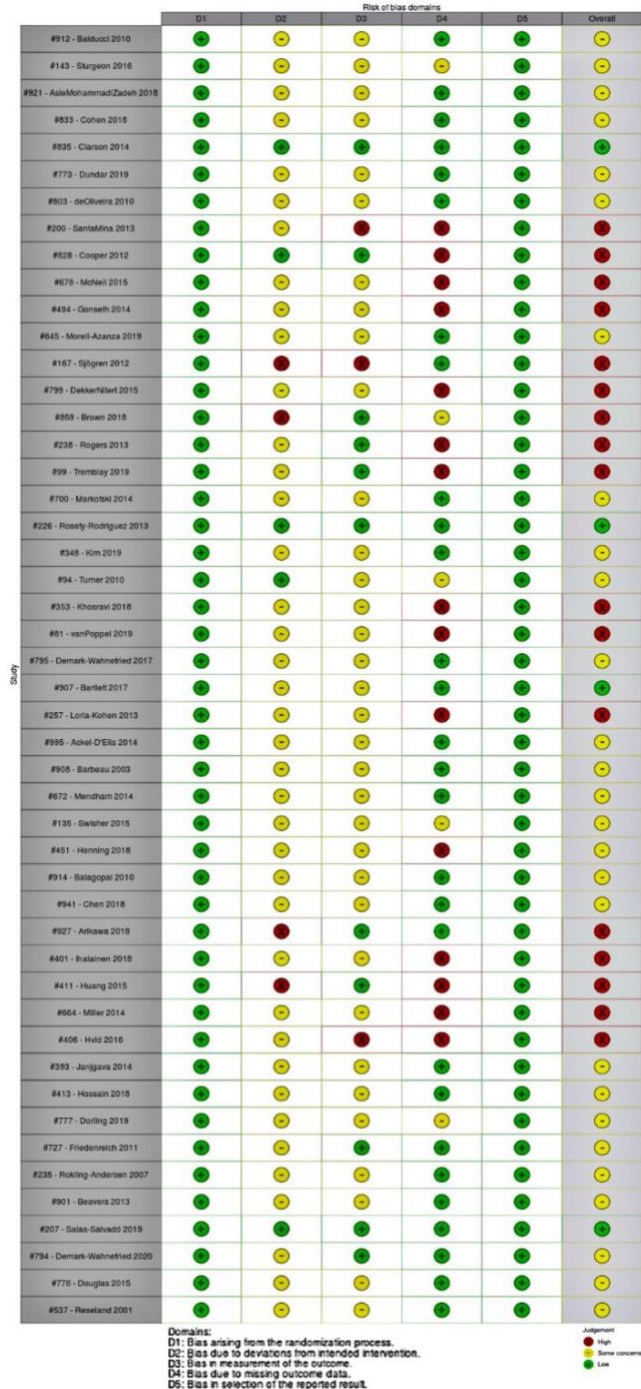

Figure 2. Risk of bias of the studies included in the systematic review using the Cochrane ROB2 tool.

Statistical Analysis

Using GraphPad Prism, results for the three two-tailed paired t-tests were obtained. In terms of the relationship between risk of bias and impact factor, the mean difference between the low/some risk group and high risk group was 0.2775 with a p-value>0.6405. Similarly, the relationships between risk of bias and author number or citation number yielded a mean difference of 2.059 with a p-value>0.0962 and a mean difference of -5.235 with a p-value >0.5551, respectively.

Discussion

Leptin is generally synthesized and secreted by white adipose tissue and acts on the hypothalamus to regulate energy homeostasis. Leptin is also found in the ovary, skeletal muscle, pituitary gland, and some lymphoid tissue. Leptin synthesis is stimulated by estrogen and is inhibited by testosterone. It is increased by glucocorticoids, proinflammatory cytokines and insulin [26]. Conversely, it is decreased by catecholamines. This systematic review found that circulating leptin levels are inversely proportional to the amount of physical activity [15]. Herein, we describe the mechanism of leptin, a hormone with a sexually dimorphic expression, and its effects on obesity.

Leptin mediates its effects by binding to leptin receptors (Figure 3). There are a multitude of alternatively spliced isoforms, but the most common one is the long isoform (LepRb) and is responsible for leptin signalling [38]. When leptin is secreted, it binds to LepRb and subsequently activates Janus kinase 2 (JAK2)/Signal transducer and activator of transcription 3 (STAT3). JAK2 phosphorylates itself and Tyrosine 985 (Tyr985), Tyr1077 and Tyr1138 of LepRb [30]. Activated STAT3 dimers will translocate to the cell nucleus and activate the transcription of target genes that mediate leptin's effect [30]. Protein tyrosine phosphatase 1B inhibits leptin signaling through dephosphorylation of JAK2 and regulates this in a negative feedback manner [29]. Downstream, AMP-activated protein kinase (AMPK) and phosphoinositide 3-kinase (P13K) are activated which eventually phosphorylates the mammalian target of rapamycin (mTOR) [18]. mTOR is a central regulator of cell metabolism, growth, survival and proliferation and thus has many implications in adiposity. Current studies suggest that overactivation of mTOR causes elevated serine phosphorylation of insulin receptor substrate 1 (IRS-1), which leads to impaired insulin signalling to protein kinase B (Akt), contributing to the development of obesity [18].
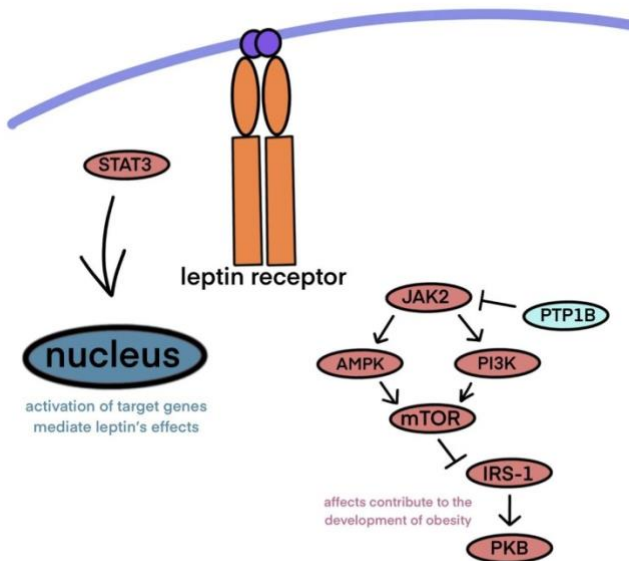
Figure 3. Overview of the leptin signalling pathway illustrating signalling factors involved in mediating leptin's effects.

Our systematic review finds that physical activity inhibits mTOR, which promotes insulin sensitization, promotes fat-loss, and reduces leptin expression and signalling. Of the forty-eight studies, thirty-nine studies reported that physical exercise results in a statistically significant decrease in leptin levels as compared to the control group. This supports the notion that weight loss, which is attributed to reduced fat, results in lower leptin levels. However, nine studies reported that physical exercise can result in no change or even an increase in leptin levels. This may be due to variability in the studies at the current level of statistical power. As a result, this highlights the varying relationship between leptin, physical activity and adiposity, and is an area of research that still needs to be further analyzed.

In terms of the risk of bias analysis, statistical analysis yielded no difference between high risk of bias studies and some/low risk of bias studies in relation to the number of authors, number of citations, journal impact factor and change in leptin ($p > 0.05$). As a result, no conclusions can be made as to whether impact factor, citation number and journal impact factor can be used as a marker of whether a study should be used in clinical practice. However, further research is recommended to validate and explore the relationship between quality of research and variability in measurement of physical interventions. For instance, with a larger sample size of studies, an analysis which includes three categories, low risk, some concerns and high risk, as opposed to two categories can be conducted. The following analysis can yield more accurate information on the relationship between risk of bias and the characteristics examined above.

Conclusion

The narrative review has highlighted that there is an inverse correlation between physical exercise and leptin. Specifically, an overactivation of mTOR contributes to the development of obesity, with this pathway being inhibited by physical activity. By better understanding the relationship between the leptin pathway, physical activity and mTOR, clinicians can implement this learning into practice and aid in curbing society's increasingly prevalent issue of obesity. Further research is needed to address the varying effects of physical activity on leptin and to define a more concrete relationship between risk of bias and the characteristics of studies in this field.

List of Abbreviations
RCT: randomized control trial
ROB: risk of bias
BMI: body mass index
PRISMA: preferred reporting items for systematic reviews and meta-analyses
mTOR: mammalian target of rapamycin
IRS-1: insulin receptor substrate 1
Akt: protein kinase B
P13K: phosphoinositide 3-kinase
LepRb: leptin isoform
JAK2: janus kinase 2
STAT3: signal transducer and activator of transcription 3
Tyr: tyrosine
AMPK: AMP-activated protein kinase

Conflicts of Interest
The authors report no competing conflicts of interest.

Ethics Approval and/or Participant Consent
The study type, a systematic review, does not require ethics approval or participant consent.

Authors' Contributions
RT: made substantial contributions to the design of the study, the collection of data as well as interpretation and analysis of the data, and wrote and revised the manuscript critically.
ZE: made substantial contributions to the design of the study, the collection of data as well as interpretation and analysis of the data, and wrote and revised the manuscript critically.
HT: contributed to resolving conflict in the process of study selection, data extraction and ROB analysis, and revised the manuscript critically.
SF: contributed to resolving conflict in the process of study selection, data extraction and ROB analysis, and revised the manuscript critically.

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