Artificial Sweeteners: Systematic Review with ☸SAIMSARA

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Abstract: The aim of this paper is to systematically review and synthesize the diverse research findings on artificial sweeteners, covering their physiological effects, environmental presence, and implications for human health, to identify key themes, clinical implications, and future research directions. The review utilises 781 studies with 401682 total participants (naïve ΣN). Higher consumption of artificial sweeteners is associated with an increased risk of cardiovascular and cardiometabolic disorders, with a median reported Odds Ratio or Hazard Ratio of 1.17 (range 1.0015-1.89). These associations extend to type 2 diabetes, certain cancers, and adverse reproductive outcomes, while also highlighting widespread environmental contamination. The primary limitation affecting the certainty of these findings is the predominance of observational study designs, which preclude definitive causal inference. Clinicians should advise patients, particularly pregnant women and those with cardiometabolic risks, to exercise caution regarding artificial sweetener intake, and future research should prioritize long-term, well-controlled human randomized controlled trials to establish causality.

Review Stats

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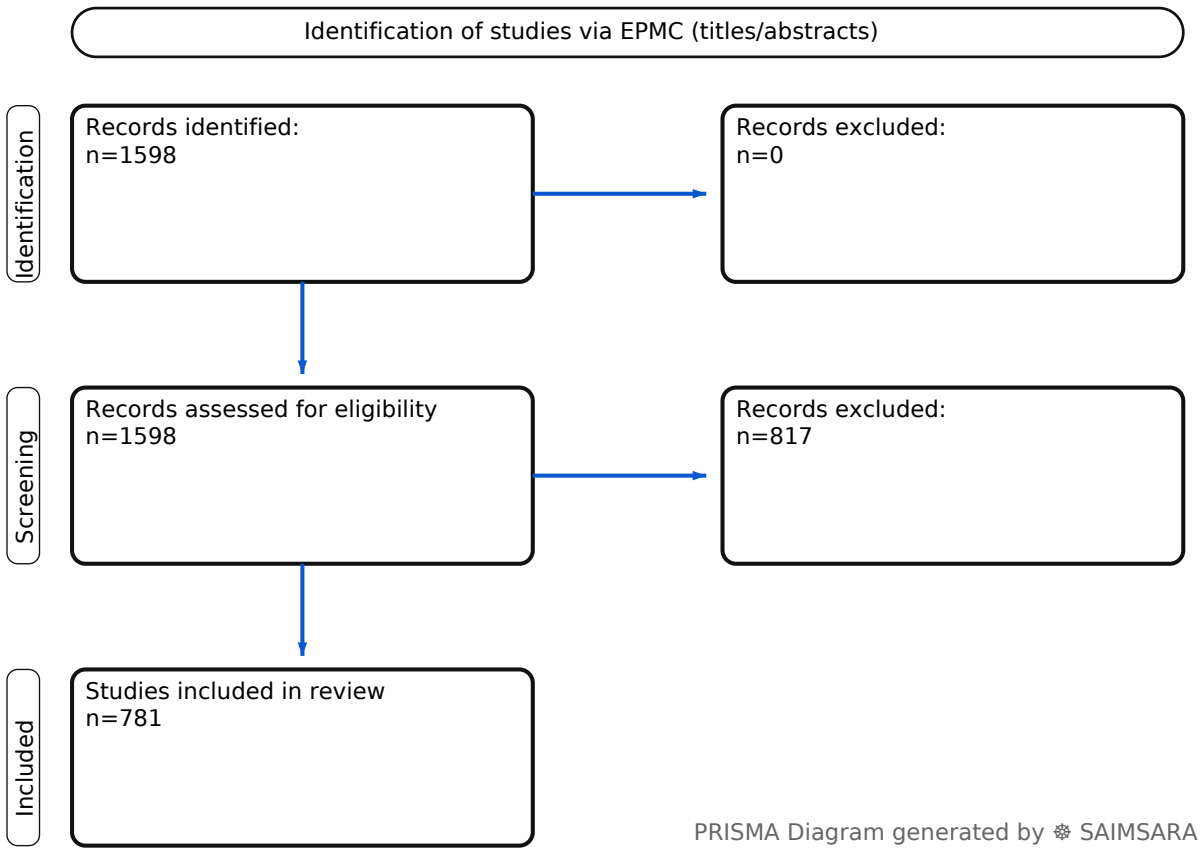
- Included original Abstracts/Papers: 781
- Total study participants (naïve ΣN): 401682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Records excluded:
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n=817
Included
Studies included in review
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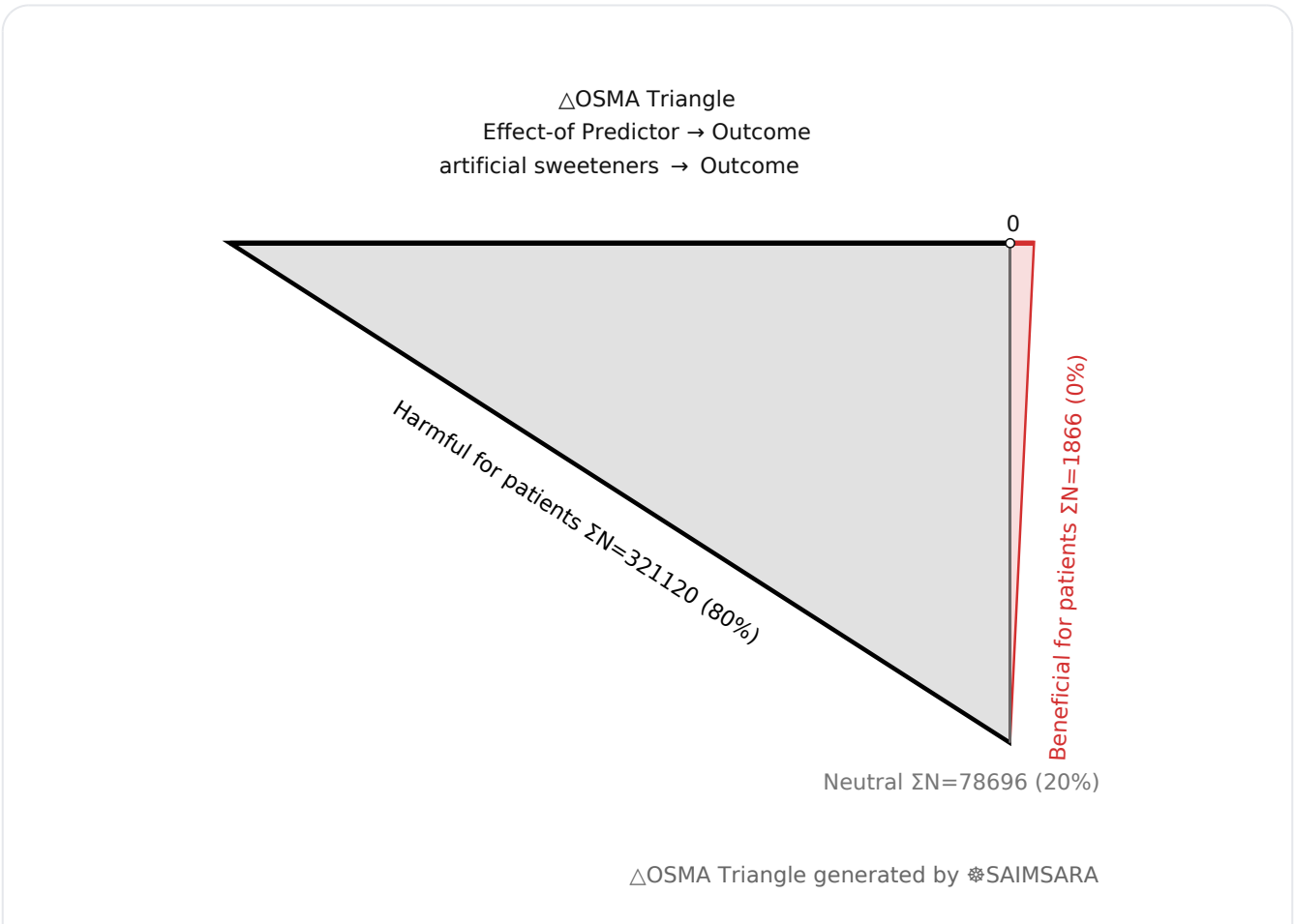
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Effect-of Predictor → Outcome
artificial sweeteners → Outcome
0
Harmful for patients ΣN=321120 (80%)
Beneficial for patients ΣN=1866 (0%)
Neutral ΣN=78696 (20%)
△OSMA Triangle generated by ☸SAIMSARA

Outcome-Sentiment Meta-Analysis (OSMA): *(LLM-only)*

Frame: Effect-of Predictor → Outcome • *Source*: Europe PMC

Outcome: Outcome Typical timepoints: 5-y, 60-y. Reported metrics: %, CI, p.

Common endpoints: Common endpoints: mortality, functional, complications.

Predictor: artificial sweeteners — exposure/predictor. Doses/units seen: 843.0 µg, 5.2 mg, 192 mg, 16 µg, 7.96 mg, 200 mg…. Routes seen: oral, sc. Typical comparator: control groups, control, unsweetened beverages, lactobacillus strains when….

- **1) Beneficial for patients** — Outcome with artificial sweeteners — [15], [37], [45], [55], [87], [119], [158], [165], [194], [196], [230], [231], [244], [252], [278], [282], [290], [291], [347], [393], [435], [442], [445], [466], [467], [475], [486], [518], [520], [523], [524], [533], [565], [599], [603], [630], [636], [651], [708], [718], [748] — ΣN=1866
- **2) Harmful for patients** — Outcome with artificial sweeteners — [1], [2], [4], [7], [10], [13], [14], [21], [26], [29], [31], [32], [35], [38], [40], [41], [43], [44], [49], [53], [61], [69], [72], [73], [74], [75], [78], [82], [86], [88], [92], [93], [94], [99], [100], [101], [104], [105], [106], [107], [111], [113], [115], [117], [120], [121], [124], [125], [126], [128], [136], [140], [141], [143], [147], [150], [153], [155], [168], [174], [176], [179], [182], [184], [186], [188], [192], [198], [199], [201], [204], [206], [209], [212], [215], [218], [222], [223], [224], [225], [228], [233], [239], [240], [242], [245], [246], [251], [253], [254], [255], [258], [261], [265], [267], [268], [286], [287], [295], [311], [315], [320], [323], [325], [328], [331], [332], [333], [341], [349], [351], [352], [356], [358], [360], [361], [366], [367], [369], [377], [380], [381], [384], [387], [395], [403], [409], [417], [425], [440], [446], [448], [454], [459], [460], [471], [474], [476], [478], [479], [488], [491], [495], [496], [511], [531], [539], [541], [547], [550], [564], [567], [586], [588], [606], [618], [625], [629], [634], [642], [652], [653], [659], [668], [673], [674], [682], [696], [704], [729], [731], [743], [745], [759], [767], [768], [781] — ΣN=321120
- **3) No clear effect** — Outcome with artificial sweeteners — [3], [5], [6], [8], [9], [11], [12], [16], [17], [18], [19], [20], [22], [23], [24], [25], [27], [28], [30], [33], [34], [36], [39], [42], [46], [47], [48], [50], [51], [52], [54], [56], [57], [58], [59], [60], [62], [63], [64], [65], [66], [67], [68], [70], [71], [76], [77], [79], [80], [81], [83], [84], [85], [89], [90], [91], [95], [96], [97], [98], [102], [103], [108], [109], [110], [112], [114], [116], [118], [122], [123], [127], [129], [130], [131], [132], [133], [134], [135], [137], [138], [139], [142], [144], [145], [146], [148], [149], [151], [152], [154], [156], [157], [159], [160], [161], [162], [163], [164], [166], [167], [169], [170], [171], [172], [173], [175], [177], [178], [180], [181], [183], [185], [187], [189], [190], [191], [193], [195], [197],

[200], [202], [203], [205], [207], [208], [210], [211], [213], [214], [216], [217], [219], [220], [221], [226], [227], [229], [232], [234], [235], [236], [237], [238], [241], [243], [247], [248], [249], [250], [256], [257], [259], [260], [262], [263], [264], [266], [269], [270], [271], [272], [273], [274], [275], [276], [277], [279], [280], [281], [283], [284], [285], [288], [289], [292], [293], [294], [296], [297], [298], [299], [300], [301], [302], [303], [304], [305], [306], [307], [308], [309], [310], [312], [313], [314], [316], [317], [318], [319], [321], [322], [324], [326], [327], [329], [330], [334], [335], [336], [337], [338], [339], [340], [342], [343], [344], [345], [346], [348], [350], [353], [354], [355], [357], [359], [362], [363], [364], [365], [368], [370], [371], [372], [373], [374], [375], [376], [378], [379], [382], [383], [385], [386], [388], [389], [390], [391], [392], [394], [396], [397], [398], [399], [400], [401], [402], [404], [405], [406], [407], [408], [410], [411], [412], [413], [414], [415], [416], [418], [419], [420], [421], [422], [423], [424], [426], [427], [428], [429], [430], [431], [432], [433], [434], [436], [437], [438], [439], [441], [443], [444], [447], [449], [450], [451], [452], [453], [455], [456], [457], [458], [461], [462], [463], [464], [465], [468], [469], [470], [472], [473], [477], [480], [481], [482], [483], [484], [485], [487], [489], [490], [492], [493], [494], [497], [498], [499], [500], [501], [502], [503], [504], [505], [506], [507], [508], [509], [510], [512], [513], [514], [515], [516], [517], [519], [521], [522], [525], [526], [527], [528], [529], [530], [532], [534], [535], [536], [537], [538], [540], [542], [543], [544], [545], [546], [548], [549], [551], [552], [553], [554], [555], [556], [557], [558], [559], [560], [561], [562], [563], [566], [568], [569], [570], [571], [572], [573], [574], [575], [576], [577], [578], [579], [580], [581], [582], [583], [584], [585], [587], [589], [590], [591], [592], [593], [594], [595], [596], [597], [598], [600], [601], [602], [604], [605], [607], [608], [609], [610], [611], [612], [613], [614], [615], [616], [617], [619], [620], [621], [622], [623], [624], [626], [627], [628], [631], [632], [633], [635], [637], [638], [639], [640], [641], [643], [644], [645], [646], [647], [648], [649], [650], [654], [655], [656], [657], [658], [660], [661], [662], [663], [664], [665], [666], [667], [669], [670], [671], [672], [675], [676], [677], [678], [679], [680], [681], [683], [684], [685], [686], [687], [688], [689], [690], [691], [692], [693], [694], [695], [697], [698], [699], [700], [701], [702], [703], [705], [706], [707], [709], [710], [711], [712], [713], [714], [715], [716], [717], [719], [720], [721], [722], [723], [724], [725], [726], [727], [728], [730], [732], [733], [734], [735], [736], [737], [738], [739], [740], [741], [742], [744], [746], [747], [749], [750], [751], [752], [753], [754], [755], [756], [757], [758], [760], [761], [762], [763], [764], [765], [766], [769], [770], [771], [772], [773], [774], [775], [776], [777], [778], [779], [780] — ΣN=78696

1) Introduction

Artificial sweeteners (ASs), also known as non-nutritive sweeteners (NNS) or low-calorie sweeteners (LCSs), are widely consumed as sugar substitutes, driven by perceived benefits for weight management and glycemic control. However, a growing body of research increasingly challenges these assumptions, revealing complex interactions with human physiology and the environment. Recent studies explore their impact on various health outcomes, including cardiometabolic disorders, cancer, gut microbiome alterations, and neurobehavioral changes. Concurrently, the environmental persistence and widespread detection of ASs in aquatic systems highlight their emerging role as environmental contaminants. This paper synthesizes the current scientific understanding of artificial sweeteners, drawing from a comprehensive review of recent literature.

2) Aim

The aim of this paper is to systematically review and synthesize the diverse research findings on artificial sweeteners, covering their physiological effects, environmental presence, and implications for human health, to identify key themes, clinical implications, and future research directions.

3) Methods

Systematic review with multilayer AI research agent: keyword normalization, retrieval & structuring, and paper synthesis (see SAIMSARA About section for details).

- **Bias:** The included studies predominantly comprise cohort studies, experimental animal models, and *in vitro* investigations, which are susceptible to confounding and may not establish causality. While some randomized controlled trials (RCTs) exist, their limited number and duration, particularly in human populations, introduce potential for bias and limit generalizability. Cross-sectional studies are inherently limited in establishing temporal relationships. Environmental studies, while crucial for understanding ecological impact, do not directly address human health outcomes.

4) Results

4.1 Study characteristics:

The body of research on artificial sweeteners encompasses a wide array of study designs, including numerous cohort studies (e.g., [1, 2, 4, 8, 14, 16, 21, 29, 30, 34, 36, 37, 72, 73, 87, 93, 104, 115, 118, 124, 127, 136, 215, 292, 323, 333, 336, 337, 360, 368, 371, 384, 417, 430, 438, 442, 447, 449, 450, 451, 464, 469, 472]), mixed-methods studies combining observational data with experimental or *in vitro* approaches (e.g., [3, 5, 7, 10, 15, 17, 26, 27, 28, 31, 32, 33, 35, 38, 39, 40, 41, 42, 43, 45, 46, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 88, 89, 90, 91, 92, 94, 96, 97, 98, 99, 100, 101, 102, 103, 106, 107,

108, 109, 110, 111, 112, 113, 114, 116, 117, 119, 120, 121, 122, 125, 126, 128, 129, 130, 131, 132, 133, 134, 135, 137, 138, 139, 140, 141, 142, 144, 145, 146, 147, 148, 149, 151, 152, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 169, 170, 171, 172, 173, 174, 175, 177, 178, 179, 180, 181, 182, 183, 184, 186, 187, 188, 189, 190, 192, 193, 194, 195, 196, 197, 198, 201, 202, 203, 204, 205, 206, 207, 209, 210, 211, 212, 213, 214, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 237, 238, 239, 241, 242, 243, 244, 246, 247, 248, 249, 250, 251, 253, 254, 256, 257, 258, 259, 260, 261, 262, 263, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 283, 284, 285, 288, 289, 290, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 324, 325, 326, 327, 329, 330, 331, 332, 334, 335, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 357, 358, 359, 361, 362, 365, 366, 367, 369, 370, 372, 373, 374, 375, 376, 377, 378, 379, 380, 382, 383, 385, 386, 387, 388, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398, 400, 401, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 415, 416, 418, 419, 420, 421, 422, 423, 424, 426, 427, 428, 429, 431, 434, 435, 439, 443, 445, 446, 448, 456, 458, 460, 461, 462, 463, 465, 466, 468, 469, 471, 475, 476, 479, 482, 483, 484, 485, 487, 489, 490, 491, 492, 494, 495, 496, 497, 498, 499]), cross-sectional studies (e.g., [9, 19, 22, 44, 93, 95, 129, 139, 140, 173, 208, 245, 252, 254, 256, 309, 310, 322, 328, 401, 433, 443, 446, 484]), and randomized controlled trials (RCTs) (e.g., [16, 59, 236, 264, 364, 441, 444, 453, 467, 470, 473, 480, 486, 493, 500]). Populations range from large human cohorts (e.g., UK Biobank [29, 30, 136], NutriNet-Santé [72, 104, 124, 141, 454]), pregnant women and their offspring [4, 105, 240, 333, 381, 384, 417], and specific patient groups (e.g., PCOS [1], cancer patients [2], T2D [16, 245], IBD [47, 94, 212, 251, 258, 401]), to animal models (e.g., mice [8, 26, 43, 58, 64, 75, 88, 108, 113, 125, 128, 138, 143, 147, 150, 153, 168, 179, 184, 204, 206, 216, 217, 222, 224, 242, 246, 267, 273, 281, 282, 294, 295, 296, 299, 317, 320, 321, 325, 331, 332, 351, 358, 360, 361, 363, 366, 372, 377, 387, 389, 395, 407, 408, 409, 411, 432, 435, 436, 440, 454, 455, 457, 463, 474, 476, 478, 480, 481, 491, 493], rats [43, 64, 74, 143, 147, 175, 204, 217, 295, 307, 311, 317, 320, 321, 331, 332, 358, 361, 369, 372, 377, 395, 425, 440, 445, 494], Drosophila [6, 18, 112, 138, 294, 363]),*in vitro* models (e.g., Caco-2 cells [5, 186, 188, 190, 192, 495, 496], human sweet receptor [24, 79, 272, 308, 463], pancreatic islet cells [148], prostate cancer cells [45], HepG2 cells [179, 184], human microglial cells [198]), and environmental samples (e.g., water, soil, sediment, wastewater [20, 23, 25, 34, 57, 60, 63, 78, 80, 84, 85, 86, 89, 91, 96, 100, 116, 146, 151, 161, 162, 166, 167, 169, 170, 180, 181, 202, 207, 211, 214, 218, 220, 228, 229, 232, 237, 262, 266, 269, 271, 274, 276, 277, 280, 283, 289, 292, 293, 298, 301, 303, 304, 315, 316, 319, 335, 336, 337, 340, 342, 344, 350, 371, 373, 375, 378, 379, 380, 385, 386, 402, 404, 405, 410, 412, 413, 415, 416, 418, 420, 422, 427, 429, 430, 437, 438, 447, 449, 450, 472, 477, 483, 489, 492, 497, 499]). Follow-up periods vary significantly, with many studies not specifying, while others range from acute (e.g., 24-48 hours [5]) to long-term (e.g., 1 year [8], 8 years [73], 9.1 years [72], 12.6 years [30]).

4.2 Main numerical result aligned to the query:

Across multiple human cohort studies, consumption of artificial sweeteners is associated with an increased risk of cardiovascular and cardiometabolic disorders. The median reported Odds Ratio (OR) or Hazard Ratio (HR) for these outcomes is 1.17, with values ranging from 1.0015 to 1.89 [14, 21, 29, 69, 104, 115, 124]. For instance, a study in Hungary reported an OR of 1.21 for cardiovascular disease prevalence [14], while another found a HR of 1.17 for overall cardiovascular disease [104]. Similarly, a large prospective cohort study reported an HR of 1.09 for cardiovascular diseases [124]. This heterogeneity in reported effect sizes reflects variations in study populations, specific sweeteners examined, and outcome definitions.

4.3 Topic synthesis:

- **Cardiometabolic and Mortality Risks:** Artificial sweetener intake is associated with increased risks of cardiometabolic disorders (median HR/OR 1.17, range 1.0015-1.89 [14, 21, 29, 69, 104, 115, 124]), type 2 diabetes (median HR/OR 1.69, range 1.265-3.74 [21, 72, 215]), gestational diabetes mellitus (aRR 1.88 [105], OR 2.66 [4]), and higher all-cause and cardiovascular mortality (HR 1.14 and 1.29, respectively [115]). Erythritol, specifically, is associated with increased risk of coronary heart disease, myocardial infarction, and stroke (ORs 1.0020-1.0463 [69]).
- **Cancer Associations:** Findings are mixed, with some studies showing increased risks for overall cancer (HR 1.13 [141]), specific cancers like colorectal (OR 1.58 [140]), stomach (OR 2.27 [140]), oral/pharyngeal (OR 1027.54 [53]), ovarian, and lung cancers [46, 117, 126], and hepatocellular carcinoma progression (acesulfame potassium [92]). Other studies report no significant association with overall cancer risk [17, 99, 103, 117, 130] or even reduced risk for some cancers (e.g., breast, gastric, colorectal, prostate, kidney [46], urinary system in women [130]). Aspartame is declared a possible carcinogen by IARC [40].
- **Gut Microbiome and Metabolic Effects:** Artificial sweeteners significantly reduce microbial diversity [10, 122], alter gut microbiota composition [90, 108, 122, 131, 135, 156, 164, 169, 189, 242, 354, 358, 360, 377, 409, 411], and function [122, 189], leading to insulin resistance [1, 114, 179, 184, 245, 454], glucose intolerance [179, 184, 224, 454], and systemic inflammation [1, 7, 43, 68, 113, 120, 186, 317]. Some studies suggest minimal or no effect on gut microbiota at realistic doses [236, 480, 493].
- **Neurological and Behavioral Impacts:** Artificial sweeteners can induce neurobehavioral alterations, including anxiety-like behavior (zebrafish [222], rats [366, 403]), depressive-like behaviors (mice [204]), impaired cognitive memory [73, 128, 367, 474, 478], and altered reward processes [206, 432, 473]. They also generate complex gustatory signals beyond sweetness, involving bitter co-activation [6, 18, 12].

- **Reproductive and Developmental Effects:** Maternal consumption of artificial sweeteners is linked to increased risk of infant overweight/obesity (0.20-unit increase in BMI z score [417], 2-fold higher risk [417], increased risk [240, 333, 384]), preterm delivery (RR 1.18 [381]), and decreased gestational age [381]. Aspartame and saccharin may negatively impact male and female reproductive parameters in rats, including hormonal levels, ovarian toxicity, and sperm quality [49, 74, 153, 320, 331, 332, 356, 425], and can lead to congenital malformations in offspring [267].
- **Environmental Contamination and Persistence:** Artificial sweeteners are widely detected in surface waters, groundwater, wastewater, soil, and plants globally [20, 23, 25, 34, 57, 60, 78, 80, 85, 86, 91, 96, 116, 146, 151, 161, 162, 166, 167, 169, 170, 181, 202, 207, 211, 214, 218, 220, 228, 229, 232, 262, 266, 269, 274, 276, 277, 280, 283, 289, 292, 298, 301, 303, 304, 315, 316, 319, 336, 337, 340, 342, 344, 371, 373, 375, 378, 379, 380, 385, 386, 402, 404, 405, 410, 412, 413, 415, 416, 418, 420, 422, 427, 430, 437, 438, 447, 449, 450, 472, 477, 483, 497, 499]. Sucralose and acesulfame are particularly persistent and serve as markers of wastewater contamination [20, 25, 337, 373, 379, 405].
- **Taste Perception and Consumer Behavior:** Artificial sweeteners bind to human sweet receptors (T1R2/T1R3) [24, 79, 272, 308, 463], but also exhibit bitter co-activation [6, 18, 12], influencing feeding behavior [6, 18, 56]. Consumer perception of healthiness and naturalness influences their acceptance of sweeteners [134, 199, 200, 256, 263], with a high prevalence of use often driven by weight management goals despite health concerns [19, 208, 241, 314, 322].

5) Discussion

5.1 Principal finding:

The central finding of this review is that consumption of artificial sweeteners is associated with an increased risk of cardiovascular and cardiometabolic disorders, with a median reported Odds Ratio or Hazard Ratio of 1.17 (range 1.0015-1.89) [14, 21, 29, 69, 104, 115, 124]. This suggests that despite their intended role as healthier alternatives, artificial sweeteners may contribute to adverse health outcomes.

5.2 Clinical implications:

- **Patient Counseling:** Clinicians should counsel pregnant women about the potential link between artificial sweetener consumption and increased risks of infant overweight/obesity [240, 333, 417], preterm delivery, and altered offspring metabolism [381, 384].
- **Cardiometabolic Risk Assessment:** For individuals at risk of or with existing cardiometabolic conditions, including type 2 diabetes and cardiovascular disease, caution

regarding artificial sweetener intake is warranted given observed associations with increased risk [14, 21, 29, 69, 72, 104, 115, 124, 215, 245].

- **Gut Health Considerations:** Patients with inflammatory bowel disease (IBD) or other gastrointestinal symptoms may benefit from reducing artificial sweetener consumption, as these compounds can alter gut microbiota and intestinal barrier function [47, 68, 90, 94, 120, 122, 186, 189, 209, 212, 251, 258, 351, 401, 409, 491, 495].
- **Weight Management Strategies:** While often used for weight management, artificial sweeteners may not consistently lead to weight loss and could even be associated with increased appetite or weight gain in some contexts [77, 223, 440, 444, 460]. Alternative strategies or natural sweeteners like thaumatin [263] or stevia [58, 112, 249] should be considered.
- **Medication and Supplement Review:** Healthcare providers should be aware of the presence of artificial sweeteners in medications and supplements [51, 157, 346], especially for vulnerable populations or those with specific health conditions.

5.3 Research implications / key gaps:

- **Longitudinal Human RCTs:** Conduct long-term, well-controlled randomized controlled trials in diverse human populations to definitively establish causality between specific artificial sweeteners and cardiometabolic, neurological, and reproductive outcomes [149, 238, 250].
- **Mechanistic Studies on Microbiome-Gut-Brain Axis:** Investigate the precise molecular mechanisms by which artificial sweeteners alter gut microbiota, influence the gut-brain axis, and contribute to neurobehavioral changes and metabolic dysfunction [90, 189, 206, 321, 349, 361, 408, 409, 432].
- **Dose-Response and Individual Variability:** Characterize dose-dependent effects and individual variability (e.g., genetic predispositions, gut enterotypes [484], existing health conditions) in response to different artificial sweeteners across various health endpoints [177, 238, 332].
- **Environmental Impact and Biodegradation:** Further research is needed on the long-term ecological impacts of artificial sweeteners, their biodegradation pathways in various environmental matrices, and the potential for bioaccumulation and toxicity in non-human species [60, 89, 131, 169, 207, 218, 222, 237, 283, 298, 315, 342, 344, 465, 492, 499].
- **Multi-exposure and Mixture Effects:** Study the combined effects of artificial sweeteners with other food additives, contaminants, or dietary components (e.g., ultra-processed foods [109, 136], nicotine [26], caffeine [28, 85, 102]) on human health and environmental systems.

5.4 Limitations:

- **Causality Inference** — Many studies are observational (cohort, cross-sectional), limiting the ability to establish definitive causal relationships between artificial sweetener consumption and observed health outcomes.
- **Heterogeneity of Sweeteners** — The term "artificial sweeteners" encompasses diverse chemical compounds, and their individual effects may vary, making generalized conclusions challenging.
- **Confounding Factors** — Dietary patterns, lifestyle choices, and underlying health conditions are often difficult to fully control for, potentially confounding associations.
- **Reporting Bias** — Self-reported consumption data, common in human studies, may be subject to recall bias and under/overestimation of intake.
- **Animal Model Extrapolation** — Findings from animal and *in vitro* studies may not directly translate to human physiology and long-term health effects.

5.5 Future directions:

- **Standardize Research Protocols**
- **Investigate Long-Term Human Outcomes**
- **Elucidate Microbiome Mechanisms**
- **Assess Environmental Degradation Pathways**
- **Develop Safer Sweetener Alternatives**

6) Conclusion

Higher consumption of artificial sweeteners is associated with an increased risk of cardiovascular and cardiometabolic disorders, with a median reported Odds Ratio or Hazard Ratio of 1.17 (range 1.0015-1.89) [14, 21, 29, 69, 104, 115, 124]. These associations extend to type 2 diabetes, certain cancers, and adverse reproductive outcomes, while also highlighting widespread environmental contamination. The primary limitation affecting the certainty of these findings is the predominance of observational study designs, which preclude definitive causal inference. Clinicians should advise patients, particularly pregnant women and those with cardiometabolic risks, to exercise caution regarding artificial sweetener intake, and future research should prioritize long-term, well-controlled human randomized controlled trials to establish causality.

References

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Figure 1. Publication-year distribution of included originals

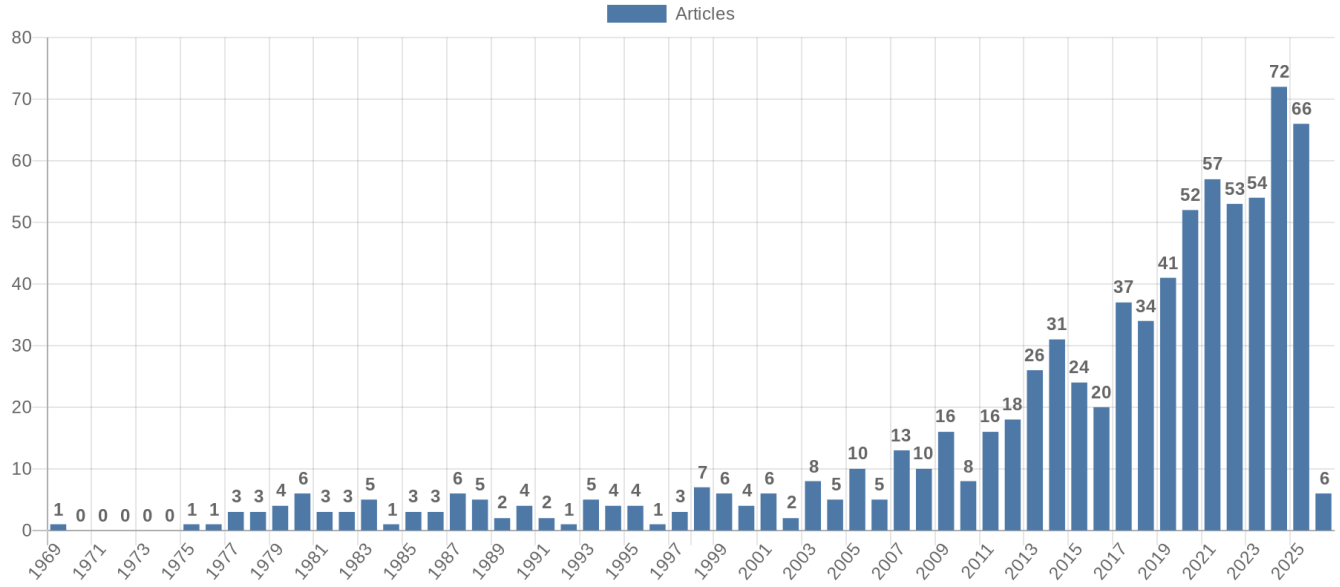

Figure 2. Study-design distribution of included originals

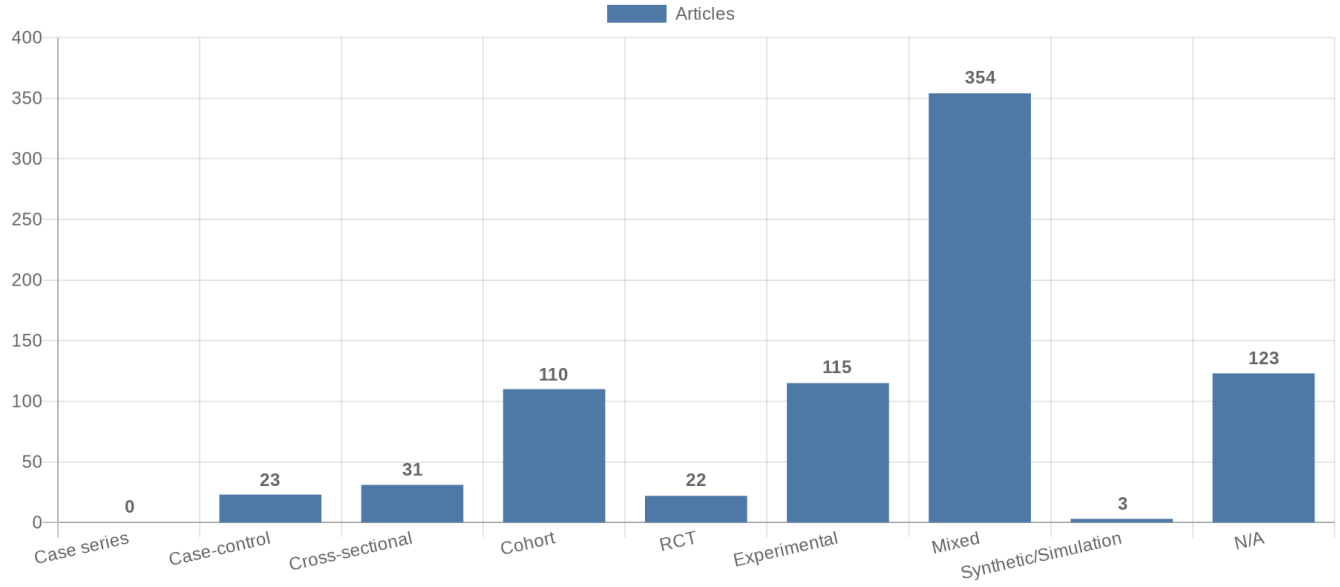

Figure 3. Study-type (directionality) distribution of included originals

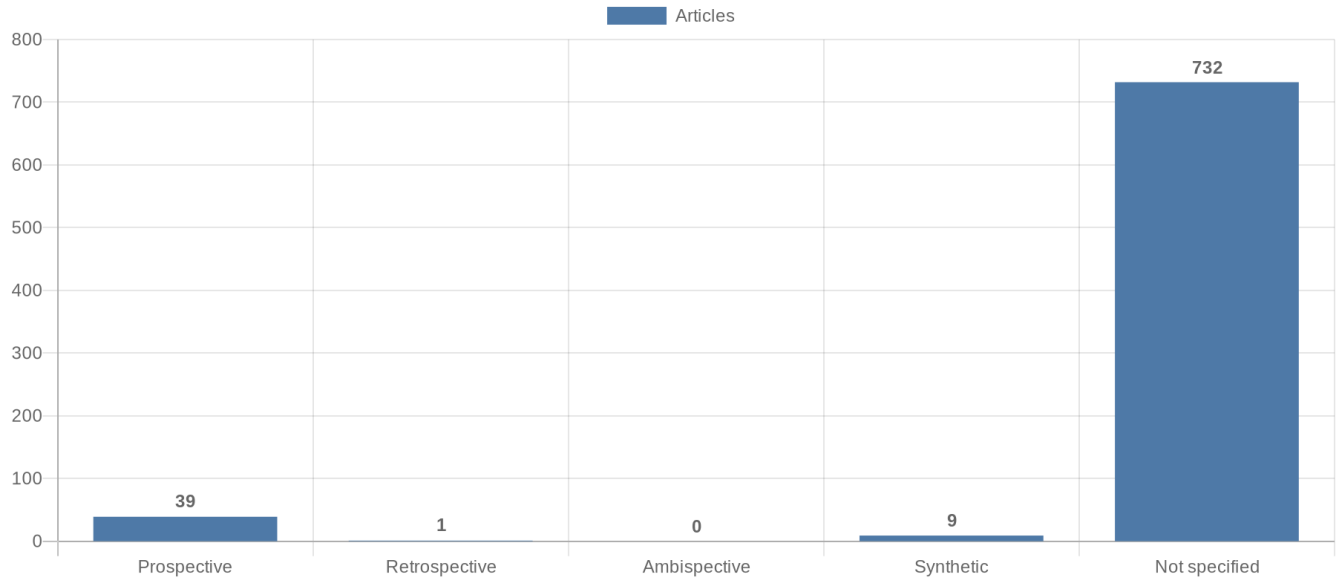

Figure 4. Main extracted research topics

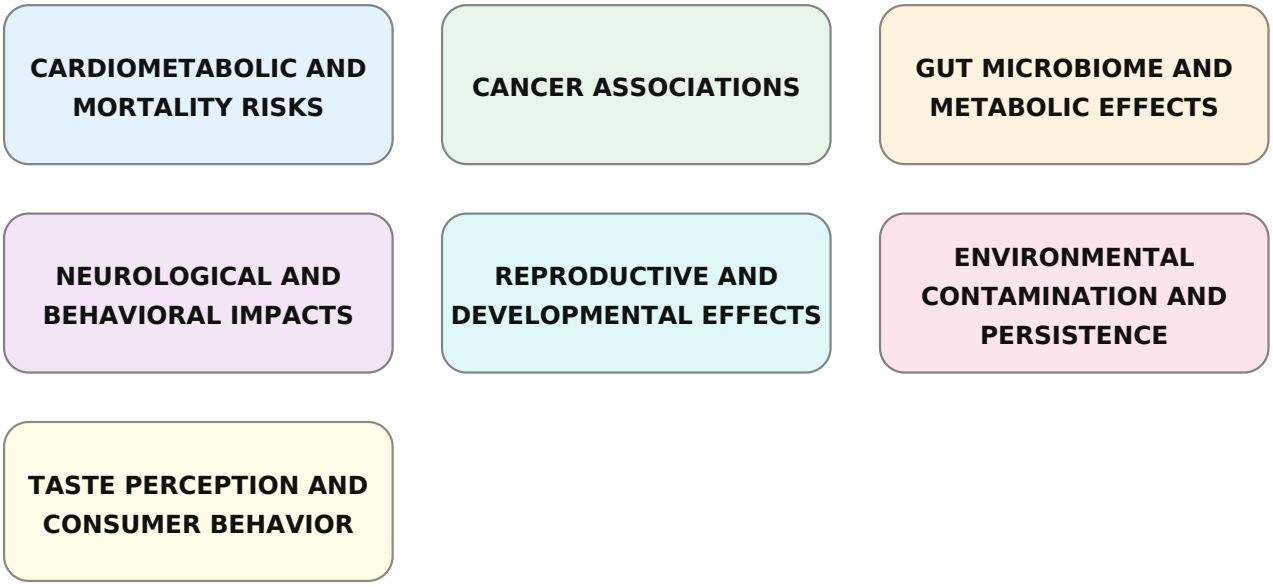

Figure 5. Limitations of current studies (topics)

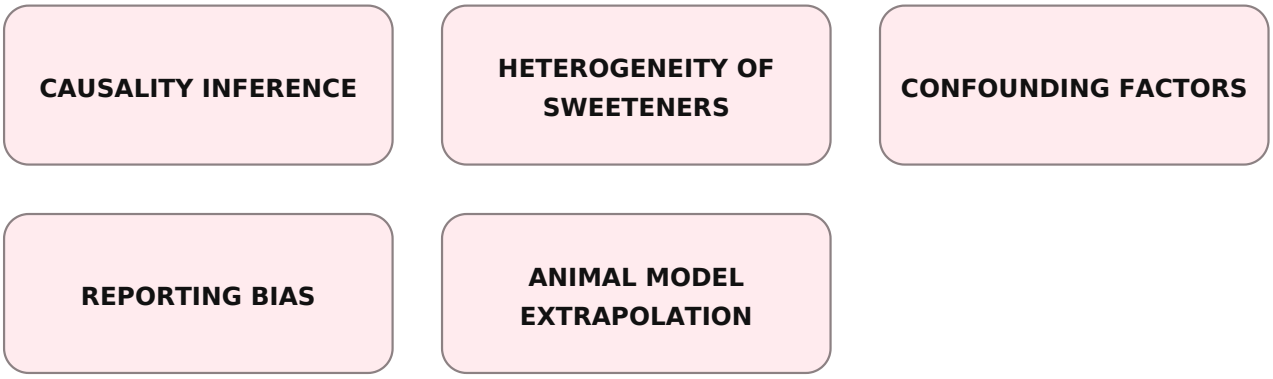

Figure 6. Future research directions (topics)

LONGITUDINAL HUMAN RCTS

MECHANISTIC STUDIES ON MICROBIOME-GUT-BRAIN AXIS

DOSE-RESPONSE AND INDIVIDUAL VARIABILITY

ENVIRONMENTAL IMPACT AND BIODEGRADATION

MULTI-EXPOSURE AND MIXTURE EFFECTS

STANDARDIZE RESEARCH PROTOCOLS

INVESTIGATE LONG-TERM HUMAN OUTCOMES