

Butyrate, Postbiotic Strategies and the Indian Polycystic Ovary Syndrome Phenotype: Dietary Fibre, Gut Microbiome and the Capacity-Substrate Mismatch Hypothesis

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Abstract

Review Article

Polyendocrine metabolic ovarian syndrome (PMOS, formerly polycystic ovary syndrome, PCOS) is common in India and presents with a characteristic phenotype: high prevalence, frequent lean or normal-weight presentation, and central adiposity with insulin resistance at body mass indices that would be considered unremarkable in European populations. Depletion of short-chain fatty acid-producing bacteria is among the more reproducible microbial findings in PMOS internationally, which invites the assumption that Indian populations, traditionally regarded as consuming high-fibre diets, should be relatively protected. This review examines that assumption and finds it inverted. Contemporary Indian dietary fibre intake is low and falling, at roughly 15 to 20 g per day against a recommended 25 to 30 g, with fewer than one in seven adults meeting the recommendation, and with refined cereals displacing whole grains and pulses across all geographic zones. Yet the Indian gut microbiome retains a distinctive Prevotella-dominant configuration enriched in complex plant-polysaccharide-degrading enzymes, a signature that erodes with dietary acculturation on migration. India therefore presents not fibre without fermentation but the converse: a microbial community with high fermentative capacity encountering a diminishing supply of fermentable substrate. We propose that this capacity-substrate mismatch is a candidate contributor to the lean insulin-resistant Indian PMOS phenotype, set out what the single available Indian study of faecal short-chain fatty acids in PMOS does and does not show, explain why faecal concentration cannot resolve the question, and specify the healthy population-representative reference cohort that India currently lacks. We distinguish substrate-directed from metabolite-directed intervention, situate the latter within postbiotic and butyrate-delivery strategies, and argue that the mismatch described here is a measurement problem before it is an intervention opportunity.

Keywords Butyrate - dietary fibre - gut microbiome - India - nutrition transition - polyendocrine metabolic ovarian syndrome - postbiotics - Prevotella - short-chain fatty acids.

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1. INTRODUCTION

Polycystic ovary syndrome was renamed polyendocrine metabolic ovarian syndrome (PMOS) in May 2026 following a multistep global consensus process, on the grounds that the ovarian-morphological name misrepresented a disorder of metabolism, reproduction and mental health. Diagnostic criteria were unchanged by the rename, and a transition period extends to the 2028 international guideline update. We use PMOS throughout and retain PCOS where citing work published under the former term.

PMOS is common in India and its presentation differs from the European pattern in ways that matter

mechanistically. The national study conducted across five zones and enrolling 8,993 women reported prevalence of 7.2 per cent by National Institutes of Health criteria, 19.6 per cent by Rotterdam criteria and 13.6 per cent by Androgen Excess and PCOS Society criteria, with phenotype C predominant and a striking comorbidity burden: dyslipidaemia in 91.9 per cent, obesity in 43.2 per cent, non-alcoholic fatty liver disease in 32.9 per cent and metabolic syndrome in 24.9 per cent [1]. Earlier national reviews report a range of 3.7 to 22.5 per cent depending on population and criteria [2].

The phenotype is distinctive. In a community-based study of 600 adolescents and young women in

Mumbai, 22.5 per cent met Rotterdam criteria and 71.8 per cent of those diagnosed were non-obese [3]. In a North Indian community sample, only 12 per cent of women with PMOS had a body mass index at or above 27.5 kg/m², while 44 per cent had a waist-hip ratio above 0.81 [4]. Indian PMOS is therefore frequently a lean, centrally adipose, insulin-resistant presentation, which is precisely the phenotype in which microbial and metabolic contributors are most likely to be informative and least likely to be explained by adiposity alone [5].

The mechanistic relevance follows from what butyrate does. Butyrate is the principal oxidative substrate of the colonocyte and a regulator of epithelial barrier integrity; loss of butyrate production is associated with increased intestinal permeability, translocation of bacterial lipopolysaccharide and low-grade systemic inflammation, which is one of the better-characterised routes from gut dysbiosis to insulin resistance [6]. In a phenotype defined by insulin resistance at low body mass index, a mechanism that generates metabolic dysfunction without requiring adiposity is of obvious interest. The relevant question for India is therefore not whether butyrate matters, which is reasonably established, but whether Indian butyrate production is in fact adequate.

2. Search strategy

We searched an academic literature aggregator indexing PubMed, Scopus, Semantic Scholar and arXiv between 23 and 25 September 2026, using combinations of *polycystic ovary syndrome*, *polyendocrine metabolic ovarian syndrome*, *India*, *prevalence*, *dietary fibre*, *nutrition transition*, *gut microbiome*, *Prevotella*, *butyrate*, *short-chain fatty acids* and *reference values*. Both the former and current disease names were searched. No language restriction was applied. Reference lists of retrieved reviews were hand-searched. This is a narrative synthesis.

3. Relationship to companion reviews

This review is one of four by the same author group examining a single question -- whether colonic butyrate supply is a modifiable determinant of disease -- in two clinical domains where the evidence is incomplete in different ways. Because the four share a mechanistic core, the boundary between them is stated here explicitly.

Within the polyendocrine metabolic ovarian syndrome domain, this review addresses the adult Indian phenotype and the population-level question of whether fermentable substrate supply has fallen out of step with fermentative capacity. The companion review addresses the adolescent window, where the metabolic trajectory is set and where any preventive intervention would have to be delivered, and concludes that timing and formulation rather than dose are the decisive variables [7]. The two are complementary rather than overlapping: this article is epidemiological and methodological and ends in a measurement agenda, that one is interventional in orientation and ends in trial design.

The same butyrate-supply question is examined in the infection domain in two further reviews by this group, on the intestinal uropathogen reservoir in recurrent urinary tract infection [8] and on the depletion of butyrate-producing bacteria by antimicrobial therapy [9]. The relevance here is methodological as much as mechanistic: all four encounter the same measurement problem, that faecal short-chain fatty acid concentration is a residue rather than a production rate, and the same translational problem, that delivering a butyrate precursor to the distal colon in humans is unsolved.

4. The assumption under examination

Depletion of short-chain fatty acid-producing taxa is among the more reproducible findings in the PMOS microbiome literature. A meta-analysis of 28 studies comprising 1,022 patients and 928 controls found reduced microbial evenness and phylogenetic diversity, with depletion of *Lachnospira* and *Prevotella* and enrichment of *Bacteroides*, *Lactobacillus*, *Fusobacterium* and *Escherichia/Shigella* [6]. An individual-level reanalysis of 948 participants across 14 publications confirmed that composition differs while alpha diversity does not, and reported regional divergence: *Alistipes* enriched in predominantly European cohorts, *Blautia* and *Roseburia* more abundant in Chinese cohorts [10]. Regional divergence is the point of departure for this review.

If reduced fibre fermentation contributes to PMOS, and if Indian diets are high in fermentable fibre, Indian populations should show a milder microbial phenotype. That syllogism has an unexamined premise.

5. Indian dietary fibre intake is low, and falling

Mean dietary fibre intake among Indian adults is approximately 15 to 20 g per day against a recommended 25 to 30 g, and fewer than 10 to 15 per cent of adults meet the recommendation [11]. The direction of change is unfavourable. The nutrition transition has substituted refined cereal staples for whole grains and pulses across all geographic zones, with white rice predominating in the south and east and refined wheat in the north and west, accompanied by reduced intake of vegetables, fruit and fibre [12]. The metabolic consequence has been quantified: in 1,843 urban south Indian adults, refined grain intake was associated with newly detected type 2 diabetes with an odds ratio of 5.31 (95% CI 2.98-9.45) comparing highest with lowest quartiles, while dietary fibre was inversely associated (OR 0.31, 95% CI 0.15-0.62) [13].

The contrast with the traditional diet is instructive rather than nostalgic. A 1995 survey of northern Indian vegetarian populations reported dietary fibre intakes far in excess of contemporary estimates, although measured by detergent-fibre methods that are not directly comparable with modern total dietary fibre assays [14]. Even allowing generously for

methodological difference, the direction of travel is not in doubt. Against a global dose-response analysis identifying 25 to 29 g per day as the intake associated with greatest risk reduction across non-communicable disease [15], contemporary Indian intake sits well below the threshold at which benefit accrues. India is not a high-fibre population. It is a population that used to be one.

Two caveats apply to this section. Fibre intake estimates in India derive from heterogeneous instruments, with food frequency questionnaires and 24-hour recalls giving different answers, and Indian food composition tables have incomplete fibre data for many traditional preparations. And national means conceal substantial variation between rural and urban populations and between socioeconomic groups [11,12]. Neither caveat alters the direction or the magnitude of the gap against recommended intake, but both argue against treating any single national figure as precise.

6. The microbiome that the former diet built

The Indian gut microbiome nevertheless retains the signature of that former diet. Multi-omic profiling of 110 healthy individuals from two distinct regions found the North-Central, predominantly plant-based cohort associated with *Prevotella*, and the Southern, omnivorous cohort associated with *Bacteroides*, *Ruminococcus* and *Faecalibacterium* with enrichment of the short-chain fatty acid biosynthesis pathway [16]. In a population-wide comparison including a 200-sample Indian cohort, Indian and other non-westernised populations showed higher abundance and diversity of *P. copri* enriched in enzymes that metabolise complex plant polysaccharides, including pullulanase-containing polysaccharide-utilisation loci [17]. The *P. copri* complex as a whole is specifically underrepresented in westernised populations, a pattern attributed to multigenerational dietary change [18].

That signature is not fixed. In a cross-sectional comparison of Indians resident in India, Indo-immigrants and Indo-Canadians against European-Canadian controls, Indians and recent immigrants showed high abundance of *Prevotella* species and carbohydrate-active enzymes reflecting a high complex-carbohydrate diet, while Indo-Canadians exhibited a transitional, westernising microbiome mirroring increasing dietary acculturation [19]. The community tracks the diet, but with a lag.

7. Capacity without substrate

These two observations are usually reported separately and are seldom set against each other. Taken together they describe a mismatch. The Indian gut carries a microbial community configured by generations of high complex-carbohydrate intake and equipped, at the level of glycoside hydrolase gene content, to ferment plant polysaccharides [16-18]. The diet now presented to that community is increasingly refined and fibre-poor [11-13]. The question this review poses is what happens

to butyrate production when fermentative capacity and fermentable substrate come apart, and whether the resulting state contributes to the lean, insulin-resistant PMOS phenotype characteristic of India. An adjacent argument has been advanced for the Indian thin-fat obesity phenotype, invoking impaired fibre fermentation, reduced short-chain fatty acid signalling and metabolic endotoxaemia, and proposing synbiotic supplementation as a scalable response [20]. The present review differs from it in three respects: the target condition is PMOS rather than obesity; the claim is a dissociation between fermentative capacity and substrate supply rather than impaired fermentation as such; and the proposed next step is measurement rather than intervention.

Two features of the Indian microbiome make the question more than theoretical. First, *Prevotella*-dominant communities are substrate-dependent in a way that *Bacteroides*-dominant communities are not, so a fall in complex carbohydrate may reduce output disproportionately. Second, the community is not homogeneous across India: regional cohorts differ in both taxa and in SCFA pathway enrichment [16], tribal populations differ again with dairy and grain intake [21], and a population-scale survey of 575 adults drawn from ten South Asian communities, each sampled in its ancestral village and in an urban centre, found the microbiome response to urbanisation to be community-specific rather than uniform, with geography and community membership explaining more variance than lifestyle [22]. Any study of Indian butyrate production must treat 'the Indian diet' as plural.

A third element belongs in this picture and has not been systematically studied in relation to PMOS. Colonic transit time and stool output in Indian populations have historically differed markedly from Western norms, and both determine the relationship between production and excretion of short-chain fatty acids. A faster transit, for a given production rate, delivers a lower concentration and a shorter mucosal contact time; this is one of the specific reasons that faecal concentration is an unreliable proxy [23]. Any Indian study that measures faecal short-chain fatty acids without recording transit is measuring an uninterpretable composite, and we are not aware of an Indian PMOS study that has recorded both.

8. Is *Prevotella*-dominant capacity actually an asset?

The inference that unused fermentative capacity is a latent asset deserves examination, because two independent lines of evidence indicate that *Prevotella copri* carriage is not uniformly favourable. In a cohort of 307 men profiled by shotgun metagenomic and metatranscriptomic sequencing, higher dietary fibre intake was associated with significantly greater reduction in C-reactive protein only among individuals without substantial *P. copri* carriage; carriers maintained stable C-reactive protein irrespective of fibre intake [24]. If that

interaction holds in Indian women, the therapeutic corollary most readily drawn from a capacity-substrate mismatch, that supplying the substrate will cause the capacity to be used to the host's benefit, does not follow automatically.

The second line comes from PMOS itself. Among 83 women with PMOS and 63 controls, faecal propionate was higher in PMOS than in controls and higher again in the insulin-resistant subgroup, while *P. copri* and *Megamonas funiformis* were more abundant in insulin-resistant than in non-insulin-resistant cases; propionate together with these two taxa discriminated PMOS with an area under the curve of 78.0 per cent [25]. A simple substrate-deficiency model does not predict this pattern. The objection that the study measured faecal rather than plasma concentrations is legitimate but cuts in both directions, and does not dispose of the taxonomic finding.

Two reconciliations are available and neither has been tested in India. The first is that the *P. copri* complex comprises four distinct clades of differing metabolic repertoire [18], so that species-level abundance may simply be the wrong unit of analysis. The second is that propionate and butyrate are differently regulated within the same fermentative community, so that a shift toward propionate at the expense of butyrate would be consistent both with high polysaccharide-degrading gene content and with an adverse metabolic phenotype. Both are addressable with clade-resolved metagenomics and paired propionate and butyrate measurement, and both should be addressed before any mechanistic fibre recommendation is issued for Indian women with PMOS.

9. What is known about butyrate in Indian PMOS

One study has measured this directly. In 57 Indian women with PMOS and 30 controls from western India, 16S rRNA profiling showed significantly altered beta diversity driven by hyperandrogenism, with enrichment of *Ligilactobacillus* and *Collinsella* species and markedly reduced SCFA-producing Oscillospiraceae; faecal butyric acid and the barrier marker zonulin were significantly altered, and altered taxa correlated with gonadotropin and sex hormone-binding globulin levels [26]. This is a valuable and, to our knowledge, singular contribution. It is also a single-centre study from one region of a country with marked regional microbiome variation, and it compares women with PMOS against controls rather than establishing what butyrate production looks like in the healthy Indian population at large.

10. Why faecal short-chain fatty acids cannot answer the question

A methodological caution is unavoidable, and it applies to the study above as it does to the wider literature. Luminal and faecal short-chain fatty acid concentrations do not reflect production rate and should

not be used as measures of it, because rapid absorption, transit time, mucus and biofilm structure all intervene between production and excretion [23]. The scale of that disconnect is substantial: in a stable-isotope study, systemic availability of colonically administered butyrate was approximately 2 per cent, against 36 per cent for acetate and 9 per cent for propionate [27]. A faecal butyrate concentration is therefore a residue, not an output. In a population with distinctive transit characteristics and a distinctive microbial configuration, interpreting that residue against reference intervals derived elsewhere compounds the problem.

11. The missing baseline

This is where the deficiency in Indian data is real and specific. It is not correct to say that no Indian short-chain fatty acid measurements exist; they do, in women with PMOS [26]. What does not exist is a healthy, population-representative Indian reference dataset for faecal and plasma short-chain fatty acids, stratified by region, diet pattern, age and sex. A comparable dataset has been generated elsewhere in Asia: quantification in 157 medically confirmed healthy Thai individuals established total faecal short-chain fatty acids at 34.1 (SD 15.3) micromol/g and plasma at 60.0 (SD 45.9) micromol/l, with acetate, propionate and butyrate accounting for 89 per cent of faecal total and acetate for 93 per cent of plasma total [28]. Without an Indian equivalent, no Indian study of PMOS, or of any other condition, can state whether an observed value is low.

12. Implications for Indian clinical practice

Two implications are already defensible. The first concerns dietary advice. Fibre recommendations for Indian women with PMOS are currently generic, and the evidence reviewed here suggests they should be specific and quantified, since the gap between actual and recommended intake is large, the direction of change is adverse, and the population may carry unusually high capacity to use fibre if it is supplied [11,15,17]. The second concerns interpretation of laboratory results. Faecal short-chain fatty acid panels are increasingly offered to Indian patients. In the absence of Indian reference intervals, such results should not be reported against non-Indian ranges, and a result within a foreign reference range should not be described as normal [23,27,28].

One implication is explicitly not supported. Nothing in this review justifies recommending a butyrate supplement, a butyrate prodrug or any specific commercial preparation for PMOS in India. No trial of such an intervention in this population exists, and the argument advanced here concerns substrate supply to an existing microbial community rather than exogenous metabolite delivery.

13. Translational perspective: emerging postbiotic and butyrate-delivery strategies

Interest in microbiome-derived intervention has expanded beyond live probiotics to include postbiotic preparations and strategies designed to deliver microbial metabolites, or their precursors, to defined intestinal sites. Precision about the category is necessary before proceeding. A postbiotic was defined by international consensus as a preparation of inanimate microorganisms and/or their components that confers a health benefit on the host [29], and isolated or purified metabolites fall outside that definition [30]. Glycerol tributyrinate (tributylin), a triglyceride ester of butyric acid, is therefore not a postbiotic in the consensus sense: it contains no microbial cells or cell components. It is a butyrate precursor, and it is discussed alongside postbiotic approaches here because the two act on the same host pathway and are being developed for the same clinical purpose, not because they belong to the same regulatory or definitional category.

The argument of this review is about substrate supply to a resident microbial community, and its primary implication is therefore dietary rather than pharmacological: the community already carries the fermentative machinery, and the deficit is in what reaches it. Two circumstances would move the question from nutrition to pharmacology. The first is a population in which substrate intake cannot realistically be raised to the 25 to 30 g per day at which benefit accrues [15]. The second, and the more interesting here, is a community whose response to added substrate is attenuated: the interaction reported for *Prevotella copri* carriage, in which higher fibre intake reduced C-reactive protein only among non-carriers, raises exactly that possibility for a *Prevotella*-dominant population [24]. If that interaction holds in Indian women, supplying substrate may not produce the metabolite, and delivering the metabolite or its precursor becomes a distinct question rather than a shortcut to the same endpoint.

Where that question is asked, formulation determines whether it is being asked at all. Glycerol tributyrinate is hydrolysed by pancreatic lipases, so the site of hydrolysis, and therefore whether colonic exposure is achieved, is a property of the preparation and not of the molecule. The only published human pilot study of a tributyrin complex reported decreased faecal acetate and propionate and an interpretation of small-intestinal release and hepatic activity [31], which is not the exposure profile that a colonic-fermentation argument requires. Aeon Formulations Pvt Ltd has developed a patented technology, designated GTB, comprising a microencapsulated powder form of glycerol tributyrinate, and this technology is used in the development of the ThirdBiome platform. Microencapsulation is intended to alter where in the gastrointestinal tract the ester is hydrolysed, and therefore how much butyrate reaches the

distal intestine; whether it does so in humans is an empirical question that has not been answered for this or, with the single exception noted above, for any comparable preparation. Microencapsulated glycerol tributyrinate technologies, including the patented GTB technology developed by Aeon Formulations Pvt Ltd and used in the development of the ThirdBiome platform, are one formulation approach in this category, and characterising colonic exposure for any such preparation would be a prerequisite to testing it against the hypothesis advanced here. No trial of a butyrate precursor in Indian women with PMOS exists, the capacity-substrate mismatch is itself untested, and nothing in this review supports the use of such a preparation for PMOS in India. The measurement agenda below, and not an intervention, is what follows from the present evidence. The authors' commercial interest in this technology is declared in the competing interests statement.

14. Limitations

This is a narrative review and its central proposition is a hypothesis rather than a finding. The capacity-substrate mismatch is inferred from two separate literatures, dietary and microbiological, that have not been examined in the same individuals; no study has simultaneously measured fibre intake, butyrate-producing gene abundance and butyrate output in an Indian cohort. The PMOS-specific Indian microbiome evidence rests on one single-centre study²⁶. The historical fibre comparison relies on methods that are not directly comparable with contemporary assays¹⁴. The proposition that the mismatch contributes to the lean insulin-resistant phenotype is at present untested in either direction. And the evidence that *P. copri* carriage may attenuate rather than amplify the benefit of dietary fibre [24,25] is a material qualification of the therapeutic inference, which is why this review stops at a measurement agenda.

15. Research agenda

Three studies would resolve most of the uncertainty. The first is a healthy Indian reference cohort for faecal and plasma short-chain fatty acids, sampled across at least four geographic zones with paired dietary assessment and transit measurement, modelled on the Thai design [28]. The second is a within-India comparison of butyrate-producing gene abundance against measured fibre intake, testing directly whether fermentative capacity and substrate supply have diverged. The third is a PMOS case-control study adequately powered and stratified by body mass index and androgen status, using metagenomic functional capacity and plasma rather than faecal short-chain fatty acids as the primary microbial measures, and recruiting across more than one region [10,16].

Table I: Prevalence and phenotype of polyendocrine metabolic ovarian syndrome in Indian populations

Study	Setting and sample	Prevalence	Phenotype notes
Ganie <i>et al</i> [1]	National, five zones; 8,993 women aged 18-40 yr	7.2% NIH; 19.6% Rotterdam; 13.6% AE-PCOS	Phenotype C predominant; dyslipidaemia 91.9%, NAFLD 32.9%, metabolic syndrome 24.9%
Joshi <i>et al</i> [3]	Community, Mumbai; 600 girls aged 15-24 yr	22.5% Rotterdam; 10.7% AE-PCOS	71.8% non-obese; mild phenotype commonest (52.6%)
Gill <i>et al</i> [4]	Community, Lucknow; 1,520 women aged 18-25 yr	3.7% (2.6-4.4)	Only 12% with BMI ≥ 27.5 kg/m ² ; 44% with waist-hip ratio ≥ 0.81
Ganie <i>et al</i> [2]	Narrative review of Indian studies	Range 3.7-22.5%	Hyperandrogenism consistently linked to insulin resistance and cardiovascular risk

Table II: What is established and what is missing regarding butyrate production in Indian populations

Question	Current position	What is needed
Is Indian dietary fibre intake high?	No. Approximately 15-20 g/day; fewer than 10-15% meet recommendations; refined cereals displacing whole grains [11-13]	Repeat national dietary surveillance with fibre reported as a primary variable
Is the Indian microbiome distinctive?	Yes. <i>Prevotella</i> -dominant, enriched in plant-polysaccharide-degrading enzymes; erodes with acculturation [16-19,22]	Longitudinal sampling through the ongoing dietary transition
Has butyrate been measured in Indian PMOS?	Once, in 57 cases and 30 controls from western India [26]	Multi-region, BMI- and androgen-stratified replication
Are there healthy Indian reference values for short-chain fatty acids?	No population-representative dataset identified	A healthy reference cohort across geographic zones, modelled on the Thai design ²⁸
Can faecal short-chain fatty acids answer these questions?	Not alone; faecal concentration does not reflect production rate [23,27]	Paired plasma measurement and metagenomic functional gene abundance
Is high fermentative capacity necessarily an asset?	Unclear. Fibre-associated reduction in C-reactive protein was absent in <i>P. copri</i> carriers [24], and <i>P. copri</i> was enriched in insulin-resistant PMOS [25]	Clade-resolved metagenomics with paired propionate and butyrate measurement

16. CONCLUSIONS

The proposition that Indian populations are protected from fibre-related metabolic disease by a high-fibre diet does not survive contact with contemporary dietary data. The more accurate and more interesting description is of a population whose microbial fermentative capacity was built by a diet it no longer eats. Whether that mismatch contributes to the lean, insulin-resistant PMOS phenotype that characterises India is unknown, is biologically plausible, and is answerable with studies that are neither large nor expensive. The first and most limiting requirement is a healthy Indian baseline, without which every subsequent measurement is uninterpretable.

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18. Declarations

Competing interests.

The authors are founding members of ThirdBiome and are associated with Aeon Formulations Pvt Ltd, which has developed a patented

microencapsulated glycerol tributyrates (GTB) technology used in the development of the ThirdBiome platform. These relationships constitute a financial interest in the subject matter of this review and are the reason for the disclosure that follows. The GTB technology and the ThirdBiome platform are named once, in the translational perspective section, as one example of a butyrate-delivery formulation approach. No efficacy claim is made for either, no unpublished or proprietary data from either organisation are reported, and no recommendation for clinical use is given anywhere in this article. Neither organisation funded this review, had any role in its design, conduct, literature identification, evidence appraisal or reporting, or reviewed the manuscript before submission. The authors confirm that every evidence assessment in this review reflects the published literature independently of these commercial interests.

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Ethical clearance. Not applicable. This is a narrative review of published literature. No human participants, human material or human data were involved, and no institutional ethics committee approval was required.

Data availability. No new data were generated. The search strategy is described in the manuscript; the full list of retrieved records is available from the corresponding author on reasonable request.

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