

Journal of Orthopaedics Study and Sports Medicine

Genesis-JOSSM-4(1)-39
Volume 4 | Issue 1 | 2026
Open Access
ISSN: 3139-5635

Gut Dysbiosis as a Modifier of Tissue Repair and of Response to Regenerative Therapy: An Umbrella Review of Systematic Reviews Across the Gut–Bone, Gut–Joint, Gut–Muscle and Gut–Skin Axes

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Citation: Kume MH, Furlan B, Boaventura CG, Probst MA, Peracchi E, et al. Gut Dysbiosis as a Modifier of Tissue Repair and of Response to Regenerative Therapy: An Umbrella Review of Systematic Reviews Across the Gut–Bone, Gut–Joint, Gut–Muscle and Gut–Skin Axes. *J Orthop Study Sports Med.* 4(1):1-29.

Received: September 13, 2026 | **Published:** October 04, 2026

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Abstract

Objective: To map, appraise and integrate the totality of systematic-review-level evidence linking gut microbial dysbiosis to tissue repair and to the outcomes of regenerative and cell-based therapies, and to determine whether the microbiome can be positioned as a modifiable response modifier in regenerative medicine rather than as a parallel research interest.

Introduction: Regenerative medicine delivers biologics — platelet-rich plasma (PRP), bone marrow aspirate concentrate, mesenchymal stromal cells (MSCs), extracellular vesicles (EVs) — with little attention to the host's microbial ecology, whereas in transplantation and immuno-oncology microbial diversity and antibiotic exposure are already response-determining variables. No synthesis has connected these literatures under a formal appraisal framework.

Inclusion criteria: Systematic reviews, meta-analyses and overviews of reviews examining (i) gut microbial exposures or microbiota-directed interventions (probiotics, prebiotics, synbiotics, fibre, faecal microbiota transplantation [FMT], postbiotics) with bone, joint, muscle, skin/wound, transplant or regenerative outcomes, or (ii) cell- or vesicle-based regenerative therapies with intestinal barrier or microbiome outcomes.

Methods: PubMed/MEDLINE, PubMed Central, publisher platforms and ClinicalTrials.gov were searched to 13 September 2026. Confidence was rated with AMSTAR 2, certainty with GRADE and overlap with the corrected covered area. Two instruments are proposed: a six-domain Microbiome Evidence Quality extension (MEQ-6) grading the microbial measurement itself, and a four-tier causal ladder separating association, perturbation, restoration and response modification.

Results: Fifty-four systematic-review-level records met criteria across eight domains. Pooled signals were directionally consistent but heterogeneous: lumbar-spine bone mineral density with probiotics, standardised mean difference (SMD) 0.60 (95% CI 0.14–1.05, I^2 92.1%) in the broadest synthesis versus 0.27 (0.09–0.44, I^2 0%) in the most restrictive; knee osteoarthritis pain SMD –0.66 (–1.27 to –0.06, I^2 94.6%); muscle mass SMD 0.42 (0.10–0.74) and strength SMD 0.69 (0.33–1.06); handgrip +2.50 kg (1.33–3.66); psoriasis PASI –3.09 (–5.04 to –0.74). The largest effects occurred inside cell therapy: FMT for steroid-refractory graft-versus-host disease, remission odds ratio 5.51 (1.49–20.35) and 30-day complete response 8.44 (2.98–23.96). Conversely, MSC, MSC-EV and PRP therapies restored microbial structure and barrier integrity preclinically, but no human regenerative trial with a microbiome endpoint was identified, and no registered trial combines microbiome modulation with an orthobiologic. AMSTAR 2 confidence was low or critically low in most reviews; one applied GRADE; all composition-based reviews were measurement-limited under MEQ-6.

Conclusions: Dysbiosis is best treated not as a disease but as a measurable, modifiable modifier of regenerative response. The evidence supports mechanistic plausibility and a moderate signal on surrogate and symptom outcomes, and does not support structural or regenerative claims. A reporting minimum (MIRROR-12) and a stratified-trial agenda are proposed.

Keywords

Gut microbiota; Dysbiosis; Regenerative medicine; Mesenchymal stromal cells; Short-chain fatty acids; Umbrella review.

Introduction

Regenerative medicine has organised itself around the tissue. A degenerative joint, a non-union, a sarcopenic limb or a chronic wound is characterised anatomically and mechanically, and a biologic — PRP, bone marrow aspirate concentrate, an MSC preparation, an EV product — is delivered locally in the expectation that a local deficit will be corrected. The host is treated largely as a container.

Two bodies of evidence make that framing increasingly untenable. The first is experimental: the gut microbiota is a constitutive regulator of the very tissues that regenerative medicine targets. Germ-free mice have higher trabecular bone mass than conventionally raised littermates, with trabecular volumetric BMD of 277 ± 14 versus 208 ± 10 mg/cm³ and a 39.4% increase in bone volume fraction, a phenotype normalised by conventionalization [1]. They are also sarcopenic, with reduced insulin-like growth factor 1 and neuromuscular junction gene expression, partly rescued by microbiota transfer or short-chain fatty acids (SCFAs) [2]. Microbiota-dependent T helper 17 cells expand in the fracture callus and determine torsional stiffness and ultimate torque after femoral fracture, a response prevented by antibiotic ablation [3], and a single commensal, *Akkermansia muciniphila*, increases callus mineralised bone volume and maximum bending load [4]. Repair, in other words, is a microbially conditioned process.

The second is clinical, and it comes from the one branch of cell therapy that has already integrated the microbiome into prognosis. Across 8,767 faecal samples from 1,362 allogeneic haematopoietic-cell

transplant recipients at four centers, higher intestinal microbial diversity was associated with lower mortality, with an adjusted hazard ratio of 0.71 (95% CI 0.55–0.92) [5], replicating an earlier single-centre gradient of 36%, 60% and 67% three-year survival across diversity terciles [6]. In chimeric antigen receptor T-cell therapy, broad-spectrum antibiotic exposure in the four weeks before infusion tracked worse survival and greater neurotoxicity while *Clostridia* abundance tracked day-100 complete response [7], and an independent 172-patient cohort reproduced microbiome-based separation of long-term responders [8]. In melanoma, responder-derived FMT converted 20% of programmed cell death protein 1-refractory patients to objective response [9]. The principle is established: where a living cell product must engraft, function and be tolerated, the recipient's microbial ecology is a determinant of outcome.

Musculoskeletal and aesthetic regenerative medicine — the largest clinical volume in the field — has not inherited that principle. The two literatures have grown in parallel. Umbrella reviews exist on cell-based therapy without microbiome content [10,11] and on microbiome interventions without regenerative content [12,13]. The intersection is occupied only by narrative reviews that neither quantify nor appraise [14,15,16,17,18]. To our knowledge no overview of reviews has addressed dysbiosis and regenerative medicine jointly under AMSTAR 2, GRADE and overlap quantification. That absence is the rationale for the present work.

A second, less comfortable rationale is definitional. “Dysbiosis” has no consensus definition; its dominant characterisation as “imbalance of the microbiota” is circular because homeostasis itself is left undefined, and a semantic audit of published usage found definitions ranging from single-species to phylum-level changes, with roughly one in twelve fitting no category at all [19,20]. α -Diversity, the field's most cited summary statistic, does not reliably indicate health: high diversity accompanies bacterial vaginosis and irritable bowel syndrome, and antibiotics have increased both diversity and mortality in animal models [21]. Sequencing data are compositional, so relative abundances cannot by themselves establish direction of change; reference-frame and absolute-quantification approaches reverse conclusions in controlled experiments, and simulation work shows that relative-data transformations fail to control the false discovery rate [22,23,24]. Any umbrella review in this field therefore inherits a measurement problem that standard appraisal tools were not designed to detect. We address this explicitly rather than implicitly.

Objectives

1. To identify and characterise all systematic-review-level evidence linking gut microbial exposures or microbiota-directed interventions to bone, joint, muscle, skin/wound, ageing and regenerative or transplant outcomes.
2. To identify systematic-review-level evidence in the reverse direction: regenerative therapies (MSCs, EVs, orthobiologics) acting on intestinal barrier, microbiome composition or microbial metabolites.
3. To appraise confidence (AMSTAR 2), certainty (GRADE), primary-study overlap (CCA) and — through a purpose-built extension — the quality of the microbial measurement itself.
4. To test whether the accumulated evidence supports positioning dysbiosis as a modifiable modifier of regenerative treatment response, and to specify the trial designs, reporting standards and claim limits that follow.

Methods

This umbrella review was conducted following the PRIOR statement for overviews of reviews [25,26], with PRISMA 2020 items applied where relevant [27], and with the umbrella-review methodology of the JBI Manual for Evidence Synthesis and Chapter V of the Cochrane Handbook [28,29]. The review was not prospectively registered; PROSPERO does not currently address overviews of reviews in its published eligibility criteria [30], and this omission is declared as a limitation.

Eligibility criteria

Population: humans of any age with, or at risk of, musculoskeletal, cutaneous, intestinal or transplant-related tissue injury or degeneration; animal models were eligible when the synthesis was systematic and no human synthesis existed for that question.

Exposure or intervention: (i) gut microbial composition, diversity or metabolite exposure; (ii) microbiota-directed interventions — probiotics, prebiotics, synbiotics, dietary fibre or whole-diet patterns, FMT, live biotherapeutic products, postbiotics as defined by the International Scientific Association for Probiotics and Prebiotics [31]; or (iii) cell-based and vesicle-based regenerative therapies where a microbiome, barrier or microbial-metabolite outcome was reported.

Comparator: placebo, sham, usual care, active comparator, or non-diseased control, as reported by the included review.

Outcomes: prioritised hierarchically as (a) patient-important clinical outcomes (pain, function, fracture, healing, remission, survival); (b) structural or compositional outcomes (BMD, cartilage, muscle mass, wound closure); (c) surrogate and biomarker outcomes (α/β -diversity, SCFA concentration, zonulin, C-reactive protein [CRP], bone turnover markers). Surrogate outcomes were never permitted to substitute for clinical outcomes in the synthesis.

Study design: systematic reviews with or without meta-analysis, overviews of reviews, and systematic reviews of preclinical studies. Narrative reviews, editorials and single primary studies were excluded from the synthesis but were retained as contextual or mechanistic citations and are labelled as such throughout.

Information sources and search

PubMed/MEDLINE, PubMed Central, and the platforms of Frontiers, BMJ, Wiley, Springer Nature, Elsevier, MDPI, Oxford University Press, Cambridge University Press, The Lancet family, the American Society for Microbiology and Baishideng were searched from inception to 13 September 2026, together with ClinicalTrials.gov (application programming interface v2) for the registered-trial landscape and the websites of the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for regulatory status. Searches combined microbial terms (gut microbiota, microbiome, dysbiosis, probiotic, prebiotic, synbiotic, faecal microbiota transplantation, short-chain fatty acid, lipopolysaccharide, trimethylamine N-oxide, bile acid, indole) with tissue and therapy terms (bone mineral density, osteoporosis, fracture healing, osteoarthritis, cartilage, sarcopenia, muscle, wound healing, skin, mesenchymal stromal cell, extracellular vesicle, exosome, platelet-rich plasma, haematopoietic cell transplantation, graft-versus-host disease) and design terms (systematic review, meta-analysis, umbrella

review). Searches were domain-specific and iterative rather than a single global Boolean strategy; reference lists of included reviews and of the identified narrative reviews were hand-searched. No language restriction was applied; all included records were available in English.

Selection, data extraction and handling of overlap

Records were screened against the eligibility criteria and the following were extracted per included review: axis and domain, first author and year, journal, design, population, exposure or intervention, comparator, number of primary studies and participants, pooled effect estimates with 95% confidence intervals, heterogeneity (I^2), appraisal instrument used by the review authors, any stated certainty rating, and registration identifier. Where a publisher page displayed only an abstract and a value could not be confirmed at source, the cell was recorded as not available rather than inferred; these instances are visible in (Tables 2-6) and are counted in the limitations.

Overlap of primary studies between reviews addressing the same question was quantified with the corrected covered area, $CCA = (N - r) / (rc - r)$, where N is the number of publications including double counting, r the number of index publications and c the number of reviews, interpreted against the thresholds of slight (0–5%), moderate (6–10%), high (11–15%) and very high (>15%) overlap [32], with graphical exploration of pairwise overlap as implemented in the GROOVE tool [33]. Where reviews were discordant, they were not averaged; the more recent, more restrictive and methodologically stronger review was given interpretive priority, and the discordance itself is reported as a finding.

Quality, certainty and the microbiome-specific extension

Confidence in each included review was rated with AMSTAR 2, applying its seven critical domains — protocol registration, search adequacy, justification of exclusions, risk-of-bias assessment, meta-analytical methods, consideration of bias in interpretation and publication bias — and the published rules for high, moderate, low and critically low confidence [34,35]; the ROBIS domains were used as a cross-check for reviews whose scope or eligibility appeared unstable [36]. Certainty for each pooled outcome was expressed with GRADE, starting high for randomised bodies of evidence and low for non-randomised evidence, then downgraded for risk of bias, inconsistency, indirectness, imprecision and publication bias [37,38].

Neither AMSTAR 2 nor GRADE interrogates the validity of the microbial measurement. We therefore specified, a priori for this review, a six-domain Microbiome Evidence Quality extension (MEQ-6), applied to every included review that reported a microbial exposure (Table 7):

1. **Definitional transparency:** is “dysbiosis” operationally defined, or used as an undefined descriptor [19,20]?
2. **Quantification:** absolute or spike-in quantitative profiling versus relative abundance only [23].
3. **Compositional handling:** use of a reference frame or compositionally aware statistics versus naive relative-abundance inference [22,24].
4. **Diversity dependence:** is the claim carried by α -diversity alone, which is not a health metric [21]?
5. **Confounder control:** body mass index, diet, antibiotic exposure and physical activity, all of which attenuate or abolish microbiome–phenotype associations [39].

6. **Outcome relevance and reporting adherence:** clinical versus surrogate endpoint, and adherence to microbiome reporting standards such as STORMS [40,41].

Each domain was rated adequate, partial or inadequate; a review meeting fewer than three domains adequately was flagged as measurement-limited, and its directional claims were reported as hypothesis-generating irrespective of its AMSTAR 2 rating.

Synthesis and the causal ladder

Because the included reviews address heterogeneous populations, exposures and outcomes, no pooling across reviews was attempted; synthesis was structured, tabular and narrative, as recommended for overviews [28]. Findings were additionally classified on a four-tier causal ladder specified for this review:

- **Tier 1 Association:** dysbiosis correlates with a tissue phenotype.
- **Tier 2 Perturbation:** experimental depletion, germ-free status or colonisation changes the tissue phenotype.
- **Tier 3 Restoration:** a microbiota-directed intervention changes a patient-important outcome in controlled human studies.
- **Tier 4 Response modification:** microbial state measurably alters the outcome of a regenerative or cell-based therapy.

Tier 4 is the level at which the microbiome becomes actionable for regenerative medicine, and is the level against which the field's current claims should be judged.

Results

Overview of the included evidence

Fifty-four systematic-review-level records met the eligibility criteria and are distributed across eight domains: gut–bone (10), gut–joint (8), gut–muscle (8), gut–skin (7), ageing, frailty and inflammaging (5), FMT and transplant outcomes (5), regenerative therapy acting on the gut (8), and microbial mediators (9). Of these, 41 performed quantitative pooling; 2 were protocols without results [42,43]; 5 were systematic reviews of preclinical studies only [44,45,46,47,48]; and 3 were pre-existing umbrella reviews on one side of the question [10,12,13], plus a fourth on MSC-derived EVs without microbiome content [11]. (**Table 1**) summarises the distribution, the number of reviews reporting registration, the number reporting a formal appraisal tool and the number reporting any certainty rating.

Counts reflect what was displayed on the retrievable record for each review; absence of a displayed item was recorded as absent and is a source of provisional judgement (see Limitations). The two records reporting certainty are Peng 2026 (GRADE by outcome) and Duan 2026 (AMSTAR 2 + GRADE + corrected covered area).

Three structural features of this literature emerged immediately and shape every subsequent finding.

1. **Registration and certainty rating are the exception:** Of 54 records, 11 reported a PROSPERO identifier and only one reported GRADE certainty for its outcomes [49]. One of the pre-existing umbrella reviews applied AMSTAR 2, GRADE and CCA together [10], and one concluded that the majority of published syntheses in its field were of critically low confidence [12].

2. **Heterogeneity is extreme where effects are largest:** I^2 exceeded 90% for the headline pooled estimates in the gut–bone [50] and gut–joint [51] domains, and reached 99.7% for a circulating-biomarker synthesis [52]. Conversely, the pooled estimates with I^2 of 0% are the smallest in magnitude [53,54].
3. **The outcome hierarchy is inverted relative to clinical need:** Surrogate and symptom endpoints are abundantly meta-analysed; structural and regenerative endpoints — fracture union, cartilage volume, tendon integrity, graft incorporation — are absent from every included synthesis.

Gut–bone axis: consistent direction, unstable magnitude, no regenerative endpoint

Probiotic supplementation in postmenopausal women improved lumbar-spine BMD in every synthesis that pooled it, but the magnitude was determined almost entirely by inclusion breadth. The broadest synthesis pooled 12 randomised controlled trials (RCTs) and 1,183 participants and reported a standardised mean difference (SMD) of 0.60 (95% CI 0.14–1.05; $p = 0.01$) for lumbar spine and 0.74 (0.15–1.33) for hip, with I^2 of 92.1% and 94.5% respectively, alongside reductions in C-terminal telopeptide (SMD –1.51, –1.88 to –0.41) and bone alkaline phosphatase (SMD –1.80, –2.78 to –0.81) and a non-significant effect on N-terminal propeptide of type I procollagen [50]. A more restrictive synthesis limited to five RCTs with intervention duration beyond six months and 497 completers, all judged at low risk of bias, reported lumbar-spine SMD 0.27 (0.09–0.44) with I^2 of 0%, a non-significant hip effect (0.22, –0.07 to 0.52) and a bone-resorption reduction of the same direction but a third of the magnitude (CTX SMD –0.34, –0.60 to –0.09) [53]. A third synthesis of 10 RCTs and 1,156 patients found no significant absolute lumbar BMD gain (weighted mean difference 0.04, –0.00 to 0.09) and a significant effect only for percentage change (SMD 1.16, 0.21–2.12), with no excess of adverse events (risk ratio [RR] 1.02, 0.92–1.12) [55]. The most recent and largest pooling reported absolute gains of +0.010 g/cm² at the lumbar spine and +0.022 g/cm² at the hip with no effect on femoral-neck BMD, P1NP or CTX, and described moderate-to-high heterogeneity throughout [56].

This pattern — effect size falling as methodological restriction rises, while direction is preserved — is the signature of a real but small effect inflated by small-trial heterogeneity. It is reproduced at the level of individual trials: *Limosilactobacillus reuteri* 6475 reduced tibia total volumetric BMD loss by a mean difference of 1.02% (0.02–2.03) over 12 months in 70 completers [57], and a three-strain *Lactobacillus* mixture reduced lumbar-spine BMD loss by 0.71% (0.06–1.35; $p = 0.031$), equivalent to +7.44 mg/cm² (0.38–14.50), in 249 early postmenopausal women [58] — yet a subsequent two-year randomised evaluation of the same *L. reuteri* strain did not confirm a bone-density benefit [59]. We therefore treat the gut–bone probiotic signal as directionally consistent for BMD and bone turnover, small in absolute terms, and unproven for fracture.

Observational composition studies point the same way with weaker precision. Across 16 studies and 2,340 participants, the ACE richness index differed between osteoporosis and controls (SMD 1.05, 0.00–2.10; $p = 0.05$) and *Blautia* was reduced (SMD –0.32, –0.65 to –0.00), while Chao1, Shannon and Simpson indices and all phylum-level comparisons were non-significant [60]. Other syntheses are mutually inconsistent: taxon-level differences without pooled effects and contradictory *Lactobacillus* findings in 12 studies [61]; reduced ACE ($p = 0.04$) with raised primary bile acids, lipopolysaccharide (LPS), tumour necrosis factor α and T helper 17/regulatory T cell ratios in 1,520 postmenopausal women [62]; and no α -diversity

difference at all in 10 studies [63]. A formal reanalysis of five case–control datasets found Shannon diversity significant at $p = 0.049$ with an effect size of 0.17 and statistical power of 0.40, and no difference in the Firmicutes/Bacteroidetes ratio ($p = 0.58$) [64] — a power of 0.40 attached to the field’s most-cited diversity claim is itself a finding.

No systematic review of microbiota-directed intervention for fracture healing or bone regeneration exists. The best available evidence is a single murine femoral-osteotomy experiment in 95 animals in which pre-fracture VSL#3 raised day-3 interleukin 6 (4.33 ± 0.74 versus 2.67 ± 0.27), interleukin 17F (5.07 ± 1.34 versus 2.04 ± 0.30) and Runx2 expression, all $p < 0.05$, with no change in transforming growth factor β ($p = 0.46$) [65]. Mechanistically, microbiota-dependent T helper 17 cells are required for normal callus formation and biomechanical competence [3], Akkermansia muciniphila supplementation improves callus mineralisation and bending load [4], probiotic Limosilactobacillus reuteri prevents bone loss in a murine menopause model [66], SCFAs regulate systemic bone mass through regulatory T cells and inhibition of osteoclastogenesis [67,68], and the microbiota drives insulin-like growth factor 1-dependent bone formation [69,70]. Germ-free animals show compartment- and sex-specific alterations in bone quality, which qualifies the simple “germ-free bones are stronger” narrative [71]. On our causal ladder, gut–bone evidence reaches Tier 3 for BMD and bone turnover and Tier 2 only for fracture repair.

Gut–joint axis: the largest symptom effects with the largest uncertainty

Microbiota-targeted interventions in osteoarthritis (OA) were pooled across 18 RCTs and 2,080 participants, yielding visual analogue scale (VAS) pain SMD -0.66 (-1.27 to -0.06 ; $p = 0.03$), WOMAC pain SMD -0.62 (-0.97 to -0.27) and WOMAC function SMD -0.40 (-0.64 to -0.17), with I^2 of 94.6%, 75.5% and 36.3% [51]. Restricted to oral probiotics in confirmed knee OA, five RCTs and 694 participants gave still larger estimates (WOMAC total SMD -1.15 , -2.14 to -0.17 ; VAS SMD -1.31 , -2.50 to -0.12), with heterogeneity falling to 9% only after exclusions [72]. A three-study synthesis using unstandardised scales found no significant effect on any outcome, with confidence intervals an order of magnitude wider (WOMAC SMD -6.15 , -22.04 to 9.74 ; VAS -2.26 , -4.87 to 0.34) [73]. Across inflammatory arthritis, 12 studies gave quality-of-life SMD -0.37 (-0.59 to -0.15), pain mean difference -8.97 mm on VAS (-15.38 to -2.56) and CRP -2.33 mg/L (-4.26 to -0.41), with no excess of minor adverse events (RR 1.02, 0.69–1.51) [74]. These reviews overlap substantially in their primary trials — notably the 537-patient Lactocaseibacillus casei Shirota trial in knee OA [75,76] — so their estimates cannot be treated as independent replications.

The observational base is the strongest in this domain. A meta-analysis of 92 observational studies and 11,998 participants across 14 rheumatic diseases found reduced observed species overall (SMD -0.36 , -0.63 to -0.09 ; $p = 0.01$) and in rheumatoid arthritis specifically (SMD -0.51 , -0.78 to -0.24 ; $p < 0.001$), with Chao1 SMD -0.57 and I^2 of 88% [77]. In two population cohorts totalling 2,256 individuals, higher Streptococcus abundance was associated with higher knee WOMAC pain at $p = 1.3 \times 10^{-8}$, an effect the authors attributed to local joint inflammation and which persisted after body mass index adjustment [39]. A subsequent systematic review with meta-analysis of five studies and 756 OA patients, however, found no significant association for either Streptococcus (standardised β 0.003, -0.049 to 0.052) or plasma tryptophan-pathway markers (β 0, -0.071 to 0.070) [78]. This is the clearest instance in the review of a

single high-profile primary finding not surviving systematic pooling, and it is reported here as a discordance rather than resolved in either direction.

Mechanistic support for the gut–joint axis is substantial: *Prevotella copri* expansion correlates with new-onset untreated rheumatoid arthritis [79], segmented filamentous bacteria drive autoimmune arthritis through T helper 17 induction [80,81], short-term dietary fibre shifts the arthritic immune phenotype [82], both systemic and local LPS burden associate with knee OA severity and macrophage activation [83,84], and trimethylamine N-oxide sensitises chondrocytes to mechanical load through Piezo1 [85] while promoting osteoclastogenesis [86] and impairing osteogenic differentiation of bone-marrow stromal cells [87]; LPS additionally exacerbates neurogenic heterotopic ossification through Toll-like receptor 4 signalling [88]. No systematic review restricted to gut dysbiosis in OA with cartilage-structural endpoints was identified; intervertebral-disc evidence is confined to Mendelian randomisation, in which only the genus *Eubacterium coprostanoligenes* group survived false-discovery correction for disc degeneration [89], and to narrative review [90,91].

Gut–muscle axis: the most internally consistent human signal

Probiotic supplementation improved muscle mass (SMD 0.42, 0.10–0.74; $p = 0.009$, 10 comparisons) and global muscle strength (SMD 0.69, 0.33–1.06; $p = 0.0002$, 6 comparisons) across 24 RCTs, while total lean mass was unchanged (SMD –0.03, –0.19 to 0.13) — an internally coherent pattern in which a functional tissue compartment responds while total body lean mass does not [92]. In adults aged 55 years and over, 17 pooled studies gave muscle mass weighted mean difference 0.50 (0.01–0.99) with I^2 of 0% [93]. The most restrictive synthesis, 8 RCTs and 837 older adults, reported handgrip strength +2.50 kg (1.33–3.66; $p < 0.001$) and gait speed +0.10 m/s (0.03–0.16; $p = 0.003$), both with I^2 of 0% — but the handgrip effect collapsed to 1.16 kg (–2.45 to 4.77; $p = 0.53$) on sensitivity analysis [54]. Across 63 studies and 4,842 participants, probiotics were associated with +1.90 kg strength and +0.08 m/s gait speed [94]. A gait-speed gain of 0.10 m/s is at or above the commonly used threshold for a clinically meaningful change in older adults, which makes this the one domain where the pooled effect is plausibly patient-important; the sensitivity-analysis collapse is why we do not upgrade it further.

Composition data are correspondingly consistent. Pooled α -diversity was lower in sarcopenia across 18 studies and 3,132 participants (SMD –0.41, –0.57 to –0.26; observed species SMD –0.62, –0.82 to –0.42; Chao1 SMD –0.45, –0.67 to –0.23; Shannon SMD –0.30, –0.60 to –0.00) [95], and 17 cross-sectional studies in 4,307 participants found reduced richness with depletion of *Faecalibacterium*, *Prevotella* and *Ruminococcaceae* [96,97]. Physical activity itself alters community structure across 38 studies [98], which makes exercise both a confounder and a co-intervention here.

The mechanistic chain here is the most completely specified of the four axes: germ-free and antibiotic-treated animals are sarcopenic with reduced insulin-like growth factor 1 and impaired neuromuscular junction gene expression, partially rescued by SCFA administration [2,99]; SCFAs act directly on myotube metabolism [100,101]; antibiotic-induced microbiota depletion causes muscle atrophy through the farnesoid X receptor–fibroblast growth factor 15/19 axis [102]; aryl hydrocarbon receptor ligands of microbial tryptophan origin modulate muscle phenotype [103,104]; LPS inhibits myogenic differentiation of C2C12 myoblasts [105]; and a single *Lactobacillus plantarum* strain sustains juvenile growth under

nutritional restriction [106]. In older adults, a prebiotic formulation improved exhaustion ($p < 0.01$) and handgrip strength ($p < 0.05$) against placebo in 60 participants [107]. Human proof that fermentation capacity determines response to a non-microbial intervention exists: in 39 medication-naïve men with prediabetes, gut microbiome fermentation capacity determined the metabolic efficacy of exercise, and responder faecal transfer reproduced the benefit in mice [108]. That study is, to our reading, the cleanest published demonstration of Tier 4 response modification outside oncology and transplantation.

Gut–skin axis: the only GRADE-rated evidence, and no regenerative endpoint

Nineteen RCTs and 1,384 critically ill adults received enteral probiotics or synbiotics at 10^9 – 10^{11} colony-forming units per day for 7–21 days; certainty was moderate for wound infection, overall infection, hospital length of stay and antibiotic duration, low for intensive-care length of stay, mortality and CRP, and very low for wound-healing time [49]. This is the only included review with an explicit GRADE profile, and it is notable that the outcome closest to regeneration — healing time — carries the lowest certainty in it.

Systemic probiotics in cutaneous and mucosal wounds were reviewed across 7 studies and 348 participants without pooling; the strongest single result was a paediatric burn trial in which grafting was required in 10% versus 40% ($p = 0.028$) [109], and 22 surgical publications reported reduced antibiotic duration and hospital stay without effect sizes [110]. Animal wound data are markedly stronger than human data: pooled wound-contraction acceleration reached Hedges' g -2.55 (-3.59 to -1.50) across 12 experiments [44]. In inflammatory skin disease, adjuvant oral probiotics improved PASI change (mean difference -3.09 , -5.04 to -0.74 ; $p = 0.01$) and CRP (-2.36 , -2.77 to -1.95) without reaching significance for PASI-75 (RR 1.40, 0.98–1.98; $p = 0.06$) or dermatology-specific quality of life, with I^2 of 85% for PASI change [111]; in paediatric atopic dermatitis, continuous severity outcomes improved (mean difference -4.24 , -7.78 to -0.71) while dichotomous outcomes did not (odds ratio 1.75, 0.70–4.35) [112]; acne syntheses reported no stable pooled estimate [113].

Two mechanistic findings reframe this axis as bidirectional. Dermal wounding itself remodels the gut microbiome and increases susceptibility to colitis [114], commensal *Staphylococcus epidermidis* shapes cutaneous repair immunity [115], and chronic-wound outcome tracks the local wound microbiome [116,117,118,119]. No systematic review of gut-directed intervention in chronic or diabetic wound healing was confirmed; the only registered diabetic-foot probiotic study identified is topical rather than enteral [120].

Ageing, frailty and inflammaging: mechanism without synthesis

Seven studies in a systematic review of ageing linked an “aged-type” microbiota to raised interleukin 6, interleukin 10, tumour necrosis factor α and transforming growth factor β and to the senescence markers p16 and SAMHD1, with activation of Toll-like receptor 2/nuclear factor κB /mechanistic target of rapamycin signalling [121]. Eleven observational studies in 912 older adults found lower α -diversity in frailty in only two of seven reporting studies, with consistent depletion of *Prevotella*, *Faecalibacterium* and *Roseburia* [122,123], and a 27-study review of ageing and longevity synthesised narratively [124]. Experimental work is more decisive than the human syntheses: faecal transfer between young and aged mice transfers age-associated microbial and immune phenotypes [125,126], centenarian microbiomes

carry distinctive signatures [127,128], and the microbial metabolite phenylacetylglutamine drives cellular senescence through adrenergic signalling [129]. No systematic review pooling gut microbiota against cellular-senescence endpoints was identified, and the only registered systematic work at the dysbiosis–osteosarcopenia intersection remains a protocol [43].

Microbiota-directed therapy inside cell therapy: the strongest clinical effects in the field

The largest effect sizes in this entire review are not in musculoskeletal medicine but inside haematopoietic cell transplantation. For steroid-refractory graft-versus-host disease, FMT achieved clinical remission with an OR of 5.51 (1.49–20.35) in cohort studies, with pooled remission of 64% (51–77%) in prospective single-arm studies and 81% (62–95%) in retrospective series across 23 studies and 242 patients, and FMT-related infection in 5 of 242 (2.1%) [130]. A subsequent synthesis of 6 studies and 262 patients reported 14-day complete response OR 8.54 (2.49–29.29) and 30-day complete response OR 8.44 (2.98–23.96) for gastrointestinal acute graft-versus-host disease, with increased *Bacteroides* (SMD 1.59, 0.15–3.03) and *Bifidobacterium* (SMD 1.01, 0.41–1.60) and no increase in bacteraemia (OR 0.37, 0.13–1.01), while prophylactic use did not reduce incidence (OR 1.30, 0.10–16.72) [131]. A third-party FMT pilot in high-risk lower-gastrointestinal acute graft-versus-host disease achieved 70% organ-specific complete response at day 28 in 10 participants [132]. In autoimmune and autoinflammatory disease, 14 RCTs and 571 participants showed ulcerative-colitis clinical remission RR 1.89 (1.18–3.00), endoscopic remission RR 2.40 (1.13–5.12) and unchanged adverse-event rates (RR 1.02, 0.81–1.17) [133], consistent with an independent synthesis of 14 RCTs and 666 participants (remission RR 1.44, 1.03–2.02) [134].

These effects sit on an observational foundation already strong enough to change practice: microbiota diversity predicts mortality after allogeneic transplantation (adjusted hazard ratio 0.71, 0.55–0.92, across 1,362 patients) [5,6,135], antibiotic class and *Clostridia* abundance track CAR T-cell outcomes and neurotoxicity [7,8], and responder-derived FMT converts PD-1-refractory melanoma in a minority of patients [9,136]. The asymmetry is the point: in the one field where cells are infused and must engraft, the microbiome is already a prognostic and interventional variable, and its effect sizes dwarf anything reported in the musculoskeletal axes.

The reverse direction: regenerative therapies as microbiome-modifying agents

Evidence that regenerative therapy acts on the gut is substantial but almost entirely preclinical. MSC therapy for complex perianal fistula — the field’s most mature localised-regeneration indication — achieved short-term healing RR 2.49 (1.63–3.80; $p < 0.0001$), with attenuation over time (medium-term RR 1.25, 1.00–1.55; approximately one year RR 1.35, 1.10–1.67; beyond one year RR 1.85, 1.10–3.10) and benefit confined to Crohn’s fistulas (RR 1.43, 1.09–1.80) rather than cryptoglandular disease (RR 1.16, 0.69–1.95) [137]. Pooled healing across 43 studies and 1,160 patients was 58.1% (51.5–64.7), and in the 8 RCTs healing odds ratio (OR) was 1.81 (1.23–2.67) with complications unchanged (OR 1.00, 0.70–1.43) [138]; response persisted at 96 weeks (OR 2.08, 1.17–3.68) with disease-activity indices non-significant [139,140]. Long-term registry follow-up of darvadstrocel-treated patients reported combined remission of 53.5% versus 45.7% at 156 weeks, an interval whose confidence bounds do not exclude no difference [141]. The pre-existing umbrella review of this field rated most of its 35 included syntheses as of low or critically low confidence and reported no microbiome content whatsoever [10].

In animal models, extracellular vesicles reduced colitis disease-activity index by SMD -3.00 (-3.52 to -2.48) overall, with the MSC-derived subgroup at SMD -3.33 (-3.99 to -2.68) and the MISEV2018-compliant subset attenuated to -2.27 (-3.05 to -1.49) — the attenuation itself being an index of reporting quality [46]; a parallel synthesis of 21 studies reported disease-activity SMD -2.46 (-3.31 to -1.62) and histological score SMD -2.37 (-3.58 to -1.16) [45]. MSCs improved survival after intestinal ischaemia–reperfusion injury (day 7 RR 2.44, 1.63–3.66) and reduced mucosal injury (Chiu’s score SMD -1.96 , -2.72 to -1.19) [47]. Systemic MSC therapy remodels the gut microbiome and restores colonic farnesoid X receptor signalling in experimental colitis [142], and MSC-derived exosomes mitigate colitis through metagenomic and metabolomic remodelling [143]. Most striking for musculoskeletal practice, intra-articular platelet-rich plasma restored gut microbial richness, *Ligilactobacillus murinus* abundance, SCFA concentrations and the barrier proteins occludin and ZO-1 in rodent osteoarthritis — while the same signature failed to replicate in a 9-patient human series [144,145].

Three findings from this section are, to our knowledge, reported together here for the first time: (i) no human trial of an MSC, EV or orthobiologic product has a microbiome endpoint; (ii) no registered trial anywhere combines microbiome modulation with an orthobiologic (platelet-rich plasma, bone marrow aspirate concentrate or MSC) or with a cartilage, tendon or fracture regeneration endpoint — searches pairing probiotic or microbiome terms with mesenchymal, platelet-rich plasma, cartilage, tendon, fracture healing and spinal fusion returned none, the sole product-level pairing being a probiotic with a secretome in acne [120,146]; and (iii) the mechanistic substrate for interaction is already characterised, since LPS and Toll-like receptor ligands of microbial origin reprogramme MSC phenotype, secretome and vesicle output [147,148,149,150,151], and autologous bone-marrow MSC potency itself varies by donor in a function-associated manner [152]. A host-derived agonist that changes the product being administered is, by definition, a response modifier.

Microbial mediators: no synthesis links them to regenerative tissue endpoints

Prebiotic and SCFA interventions reduced high-sensitivity CRP (SMD -0.83 , -1.56 to -0.11) and plasma LPS (SMD -1.20 , -1.89 to -0.51) in overweight and obesity, with I^2 of 86% and 87% [153], and oral sodium butyrate 600 mg/day improved erythrocyte sedimentation rate and partial Mayo score in active ulcerative colitis [154]. Serum LPS-binding protein was higher in metabolic syndrome (SMD 5.313, 0.606–10.020) with I^2 of 99.7%, a value that makes the pooled estimate uninterpretable [52,155,156]. Circulating trimethylamine N-oxide tracked kidney function across 32 studies and 42,062 participants [157], yet the umbrella review of that literature judged most constituent syntheses to be of critically low confidence [12]. Bile-acid syntheses in obesity found fasting total bile acids unassociated with adiposity and fibroblast growth factor 19 inversely associated [158], while bile-acid receptor signalling is required for survival in bacterial sepsis [159]. Pro-, pre- and synbiotic effects on anthropometric and cardiometabolic markers were summarised across 24 reviews and 25,973 participants under AMSTAR 2 [13].

Not one of these mediator syntheses uses a bone, cartilage, tendon, muscle-structural or stem/progenitor-cell outcome. Butyrate, propionate, indoles, secondary bile acids and trimethylamine N-oxide all have documented direct effects on osteoblasts, osteoclasts, chondrocytes, myotubes and marrow stromal cells [67,68,85,86,87,102,160,161], yet the systematic-review literature has pooled them

only against metabolic, renal, cardiovascular and general inflammatory endpoints. This is the single largest synthesis-level gap identified in this review.

Methodological quality, overlap and microbiome-specific appraisal

AMSTAR 2 confidence was low or critically low for the large majority of included reviews, driven by the same three critical domains: absence of protocol registration (43 of 54 records did not report one), absence of any assessment of publication bias in the reporting available to us, and absence of explicit consideration of risk of bias when interpreting results. Because full texts and supplements were not retrievable for every record, domain-level judgements are reported as provisional where the retrievable record did not display the relevant methods, and no review is assigned high confidence on the basis of an abstract alone. Two records were protocols and were not rated [42,43].

The corrected covered area could not be computed for most domains, because primary-study lists were not extractable from the retrievable records; where denominators are known, overlap is evidently substantial rather than slight — the five-RCT bone synthesis [53] is contained almost entirely within the twelve-RCT synthesis [50], and the osteoarthritis reviews [51,72,73] share the same small set of index trials [75]. We therefore report overlap qualitatively, treat same-domain reviews as non-independent, and flag the missing CCA computation as a limitation rather than presenting an uncomputed value as slight overlap [32,33].

Applying MEQ-6 (**Table 7**) changes the picture more than AMSTAR 2 does. No included review operationally defined dysbiosis; none used absolute or quantitative microbial profiling; none applied a compositionally aware reference frame; and 11 of the composition-based reviews rested their principal claim on α -diversity alone. Under the MEQ-6 rule specified in the Methods, every composition-based review in this umbrella review is measurement-limited, and its directional taxonomic claims should be read as hypothesis-generating regardless of its AMSTAR 2 rating. The intervention reviews fare better, because a randomised probiotic exposure does not require compositional inference to be valid — which is why the intervention literature, despite its heterogeneity, carries more interpretive weight here than the far larger observational literature.

Composition-based reviews only ($n = 18$ across the bone, joint, muscle, ageing and mediator domains). Under the pre-specified rule (fewer than three domains adequate = measurement-limited), all 18 are measurement-limited, and their taxon-level claims are reported as hypothesis-generating irrespective of AMSTAR 2 confidence.

Discussion

What this review establishes, and what it does not

Read against the causal ladder specified a priori, the evidence distributes unevenly. Tier 1 association is secure across all four axes, with the caveat that every composition-based review is measurement-limited under MEQ-6. Tier 2 perturbation is secure in animals for bone, muscle, joint and wound repair, including the biomechanical competence of the fracture callus [2,3,4,44]. Tier 3 restoration is supported for bone mineral density, osteoarthritis symptoms, muscle mass, strength and gait speed, and psoriasis severity — but with effect magnitudes that shrink as methodological restriction tightens [53,54], heterogeneity that

frequently exceeds 90% [50,51], and not a single structural or regenerative endpoint anywhere in the pooled literature. Tier 4 response modification is established only in haematopoietic cell transplantation, CAR T-cell therapy and immune-checkpoint blockade [5,7,9], with one clean non-oncological human demonstration in exercise metabolism [108], and is entirely unexamined in musculoskeletal and aesthetic regenerative medicine.

The most defensible claim this evidence supports is therefore narrow and, we would argue, more useful than a broad one: dysbiosis is best treated not as a disease to be corrected but as a measurable, modifiable modifier of the response to regenerative therapy. The claim that probiotics regenerate tissue is unsupported. The claim that the microbial state of the host is irrelevant to the outcome of an infused or injected biologic is, given the transplantation and checkpoint literature, no longer tenable either.

Why the transplantation precedent is the right analogy

Allogeneic haematopoietic cell transplantation adopted the microbiome as a prognostic variable because it had three things musculoskeletal regenerative medicine currently lacks: a hard outcome measured in every patient, a mechanistic pathway from mucosal injury to systemic immune activation, and cohorts large enough to detect a diversity gradient [5,6]. The same logic transfers to orthobiologics with minimal adaptation. MSC and platelet-rich plasma products act through immunomodulation as much as through structural replacement; their phenotype and secretome are altered by Toll-like receptor ligands of microbial origin [147,148,149,150,151]; the recipient's systemic LPS burden is measurable, varies between patients and associates with joint disease severity [83,84]; and autologous product potency already varies by donor in ways that are only partly explained [152]. The field already accepts non-microbial host modifiers of injected-therapy response — obesity and radiological severity predict viscosupplementation failure in knee osteoarthritis [162] — so the objection cannot be that host stratification is foreign to the discipline. A host factor that plausibly alters both the product and the target tissue is precisely the kind of variable that should be measured before it is assumed away.

Bidirectionality is the finding most likely to be missed

Two-thirds of this literature asks whether dysbiosis impairs repair. The reverse question — whether regenerative interventions alter the microbiome — is answered affirmatively wherever it has been asked, and almost nowhere in humans. MSCs and MSC-derived exosomes remodel community structure and restore colonic farnesoid X receptor signalling in colitis [142,143]; extracellular vesicles reduce experimental colitis with large pooled effects [45,46]; MSCs preserve the barrier after intestinal ischaemia-reperfusion [47]; intra-articular platelet-rich plasma restored gut richness, *Ligilactobacillus murinus*, SCFAs and tight-junction proteins in rats and failed to replicate in nine humans [144,145]; and even a dermal wound remodels the gut microbiome [114]. The practical consequence is that the microbiome belongs in regenerative trials as a covariate and as an outcome, not one or the other. A single stool sample at baseline and at follow-up, added to trials already being conducted, would convert an unexamined question into an answerable one at negligible marginal cost.

Discordance, and how we resolved it

Three discordances in this review deserve explicit statement rather than averaging. First, gut–bone: the probiotic BMD effect ranges from SMD 0.60 with I^2 92.1% in the broadest synthesis [50] to 0.27 with I^2 0%

in the most restrictive [53], with the most recent synthesis reporting absolute gains of 0.010–0.022 g/cm² [56] and the longest individual trial of the best-studied strain failing to confirm benefit [59]. We give interpretive priority to the restrictive estimate, which implies a real effect of roughly a quarter of a standard deviation — not nothing, and not a therapy for osteoporosis. Second, gut–joint: a population-level *Streptococcus*–pain association at $p = 1.3 \times 10^{-8}$ [39] does not survive systematic pooling [78]; we report both and conclude that the taxon-level claim is unproven while the axis-level claim survives on other grounds [77]. Third, gut–skin: the same intervention class carries moderate certainty for wound infection and very low certainty for wound-healing time within a single GRADE-rated review [49] — an internal discordance that should discipline any claim that anti-infective benefit implies pro-regenerative benefit.

Claims discipline and the regulatory boundary

The distance between mechanistic plausibility and regulatory approval in this field is wide and frequently elided in clinical communication. Approved microbiome products exist, but for one indication: recurrent *Clostridioides difficile* infection, addressed by a rectally administered live biotherapeutic and an orally administered spore preparation [163,164]. Investigational faecal microbiota transplantation outside that indication carries a safety alert following transmission of multidrug-resistant organisms [165,166], and the European regulatory framework for microbiome-based products remains at the concept-paper and horizon-scanning stage [167,168]. Probiotics and postbiotics marketed as foods or supplements are not approved to treat osteoporosis, osteoarthritis, sarcopenia or wounds, and the postbiotic category itself was only recently given a consensus definition [31]. Engineered live biotherapeutics and phage approaches remain constrained by persistence, containment and manufacturing questions [169,170]. The claim ladder we recommend to clinicians is the one used in this review: mechanistic plausibility, surrogate signal, clinical benefit, regulatory approval — four separate statements, never substituted for one another.

A reporting minimum: MIRROR-12

Because no included review met more than three MEQ-6 domains, appraisal alone cannot fix this literature; the primary studies must report differently. We propose MIRROR-12 (Microbiome Reporting in Regenerative Outcomes Research), a 12-item minimum for any study combining a microbial measurement with a regenerative or cell-based intervention, set out in full in (Table 8). It spans definitional, sampling, platform, quantification, statistical, diversity-interpretation, taxonomic-resolution, exposure, covariate, product-characterisation, outcome-separation and registration items. Three of them carry disproportionate weight: absolute or spike-in quantification when a directional abundance claim is made, an explicit compositional reference frame, and prospective registration of the microbial analysis plan before unblinding — the omissions that most often reverse conclusions [22,23,24]. Items 1–7 align with and extend the STORMS reporting framework [40,41].

Research agenda

Four studies would move this field from Tier 3 to Tier 4 faster than any further observational work. (1) A microbiome-stratified orthobiologic trial: randomise knee osteoarthritis to intra-articular platelet-rich plasma with prespecified stratification by baseline SCFA-producer abundance or systemic LPS-binding protein, with pain, function and cartilage-structural endpoints — no such trial is registered [120]. (2) A

perioperative microbiome cohort in fracture and fusion surgery, with union as the outcome and antibiotic exposure as the principal exposure, testing in humans what the murine callus data predict [3,65]. (3) Addition of stool and metabolite endpoints to existing MSC and EV trials in fistula, graft-versus-host disease and osteoarthritis, converting the reverse-direction question from preclinical to clinical at marginal cost [137,142]. (4) A mediator-specific intervention trial with a musculoskeletal structural endpoint — oral butyrate or a defined fibre intervention with bone turnover, cartilage biomarkers or muscle biopsy outcomes — closing the largest synthesis gap identified here [67,153,154]. Registered activity currently sits adjacent to, but not inside, this space: synbiotics for skeletal resorption [171], perioperative probiotics in prosthetic joint infection [172], probiotics in transplantation [173] and FMT before CAR T-cell therapy [174].

Limitations

This review has five material limitations. It was not prospectively registered, and PROSPERO does not currently accept overviews of reviews in its published eligibility criteria [30]. Searches were domain-specific and iterative rather than a single global Boolean strategy executed across all databases, and the Cochrane Library was not separately retrievable in this work, so “no Cochrane review identified” should be read as unverified rather than established. Several included records were available to us as abstracts and partial methods sections; where a value, appraisal tool or registration identifier was not displayed, the cell was recorded as not available, with the consequence that some AMSTAR 2 judgements are provisional and no review is credited with high confidence on incomplete evidence. The corrected covered area could not be computed for most domains because primary-study lists were not extractable, so overlap is reported qualitatively and same-domain reviews are treated as non-independent. Finally, a substantial part of the mechanistic and reverse-direction evidence is preclinical; it is labelled as such throughout and is never advanced as human evidence. MEQ-6 and MIRROR-12 are proposed instruments, specified for this review by its authors, and have not been validated by inter-rater reliability testing or Delphi consensus.

Conclusions

Across 54 systematic reviews and meta-analyses spanning the gut–bone, gut–joint, gut–muscle and gut–skin axes, microbiota-directed interventions show consistent direction and modest, heterogeneous magnitude on surrogate and symptom outcomes, and no demonstrated effect on any structural or regenerative endpoint. The largest and most credible clinical effects of microbiome modulation in the whole field occur inside cell therapy — faecal microbiota transplantation for steroid-refractory graft-versus-host disease — while musculoskeletal regenerative medicine, which administers far more biologics to far more patients, has not yet measured the microbiome even once in a registered trial with a regenerative endpoint. The evidence supports positioning dysbiosis as a modifiable modifier of regenerative response, warrants its measurement as both covariate and outcome in trials already under way, and does not support therapeutic claims of tissue regeneration by microbiome modulation. Closing that gap requires better measurement before it requires more studies, which is the purpose of the two instruments proposed here.

Declarations

Ethics approval and consent to participate: Not applicable. This study is a secondary synthesis of previously published systematic reviews and did not involve human participants, human material or animal experimentation.

Consent for publication. Not applicable.

Availability of data and materials: All data analysed in this review are contained in the published articles cited in the reference list and in (Tables 1-8). The full extraction dataset, including the URL consulted for every extracted value, is available from the corresponding author on reasonable request.

Competing interests: None.

Funding: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Authors' contributions (CRediT): All authors: conceptualisation, methodology, formal analysis, investigation, data curation, writing – original draft, writing – review and editing, supervision. All authors read and approved the final manuscript.

Acknowledgements: None.

Use of artificial intelligence: Use of AI-assisted tools in literature identification and language editing, in accordance with the journal's policy. The authors are responsible for the accuracy of all content and for verification of every cited source.

Registration: This overview was not prospectively registered; PROSPERO does not currently accept overviews of reviews under its published eligibility criteria. The protocol is available from the corresponding author.

Reporting guideline: PRIOR (Preferred Reporting Items for Overviews of Reviews), with PRISMA 2020 items applied where relevant. Completed checklists are provided as supplementary material.

Domain	Records	With quantitative pooling	Reporting PROSPERO ID	Reporting a formal appraisal tool	Reporting certainty (GRADE)
Gut–bone	10	7	3	6	0
Gut–joint	8	6	2	4	0
Gut–muscle	8	6	2	2	0
Gut–skin	7	5	1	2	1
Ageing, frailty, inflammaging	5	0	0	0	0
FMT and transplant outcomes	5	4	1	0	0
Regenerative therapy acting on the gut	8	7	0	2	1
Microbial mediators	9	6	3	4	0
Total	54	41	11	20	2

Table 1: Distribution, registration and appraisal of the 54 included systematic-review-level records.

Counts reflect what was displayed on the retrievable record for each review; absence of a displayed item was recorded as absent and is a source of provisional judgement (see Limitations). The two records

reporting certainty are Peng 2026 (GRADE by outcome) and Duan 2026 (AMSTAR 2 + GRADE + corrected covered area).

First author, year	Design	Population / exposure	Studies; participants	Main result (95% CI)	I ²
Wang 2024 [50]	SR + MA of RCTs	Postmenopausal women; probiotics ≥3 months	12 RCTs; 1,183	Lumbar spine BMD SMD 0.60 (0.14–1.05); hip 0.74 (0.15–1.33); CTX –1.51 (–1.88 to –0.41)	92.1% / 94.5% / 95.2%
BMJ Open 2021 [53]	SR + MA of RCTs	Postmenopausal women; probiotics >6 months	5 RCTs; 497 completers	Lumbar spine BMD SMD 0.27 (0.09–0.44); hip 0.22 (–0.07 to 0.52), NS; CTX –0.34 (–0.60 to –0.09)	0% / 56.8%
Zeng 2021 [55]	SR + MA of RCTs	Osteoporosis/osteopenia; probiotics	10 RCTs; 1,156	Lumbar BMD WMD 0.04 (–0.00 to 0.09), NS; % change SMD 1.16 (0.21–2.12); AE RR 1.02 (0.92–1.12)	n.a.
Hidayat 2026 [56]	SR + MA	Adults; probiotics	Outcome-specific (16 / 9 / 7 analyses)	Lumbar aBMD +0.010; hip aBMD +0.022 g/cm ² ; femoral neck, P1NP, CTX NS	Moderate to high
Cao 2024 [60]	SR + MA, observational	Osteoporosis vs controls	16 studies; 2,340	ACE SMD 1.05 (0.00–2.10); <i>Blautia</i> –0.32 (–0.65 to –0.00); Chao1, Shannon and Simpson NS	n.a.
Lee 2025 [62]	SR + MA	Postmenopausal osteoporosis vs controls	16 studies; 1,520	ACE reduced (p = 0.04); ↑primary bile acids, ↑LPS, ↑Th17/Treg ratio	n.a.
16S synthesis 2022 [61]	SR + MA	Osteoporosis vs controls	12 studies; 2,033	Taxon-level differences only; no pooled effect size	n.a.
Ji 2024 [63]	SR	Primary osteoporosis	10 studies	No α-diversity difference; β-diversity separation	n.a.
Microbiol Spectrum 2023 [64]	Reanalysis MA	Osteoporosis vs controls	5 datasets	Shannon p = 0.049, effect size 0.17, power 0.40; F/B ratio NS (p = 0.58)	n.a.
Lashkarbolouk 2024 [48]	SR (human + animal)	Age-related musculoskeletal disorders; pre/pro/synbiotics	20 trials + 30 animal studies	Narrative: less BMD loss, higher SCFA, lower IL-1/IL-6/IL-17/TNF-α	n.a.

Table 2: Gut–bone axis: systematic-review-level evidence.

BMD, bone mineral density; CTX, C-terminal telopeptide; NS, not significant; SMD, standardised mean difference; WMD, weighted mean difference; n.a., not available on the retrievable record.

First author, year	Design	Population / exposure	Studies; participants	Main result (95% CI)	I ²
Li 2026 [51]	SR + MA of RCTs	Knee/generalised OA; probiotics, prebiotics, synbiotics, diets	18 RCTs; 2,080	VAS pain SMD –0.66 (–1.27 to –0.06); WOMAC pain –0.62 (–0.97 to –0.27); function –0.40 (–0.64 to –0.17)	94.6% / 75.5% / 36.3%
Tian 2025 [72]	SR + MA	Knee OA; oral probiotics	5 RCTs; 694	WOMAC total SMD –1.15 (–2.14 to –0.17); VAS –1.31 (–2.50 to –0.12); hsCRP –0.67 (–1.35 to 0.01)	9% after exclusions
Moyseos 2024 [73]	SR + MA	OA; probiotics	3 studies; 501	hsCRP –5.24 (–15.73 to 5.26) NS; WOMAC –6.15 (–22.04 to 9.74) NS; VAS –2.26 (–4.87 to 0.34) NS	n.a.
Lowe 2020 [74]	SR + MA	RA, spondyloarthritis; probiotics	12 studies	QoL SMD –0.37 (–0.59 to –0.15); pain –8.97 mm (–15.38 to –2.56); CRP –2.33 mg/L (–4.26 to –0.41)	n.a.
Wang 2022 [77]	SR + MA, observational	14 rheumatic diseases vs controls	92 studies; 11,998	Observed species SMD –0.36 (–0.63 to –0.09); RA –0.51 (–0.78 to –0.24)	88%
Tryptophan/OA synthesis [78]	SR + MA, observational	Symptomatic OA	5 studies (3 pooled); 756	<i>Streptococcus</i> β 0.003 (–0.049 to 0.052) NS; tryptophan markers β 0 (–0.071 to 0.070) NS	n.a.
Nadeem-Tariq 2025 [175]	SR	Orthopaedic surgery patients	18 articles	Postoperative cognitive dysfunction 16.4% → 5.1% with probiotics (no CI)	n.a.
RA protocol [42]	SR + MA protocol	RA vs healthy adults	—	No results; NOS + GRADE planned	—

Table 3: Gut–joint axis: systematic-review-level evidence.

OA, osteoarthritis; RA, rheumatoid arthritis; QoL, quality of life.

First author, year	Design	Population / exposure	Studies; participants	Main result (95% CI)	I ²
Prokopenidis 2022 [92]	SR + MA of RCTs	Adults >18 y; probiotics	24 RCTs	Muscle mass SMD 0.42 (0.10–0.74); strength 0.69 (0.33–1.06); lean mass –0.03 (–0.19 to 0.13) NS	57% / 64% / 0%
Shokri-Mashhadi 2023 [93]	SR + MA	Adults ≥55 y; probiotics	22 SR / 17 MA; 1,589	Muscle mass WMD 0.50 (0.01–0.99); in kg 0.55 (0.05–1.05)	0%
Besora-Moreno 2024 [54]	SR + MA of RCTs	Adults ≥60 y; pro/pre/synbiotics	8 RCTs; 837	Handgrip +2.50 kg (1.33–3.66); gait speed +0.10 m/s (0.03–0.16); sensitivity handgrip 1.16 (–2.45 to 4.77) NS	0%
Lapauw 2025 [94]	SR + MA	Mean age ≥50 y; diet, pre/pro/synbiotics	63 studies; 4,842	Probiotics strength +1.90 kg; gait +0.08 m/s; fibre-enriched diet +1.25 kg	n.a.
Ren 2025 [95]	SR + MA, observational	Sarcopenia vs non-sarcopenia ≥60 y	18 studies; 3,132	α-diversity SMD –0.41 (–0.57 to –0.26); observed species –0.62 (–0.82 to –0.42)	71% / 0%
Song 2024 [96]	SR + MA, 16S	Sarcopenia vs controls	17 studies; 4,307	Reduced richness; ↓ <i>Faecalibacterium</i> , <i>Prevotella</i> , <i>Ruminococcaceae</i>	n.a.
Sarcopenia diversity MA [97]	SR + MA	Sarcopenia vs controls	10 studies	Reduced diversity, consistent direction	n.a.
Dziewiecka 2022 [98]	SR	Athletes and non-athletes; physical activity	38 studies	No pooling; ≥60 min at ≥60% HRmax alters β-diversity	n.a.

Table 4: Gut–muscle axis: systematic-review-level evidence.

First author, year	Design	Population / exposure	Studies; participants	Main result (95% CI)	Certainty
Peng 2026 [49]	SR + MA of RCTs	Critically ill adults; enteral probiotics	19 RCTs; 1,384	Moderate certainty for wound infection, overall infection, length of stay, antibiotic duration	GRADE: moderate to very low by outcome
Togo 2021 [109]	SR	Skin and mucosal wounds; systemic probiotics	7 studies; 348	Paediatric burns: grafting 10% vs 40% (p = 0.028); healing 16.25 vs 20.7 days (p = 0.048)	n.a.
Mahdizade Ari 2025 [110]	SR	Surgical patients; pro/pre/synbiotics	22 publications	Reduced antibiotic duration and hospital stay; no effect sizes	n.a.
Tsiouris 2017 [44]	SR + MA, animal	Cutaneous wounds; probiotics	6 studies (12 experiments)	Wound contraction Hedges' g –2.55 (–3.59 to –1.50)	Preclinical
Zhu 2024 [111]	SR + MA of RCTs	Psoriasis; adjuvant oral probiotics	7 RCTs; 400	PASI change MD –3.09 (–5.04 to –0.74); PASI-75 RR 1.40 (0.98–1.98) NS; CRP –2.36 (–2.77 to –1.95)	n.a. (I ² 85% for PASI)
Xue 2023 [112]	SR + MA	Paediatric atopic dermatitis; probiotics	9 RCTs; 1,000	Continuous outcomes MD –4.24 (–7.78 to –0.71); dichotomous OR 1.75 (0.70–4.35) NS	Authors: limited
Lin 2025 [113]	SR + MA of RCTs	Acne; oral probiotics	9 SR / 7 MA; 623	Duration-stratified outcomes; no stable pooled estimate	n.a.

Table 5: Gut–skin axis: systematic-review-level evidence.

First author, year	Design	Population / intervention	Studies; participants	Main result (95% CI)
Qiao 2023 [130]	SR + MA	Steroid-refractory GVHD; FMT	23 studies; 242	Remission OR 5.51 (1.49–20.35); pooled remission 64% (51–77); FMT-related infection 2.1%
Zhang 2026 [131]	SR + MA	Acute GVHD prophylaxis and treatment; FMT	6 studies; 262	30-day CR OR 8.44 (2.98–23.96); 14-day CR 8.54 (2.49–29.29); incidence OR 1.30 (0.10–16.72) NS
Zeng 2022 [133]	SR + MA of RCTs	Autoimmune/autoinflammatory disease; FMT	14 RCTs; 571	UC remission RR 1.89 (1.18–3.00); endoscopic remission 2.40 (1.13–5.12); AE RR 1.02 (0.81–1.17)
Tan 2022 [134]	SR + MA of RCTs	IBD; FMT	14 RCTs; 666	Clinical remission RR 1.44 (1.03–2.02); response RR 1.34 (0.92–1.94) NS
Wang 2023 [137]	SR + MA	Complex perianal fistula; MSCs	6 trials; 487	Short-term healing RR 2.49 (1.63–3.80); Crohn's 1.43 (1.09–1.80); cryptoglandular 1.16 (0.69–1.95) NS
Emile 2025 [138]	SR + MA	Anal fistula; stem-cell therapy	43 studies; 1,160	Healing 58.1% (51.5–64.7); RCT healing OR 1.81 (1.23–2.67); complications 37.3% (27.1–47.5)
Li 2024 [46]	SR + MA, preclinical	Ulcerative colitis models; EVs	69 studies; 1,271 animals	DAI SMD –3.00 (–3.52 to –2.48); MSC-EV –3.33 (–3.99 to –2.68); MISEV-compliant –2.27 (–3.05 to –1.49)
Hou 2023 [45]	SR + MA, preclinical	Animal colitis; EVs	21 studies	DAI SMD –2.46 (–3.31 to –1.62); MPO –2.85 (–3.91 to –1.78)
Shi 2022 [47]	SR + MA, preclinical	Intestinal ischaemia–reperfusion; MSCs	18 studies	Survival day 1 RR 1.32 (1.11–1.57); day 7 RR 2.44 (1.63–3.66); Chiu's score SMD –1.96 (–2.72 to –1.19)
Duan 2026 [10]	Umbrella review	Fistula-related disease; cell-based therapy	35 SR/MA	Most included reviews low or critically low confidence; no microbiome content

Table 6: Microbiota-directed therapy in cell therapy, and regenerative therapy acting on the gut.

CR, complete response; DAI, disease-activity index; EV, extracellular vesicle; GVHD, graft-versus-host disease; MPO, myeloperoxidase; UC, ulcerative colitis.

MEQ-6 domain	Reviews rated adequate	Reviews rated partial	Reviews rated inadequate	Consequence for interpretation
1. Definitional transparency (dysbiosis operationally defined)	0	3	All others	Directional claims are descriptive, not diagnostic
2. Absolute or quantitative profiling	0	0	All	Increases and decreases are relative, not absolute
3. Compositional handling / reference frame	0	2	All others	Taxon-level direction cannot be established
4. Independence from α -diversity alone	4	3	11	α -diversity is not a health metric
5. Confounder control (BMI, diet, antibiotics, activity)	2	6	All others	Residual confounding plausibly explains small effects
6. Outcome relevance and reporting adherence (STORMS)	1	5	All others	Surrogate outcomes dominate; no structural endpoints

Table 7: MEQ-6 applied to the composition-based reviews in this umbrella review.

Composition-based reviews only (n = 18 across the bone, joint, muscle, ageing and mediator domains). Under the pre-specified rule (fewer than three domains adequate = measurement-limited), all 18 are measurement-limited, and their taxon-level claims are reported as hypothesis-generating irrespective of AMSTAR 2 confidence.

#	Item	Why it matters
1	Operational definition of dysbiosis, or explicit avoidance of the term	The term has no consensus definition and is frequently circular
2	Sample type, timing relative to intervention, storage and transport	Timing determines whether the measure is a covariate or an outcome
3	Platform, region or sequencing depth, and bioinformatic pipeline	Pipeline choice changes taxon-level results
4	Absolute or spike-in quantification when a directional abundance claim is made	Relative data cannot establish absolute direction
5	Compositional statistical approach and reference frame	Reference-frame choice can reverse conclusions
6	α - and β -diversity reported as descriptors, not as health metrics	Diversity does not reliably indicate health
7	Taxonomic resolution achieved; strain claims only from strain-level data	Strain-specific effects are not genus-level effects
8	Antibiotic, probiotic, proton-pump inhibitor and dietary exposure in prior 90 days	These dominate short-term community variance
9	BMI, physical activity and diet as prespecified covariates	Each attenuates microbiome–phenotype associations
10	Regenerative product identity, dose, potency assay, and characterisation standard	Product heterogeneity is the field’s dominant confounder
11	Clinical outcome stated separately from surrogate and imaging outcomes	Prevents surrogate-to-clinical claim drift
12	Prospective registration with the microbial analysis plan stated before unblinding	Prevents post hoc taxon selection

Table 8: MIRROR-12: minimum reporting items for studies combining microbial measurement with regenerative intervention.

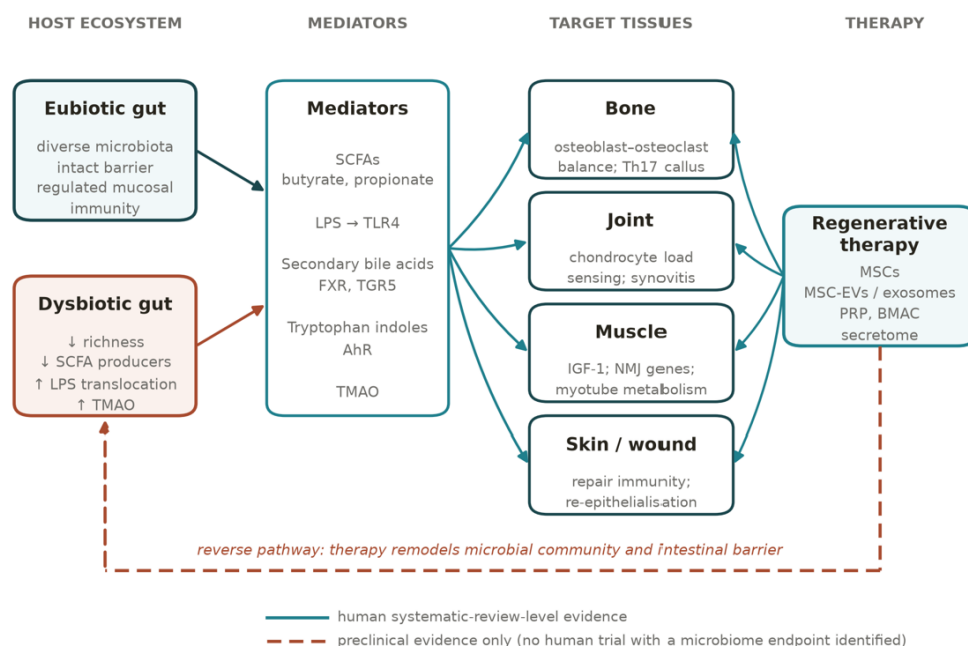


Figure 1: Bidirectional model of the gut–tissue axes in regenerative medicine, showing microbial mediators (short-chain fatty acids, lipopolysaccharide, secondary bile acids, tryptophan-derived indoles, trimethylamine N-oxide), their target cell populations in bone, joint, muscle and skin, and the reverse pathway by which cell-based and orthobiologic therapies remodel the intestinal barrier and microbial community. Solid arrows indicate pathways with human systematic-review-level evidence; dashed arrows indicate pathways supported only by preclinical evidence.

	Surrogate (diversity, biomarkers)	Symptom / function	Structural / regenerative
Gut–bone	pooled human RCT evidence	pooled human RCT evidence	preclinical only
Gut–joint	observational association	pooled human RCT evidence	no SR-level evidence
Gut–muscle	pooled human RCT evidence	pooled human RCT evidence	preclinical only
Gut–skin / wound	observational association	pooled human RCT evidence	preclinical only
Ageing / frailty	observational association	no SR-level evidence	no SR-level evidence
FMT in cell therapy	pooled human RCT evidence	response modification	pooled human RCT evidence
Regenerative therapy → gut	preclinical only	preclinical only	pooled human RCT evidence

Empty and preclinical-only cells define the research agenda proposed in the Discussion. No musculoskeletal or cutaneous axis reaches a structural or regenerative endpoint with pooled human evidence, and response modification is attained only inside hematopoietic cell therapy. Structural cells in the last two rows refer to intestinal endpoints (endoscopic remission; perianal fistula healing), not musculoskeletal regeneration.

Figure 2: Evidence matrix across the four axes and two therapeutic directions, plotting the highest evidence tier attained (association, perturbation, restoration, response modification) against outcome type (surrogate, symptom, structural) with the corresponding confidence and certainty ratings. Empty cells denote the absence of any systematic-review-level evidence and constitute the research agenda proposed in the Discussion.

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