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Supplementary Information

Effects of Antidiabetic Drugs on Longevity and Healthspan: Evidence and Controversies From Glucose-Lowering Therapy to Anti-Aging Intervention

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This appendix documents the reproducible search framework and the principal evidence groups used in the narrative synthesis. It does not claim full PRISMA compliance because the original database-hit and duplicate-removal counts were not prospectively retained.

Methods S1. Eligibility and screening framework

Inclusion: peer-reviewed randomized trials/CVOTs, observational cohorts, meta-analyses, animal lifespan or healthspan studies, and mechanistic studies of metformin, SGLT2 inhibitors, GLP-1 receptor agonists, tirzepatide, DPP-4 inhibitors, insulin, sulfonylureas, acarbose, or pioglitazone; eligible outcomes included mortality, cardiovascular death, heart failure, kidney failure, major cardiovascular events, frailty, physical function, cognition, sarcopenia/body composition, quality of life, hypoglycemia, and validated aging biomarkers.

Exclusion: duplicate publications; reports limited to short-term glycemic efficacy without a prespecified healthspan, major clinical, safety, or aging outcome; non-peer-reviewed reports; and publications with insufficient methodological or outcome information for interpretation.

Screening: titles and abstracts were independently screened by two authors. Major drug-outcome pairs were interpreted using GRADE principles. Disagreements were resolved by discussion. Because the review was initiated as a narrative synthesis, the original search log was not sufficiently detailed to reconstruct exact record counts retrospectively.



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Table S1. Database-specific search framework

Database	Core Search Framework	Coverage
PubMed / MEDLINE	((diabetes OR obesity OR prediabetes) AND (metformin OR SGLT2 OR sodium-glucose cotransporter 2 OR GLP-1 receptor agonist OR tirzepatide OR DPP-4 inhibitor OR sulfonylurea OR insulin OR acarbose OR pioglitazone) AND (longevity OR lifespan OR healthspan OR mortality OR cardiovascular death OR heart failure OR kidney failure OR frailty OR physical function OR sarcopenia OR cognition OR quality of life OR aging OR epigenetic clock))	Database inception–March 2026; targeted update through July 2026
Embase	Equivalent Emtree and free-text terms for diabetes/obesity, each drug class, and mortality/cardiorenal/functional/aging outcomes; title/abstract and subject-heading combinations.	Database inception–March 2026; targeted update through July 2026
Cochrane CENTRAL	Free-text combinations of each drug class with mortality, cardiovascular, heart failure, kidney, frailty, function, cognition, sarcopenia, quality of life, aging, and lifespan terms.	Database inception–March 2026; targeted update through July 2026
Web of Science	TS=((diabetes OR obesity) AND (drug-class terms) AND (longevity OR lifespan OR healthspan OR mortality OR cardiorenal OR frailty OR function OR sarcopenia OR cognition OR quality of life OR aging biomarker)).	Database inception–March 2026; targeted update through July 2026

Figure S1. Simplified PRISMA-style screening flow

Original records identified in PubMed/MEDLINE, Embase, CENTRAL, and Web of Science: exact count not prospectively retained
↓
Records after duplicate removal: exact count not retrospectively recoverable
↓
Titles and abstracts screened independently by two authors: exact count not retained
↓
Full-text eligibility assessment: exact count not retained
↓
Sources included in the original narrative synthesis through March 2026: 149 cited sources
↓
Reviewer-driven update through July 2026: 4 records identified and 4 included
↓
Final revised narrative synthesis: 153 cited sources

Table S2. Key randomized and cardiovascular outcome evidence

Study/Program	Population/Model	Exposure/Comparator	Main Contribution	Key Limitation / Reference
UKPDS / Follow-Up	Newly diagnosed T2D; overweight subgroup	Metformin or intensive glucose control vs conventional care	Microvascular benefit; long-term MI/mortality signal in selected groups	Legacy trial design; not a dedicated geroscience trial ^[18,19]
EMPA-REG, CANVAS, DECLARE, CREDENCE	T2D with ASCVD or high cardiorenal risk	SGLT2i vs placebo	Heart-failure and kidney protection; mortality heterogeneity	High-risk trial populations; class effects not uniform ^[36–39]
DAPA-HF, EMPEROR, DELIVER, DAPA-CKD, EMPA-KIDNEY	HF or CKD, with and without diabetes	SGLT2i vs placebo	Benefits extend beyond glucose lowering and diabetes	Primarily disease modification, not direct aging-rate evidence ^[41–47]
LEADER, SUSTAIN-6, REWIND, SELECT, SOUL	T2D/high CV risk or obesity with established CVD	GLP-1RA vs placebo	MACE reduction varies by agent; semaglutide benefit in obesity without diabetes	Limited direct frailty, cognition, or sarcopenia endpoints ^[48–55]
STEP-HFpEF, SUMMIT, FLOW	Obesity-related HFpEF or T2D with CKD	Semaglutide or tirzepatide vs placebo	Improved symptoms/function and selected HF/kidney outcomes	Follow-up remains short relative to aging outcomes ^[109,111,112]
SAVOR, EXAMINE, TECOS, CARMELINA, CAROLINA	T2D with variable CV/renal risk	DPP-4i vs placebo or active comparator	CV safety; no consistent MACE or mortality benefit	Saxagliptin HHF signal; limited longevity relevance ^[123–127]
ACCORD, ADVANCE, VADT	Long-standing T2D at high CV risk	Intensive vs standard glycemic targets	Lower HbA1c did not consistently improve survival; ACCORD harm signal	Treatment burden and hypoglycemia complicate interpretation ^[16–20]
STOP-NIDDM / ACE / PROactive / IRIS	IGT, CHD+IGT, T2D with macrovascular disease, or insulin resistance after stroke/TIA	Acarbose or pioglitazone vs control	Selected diabetes-prevention or vascular signals	No direct human lifespan-extension evidence; safety limits translation ^[134–141]

Table S3. Key observational and quantitative-synthesis evidence

Study/Program	Population/Model	Exposure/Comparator	Main Contribution	Key Limitation / Reference
Metformin mortality meta-analyses	People with T2D in observational cohorts	Metformin exposure vs other therapies/non-use	Associations with lower all-cause and CV mortality	Confounding by indication, immortal-time and healthy-user bias ^[73,77]
Metformin dementia/cancer syntheses	People with T2D	Metformin exposure	Possible lower dementia or cancer risk	Residual confounding and heterogeneous definitions ^[75,76]
SGLT2i serious adverse-event cohort	Routine-care T2D populations	SGLT2i vs DPP-4i	Real-world safety context including DKA and infections	Rare outcomes and channeling bias ^[95]
Sulfonylurea comparative cohorts	T2D treated in routine care	Sulfonylurea vs metformin	Higher mortality associations in several analyses	Comparator choice and treatment-selection bias ^[131–133]
SGLT2i DKA meta-analysis	Adults with T2D; 15 cohorts and 7 RCTs	SGLT2i vs comparator	Higher DKA risk, especially with elevated HbA1c	HbA1c ranges and event rarity limit subgroup certainty ^[96]
GLP-1/obesity drug network meta-analysis	99,791 adults in 262 RCTs	19 obesity drugs	Comparative weight, body-composition, adverse-event, CV and QoL estimates	Many trials optimized for weight rather than long-term function ^[116]

Table S4. Key animal lifespan/healthspan evidence

Study/Program	Population/Model	Exposure/Comparator	Main Contribution	Key Limitation / Reference
Metformin in <i>C. elegans</i>	<i>C. elegans</i> aging models	Metformin exposure	Lifespan/healthspan effects linked to microbial and mitohormetic pathways	Dose and host-microbe context limit translation ^[69,70]
NIA Interventions Testing Program: metformin	Genetically heterogeneous mice	Metformin at tested doses	No significant lifespan extension	Specific doses, sex and timing may not cover all contexts ^[71]
NIA Interventions Testing Program: acarbose	HET3 mice	Acarbose	Reproducible male-predominant lifespan extension	Sex difference and uncertain human translation ^[136,137]
Cardiorenal disease models	Experimental HF/CKD/metabolic models	SGLT2 inhibition	Improved organ-level function and metabolic efficiency	Healthspan surrogates rather than organismal lifespan ^[89–93]
Neuroprotection models	Experimental neurodegeneration models	GLP-1 signaling modulation	Anti-inflammatory and neurometabolic effects	Human cognitive efficacy remains unproven ^[120,121]

Table S5. Key mechanistic evidence

Study / Program	Population / Model	Exposure / Comparator	Main Contribution	Key Limitation / Reference
Metformin nutrient sensing	Cellular and tissue models	Metformin	AMPK/mTOR, energetic stress, complex I and AMPK-independent signaling	Concentration and tissue dependence are substantial ^[34,67,83]
Autophagy and mitochondrial quality control	Cellular aging models	Metabolic stress/interventions	Links mitochondrial dysfunction, autophagy, inflammation and cell death	Mechanistic plausibility does not establish human longevity ^[60,61]
Metformin–microbiome interactions	Treatment-naïve T2D and experimental models	Metformin	Changes in microbial composition and metabolite pathways	Causality and durability in humans remain uncertain ^[63–66]
SGLT2i cardiorenal mechanisms	Renal, myocardial and metabolic models	SGLT2 inhibition	Natriuresis, glomerular hemodynamics, ketone/substrate shifts and inflammation	No single mechanism fully explains rapid clinical effects ^[89–93]
GLP-1 receptor biology	Endocrine, neural and cardiovascular systems	GLP-1RA	Glucose-dependent insulin secretion, appetite, gastric emptying and vascular effects	Agent-specific pharmacology and duration matter ^[97,101]
Inflammaging and cellular senescence	Cellular/organismal aging frameworks	Metabolic and anti-inflammatory interventions	NF-κB, NLRP3 and SASP connect diabetes to multiorgan aging phenotypes	Biomarker shifts require validation against patient-centered outcomes ^[56–59]

Abbreviations

AMPK: Adenosine monophosphate-activated protein kinase
 CKD: Chronic kidney disease
 CVOT: Cardiovascular outcomes trial
 DPP-4i: Dipeptidyl peptidase-4 inhibitor(s)
 GIP: Glucose-dependent insulinotropic polypeptide
 GLP-1RA: Glucagon-like peptide-1 receptor agonist(s)
 GRADE: Grading of Recommendations Assessment, Development and Evaluation
 HbA1c: Hemoglobin A1c
 HFpEF: Heart failure with preserved ejection fraction
 MACE: Major adverse cardiovascular events
 MASH: Metabolic dysfunction-associated steatohepatitis
 mTOR: Mechanistic target of rapamycin
 NIA ITP: National Institute on Aging Interventions Testing Program
 PPAR-γ: Peroxisome proliferator-activated receptor gamma
 SASP: Senescence-associated secretory phenotype
 SGLT2i: Sodium-glucose cotransporter 2 inhibitor(s)
 T2D: Type 2 diabetes
 TAME: Targeting Aging with Metformin