

Supplementary Table 4 Secular change in key biomarkers over 16 years (35–49 years age group).

Biomarker	Sex	2010 Mean (35–49 yr)	2026 Mean (35–49 yr)	Change (%)	Direction	Interpretation
GGT (U/L)	M	32.2	43.3	+34.8	↑	Rising metabolic syndrome / NAFLD prevalence; increased hepatic steatosis at population level [10,11]
GGT (U/L)	F	19.1	23.9	+24.9	↑	Same trend as males; female GGT rising from lower baseline, consistent with post-menopausal metabolic risk accumulation
ALT (U/L)	M	27.7	34.2	+23.5	↑	ALT rise in middle-aged men is consistent with NAFLD trends in epidemiological literature; however, without BMI data, this remains a plausible hypothesis rather than a confirmed driver [9]
ALP (U/L)	F	72.1	59.2	−17.9	↓	Declining bone turnover with improved calcium/vitamin D nutrition; possible reduced Paget disease / osteomalacia prevalence
ALP (U/L)	M	85.5	72.9	−14.7	↓	Similar pattern to females; may also reflect reduced alcohol consumption at population level or improved hepatobiliary health
ALT (U/L)	F	19.7	17.8	−9.3	↓	Opposite direction from males: may reflect reduced environmental hepatotoxin exposure or iron deficiency correction
TBIL (μmol/L)	F	12.8	13.8	+7.9	↑	Mild population-level bilirubin increase; possibly related to Gilbert syndrome ascertainment or dietary changes
AST (U/L)	F	22.2	20.6	−7.2	↓	Parallels ALT decline in females; consistent with reduced non-specific hepatocellular stress
Urea (mmol/L)	F	4.0	4.8	+17.9	↑	Increased dietary protein intake; rising BUN:creatinine ratio suggests prerenal (dietary) rather than renal mechanism
UA (μmol/L)	M	337.5	393.4	+16.6	↑	Rising purine and fructose consumption; dietary transition toward Western pattern;

						fructose-driven uric acid production [11]
UA ($\mu\text{mol/L}$)	F	242.3	281.1	+16.0	↑	Same dietary drivers as males; female UA rising from lower baseline (estrogen uricosuric effect)
CREA ($\mu\text{mol/L}$)	F	72.9	66.7	−8.4	↓	Possible declining skeletal muscle mass in middle-aged women; alternatively improved hydration status or reduced meat consumption
Urea (mmol/L)	M	5.0	5.3	+5.4	↑	Milder dietary protein effect than females; male protein intake historically higher at baseline
LDL-C (mmol/L)	M	3.5	2.8	−17.6	↓	LDL decline in this medication-naïve population likely reflects secular improvements in dietary fat intake and lifestyle factors; statin use was excluded by study design [10]
TG (mmol/L)	M	1.7	1.9	+14.4	↑	Rising carbohydrate / refined sugar intake; TG elevation parallel to GGT and UA, forming a metabolic syndrome signal triad
HDL-C (mmol/L)	M	1.3	1.1	−13.0	↓	HDL decline consistent with rising TG and metabolic syndrome prevalence; HDL and TG are inversely coupled metabolically
HDL-C (mmol/L)	F	1.5	1.4	−6.2	↓	Same TG-HDL coupling as males, but attenuated; female HDL protected by residual estrogen through age 35–49
CHOL (mmol/L)	M	5.2	4.8	−5.9	↓	Total cholesterol decline parallels the LDL trend in this medication-naïve population, reflecting dietary fat reduction and lifestyle modifications; statin use was excluded by study design.