Biochemical biomarkers

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Objective Measures of Health and Wellbeing of Older Adults in Northern Ireland

The NICOLA Study Wave 1

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Northern Ireland Cohort for the Longitudinal Study of Ageing
... Understanding today for a healthier tomorrow

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Biochemical Biomarkers

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Citation

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Key Findings

- Data is available for 28 biochemical biomarkers for 3,082 individuals within the NICOLA Cohort. All individuals participating in the health assessment were also offered rapid testing and feedback for blood glucose and lipid levels.

- Approximately 54% of males and females in the NICOLA cohort had low vitamin D levels. The majority who were deficient in vitamin D were aged over 80 years.

- The majority of the 3082 participants showed results within normal ranges for all other serum-based biochemical biomarkers.

- NICOLA welcomes expressions of interest to collaborate and make maximal use of the data generated. Please contact our NICOLA team for further information: nicola-research@qub.ac.uk

7.1 Introduction

Analysing biological samples allows us to objectively evaluate biomarkers that help provide information about a person's health. For example, testing biomarkers such as blood glucose (blood sugar) levels can identify people with undiagnosed diabetes, while analysing blood lipid levels can provide important information about a person's risk of cardiovascular disease. Often biomarkers can provide an early indication of disease before symptoms develop, provide us with information on how a disease is progressing and / or suggest therapies.

Biological samples (urine and blood for DNA, RNA, plasma and serum) were collected at Wave 1 to provide baseline data for 3514 participants in this long-term prospective cohort study. We plan to collect additional biological samples during subsequent Waves of NICOLA.

Multiple biomarker studies have been performed using this early baseline data with biological material safely stored for future biochemistry-based biomarker studies. A full list of the biochemical biomarkers currently available in the NICOLA cohort are presented in Table 7.1 This chapter presents the findings from the biochemical analysis of the samples.

Table 7.1: Overview of biochemical biomarkers and derived phenotypes currently available in the NICOLA cohort

Biomarker	Derived variables
Apolipoprotein A	
Apolipoprotein B	
Cholesterol	
Direct low-density lipoprotein	
Gamma glutamyltransferase	
High-density lipoprotein-cholesterol	
Lipoprotein (a)	
Triglycerides	
Alkaline phosphatase	
Calcium	
Rheumatoid factor	
Vitamin D	
Oestradiol	
Sex hormone-binding globulin	
Testosterone	
Glucose	

Creatinine	eGFR equation based on serum creatinine
	eGFR combined equation based on serum creatinine and serum cystatin C
	Chronic Kidney Disease
	Chronic Kidney Disease Stage
	End-Stage Renal Disease
Cystatin C	eGFR equation based on serum cystatin C
	eGFR combined equation based on serum creatinine and serum cystatin C
Phosphate	
Total protein	
Urate	
Urea	
Alanine aminotransferase	
Albumin	
Aspartate aminotransferase	
Direct Bilirubin	
Gamma Glutamyltransferase	
Total Bilirubin	
Abbreviation: eGFR: estimated glomerular filtration ratio	

7.2 Measurement of biochemistry-based biomarkers

Blood samples for biochemical biomarkers were collected in EDTA / clot activator tubes. Samples for glucose testing were collected in tubes containing potassium oxalate / sodium fluoride as a glycolysis inhibitor. The serum tubes were allowed to clot for at least 3 minutes and centrifuged at 3,000 rpm for 10 minutes at 4°C.

All samples were analysed in Hamburg at our collaborator Prof Tanja Zeller's laboratory. An Abbott ARCHITECT i2000 system was used for Testosterone, sex hormone-binding globulin (SHBG) and vitamin D analyses, while the reminder of the tests were carried out on the Abbott ARCHITECT c8000 system. Serum biomarkers were analysed for 3082 participants in the NICOLA Wave 1 cohort, of whom 52.5% were women (n = 1617). The percentage of missing values was 0.29% for SHBG (n = 9); 0.16% for oestradiol (n = 5); 0.13% for testosterone, vitamin D, rheumatoid factor and total bilirubin (n = 4); 0.10% (n = 1) for Lipoprotein (a) (Lp(a)), and 0.06% (n = 2) for the remaining biomarkers analysed. The data presented for the biomarkers below does not take into account any medication that a participant may have been taking, nor any diseases diagnosed. Values in this chapter are presented as mean ± SD or median (interquartile range).

7.3 Cardiovascular biomarkers

Cardiovascular disease (CVD) has become the leading cause of death globally (1). Approximately 485.6 million people were living with CVD in 2017, 72.7 million new cases were diagnosed and 17.8 million died as a consequence of CVD, which represents 31.8% of all causes of death (1,2). CVD also causes substantial morbidity, estimated to cost €210 billion a year to the EU economy (3).

Dyslipidaemias, characterized by increased plasma levels of low-density lipoprotein cholesterol (LDL), very low-density lipoprotein cholesterol (VLDL), triglyceride (TG), and reduced plasma levels of high-density lipoprotein cholesterol (HDL) are among the modifiable lifestyle risk factors with a high impact on cardiovascular diseases (CVD) (4–8). Their management is therefore crucial in the prevention of CVD. Apolipoproteins are proteins that bind lipids to form lipoproteins (VLDL, LDL and HDL), whose function is to transport lipids in blood, cerebrospinal fluid and lymph. VLDL and LDL both contain one molecule of the major structural glycoprotein apolipoprotein B-100 whereas lipoprotein(a) or Lp(a) contains an additional large glycoprotein, apolipoprotein(a) (9). HDL contains ApoA1 as its major structural protein, being the only non-ApoB-containing lipoprotein in the blood (9).
One of the key components in the development of CVD is the persistent elevation of certain pro-inflammatory biomarkers, like the C-reactive protein (CRP), one of the earliest reversible precursors of atherosclerosis (10–12).

Cholesterol

Cholesterol levels above 5.2 mmol/L are generally considered elevated and related to a higher risk of adverse cardiovascular events. Women in the NICOLA cohort had higher median cholesterol (5.84 mmol/L) levels than men (4.98 mmol/L) (Figure 7.1).
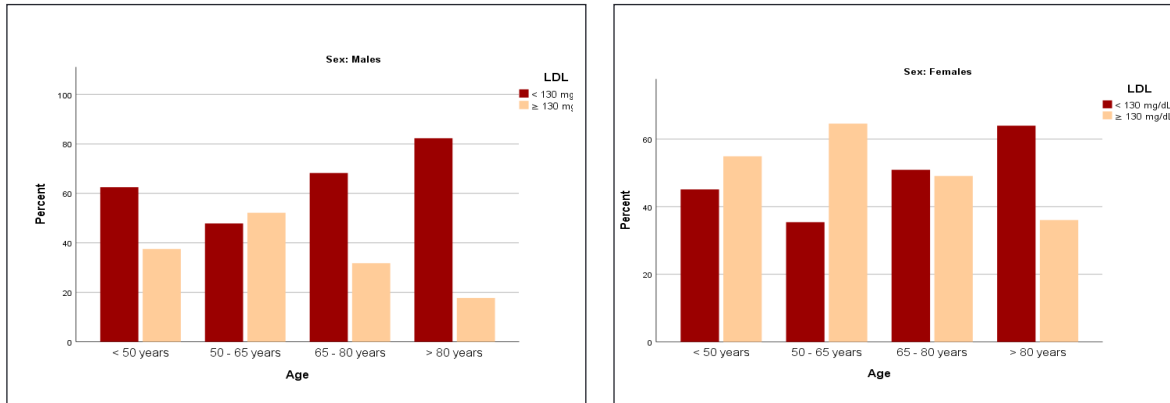
Figure 7.1: Percentage of NICOLA participants with serum levels of cholesterol above / below 5.2 mmol/L, by age group and sex.
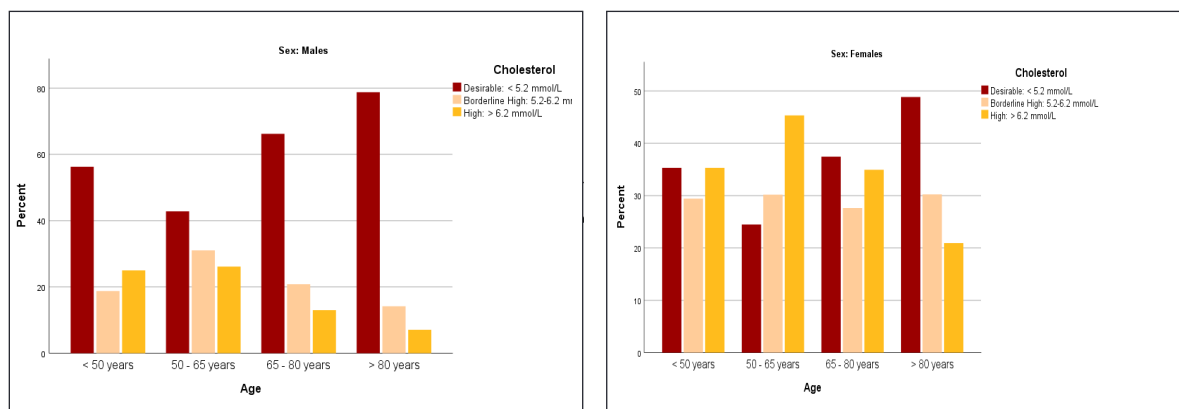
Direct Low Density Lipoprotein

Men in the NICOLA cohort had LDL (median) levels of 118 mg/dL versus 136 mg/dL in women. 43.0% of women had normal LDL levels (< 130 mg/dL); 59.6% of men had normal LDL levels (Figure 7.2).

Figure 7.2: Percentage of NICOLA participants with serum levels of low-density lipoproteins above / below 130 mg/dL, by age group and sex.

HDL-Cholesterol

Men in the NICOLA cohort had HDL (median levels) of 54 mg/dL versus 67 mg/dL in women. Women had better/best HDL levels in 88% of cases, versus 91% of men (Figure 7.3).

Figure 7.3: Percentage of NICOLA participants with low / normal / high serum levels of high-density lipoproteins, by age group and sex.

Triglycerides

Men in the NICOLA cohort had TG (median levels) of 136 mg/dL versus 121 mg/dL in women. Men had normal TG levels (< 200 mg/dL) in 79% cases, whereas this percentage was 86% in women (Figure 7.4).
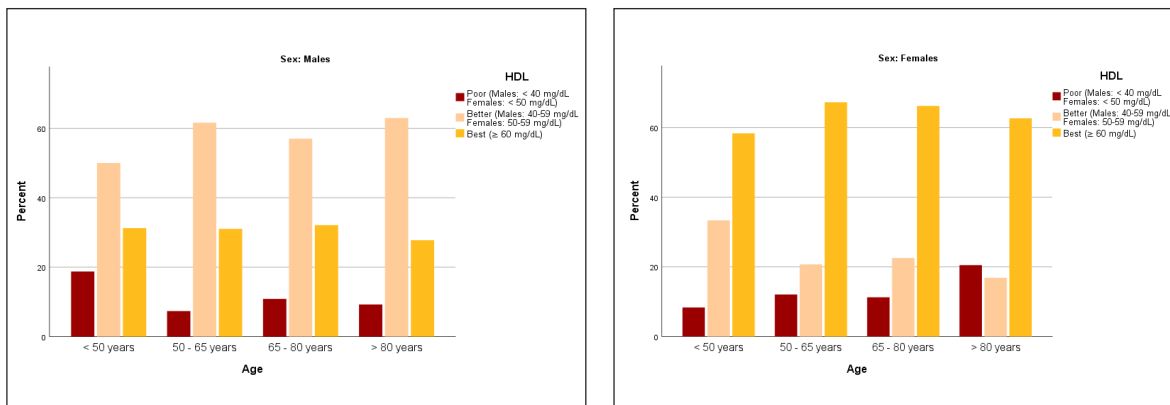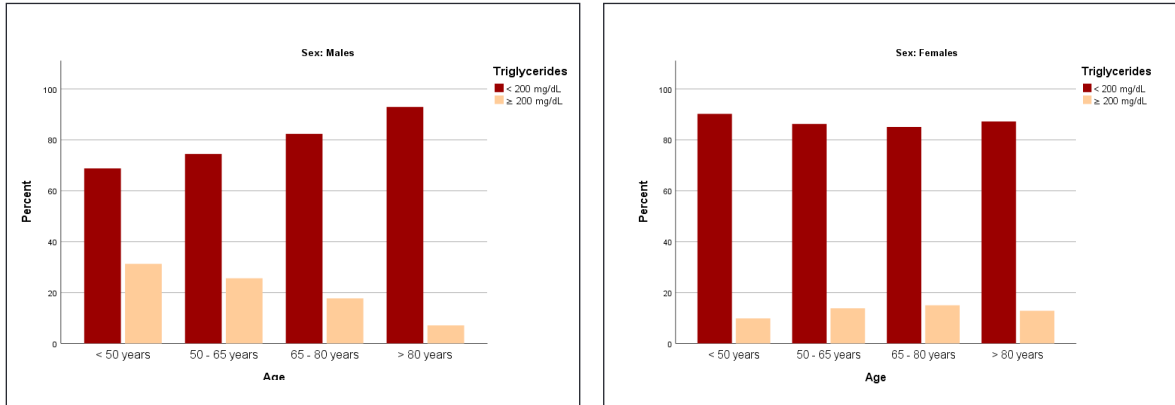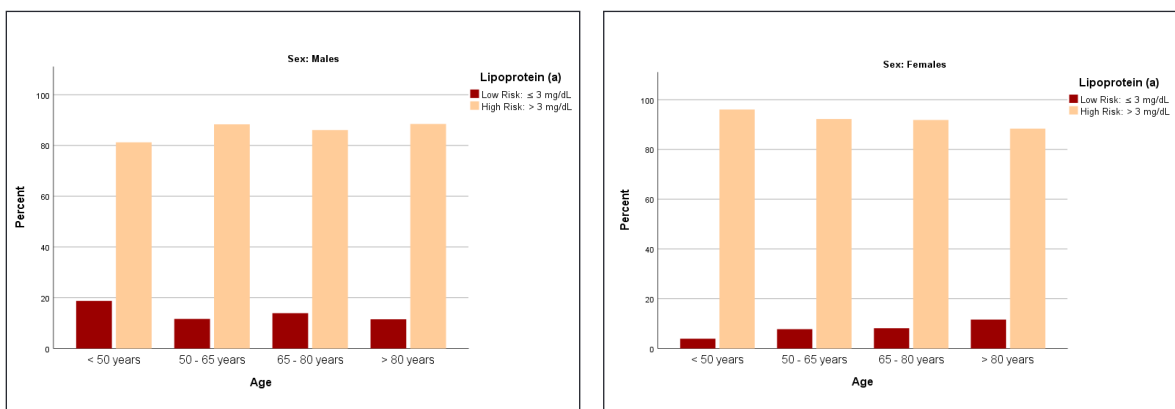
Figure 7.4: Percentage of NICOLA participants with serum levels of triglycerides above / below 200 mg/dL, by age group and sex.

Lipoprotein (a)

Lipoprotein(a), Lp(a), is a modified atherogenic LDL particle that contains apolipoprotein(a), with variable levels in the population. The consensus statement by HEART UK, based on the evidence that Lp(a) is an independent CVD risk factor, recommends its measurement in adults with a personal or family history of premature atherosclerotic CVD, those with first-degree relatives who have Lp(a) levels >200 nmol/l, patients with familial hypercholesterolemia, calcific aortic valve stenosis and those with risk of a cardiovascular event (13). Median levels of Lp(a) in the cohort was 13 mg/dl, and 87% of male and 92% of females had Lp(a) levels above 3 mg/dL, associated with higher CVD risk, regardless of age (Figure 7.5).

Figure 7.5: Percentage of NICOLA participants with serum levels of Lipoprotein (a), above / below 3 mg/dL, by age group and sex.

Apolipoprotein A1

Almost all NICOLA participants had normal levels of ApoA1 (99% males; 98% females), independent of age (Figure 7.6). Median ApoA1 levels were 1.68 g/dL.

Figure 7.6: Percentage of NICOLA participants with low / normal / high serum levels of apolipoprotein A1 (ApoA1), by age group and sex.
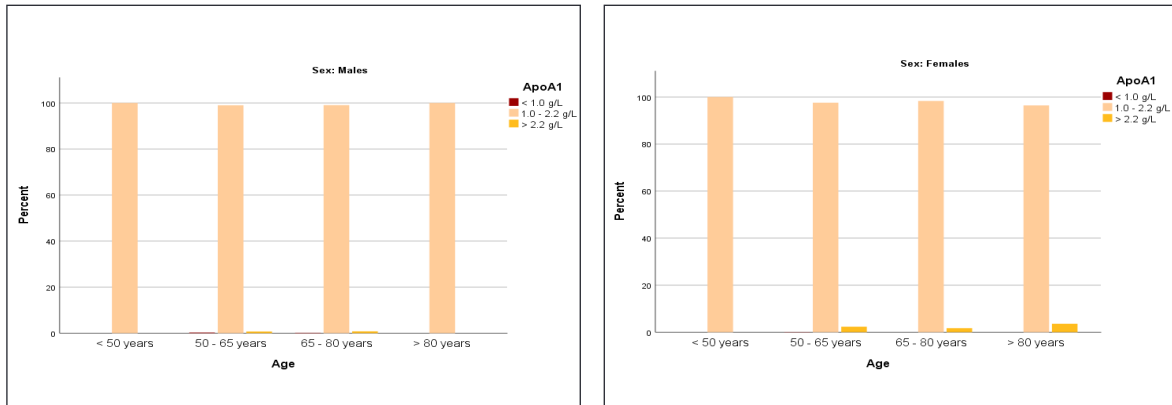
Apolipoprotein B

The majority of NICOLA participants had normal levels of ApoB (86% males; 88% females), regardless of age (Figure 7.7). Median levels of ApoB were 1.04 g/dL in women and 1.0 g/dL in men.

Figure 7.7: Percentage of NICOLA participants with normal / high serum levels of apolipoprotein B, by age group and sex.

C-reactive protein

Approximately 80% of NICOLA participants had CRP levels ≤ 5 mg/L, independent of age and sex (Figure 7.8). Median CRP levels in the cohort were 1.63 mg/L.

Figure 7.8: Percentage of NICOLA participants with serum levels of C-reactive protein, above / below 5 mg/L, by age group and sex.

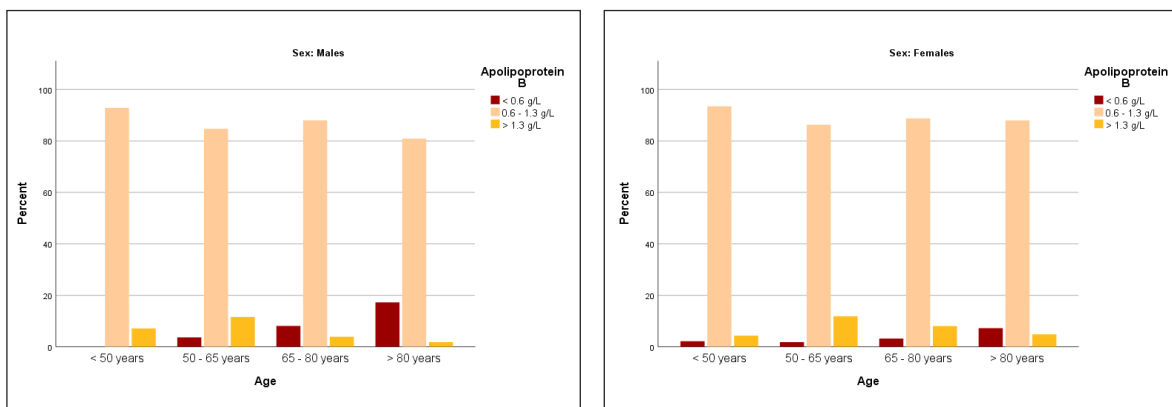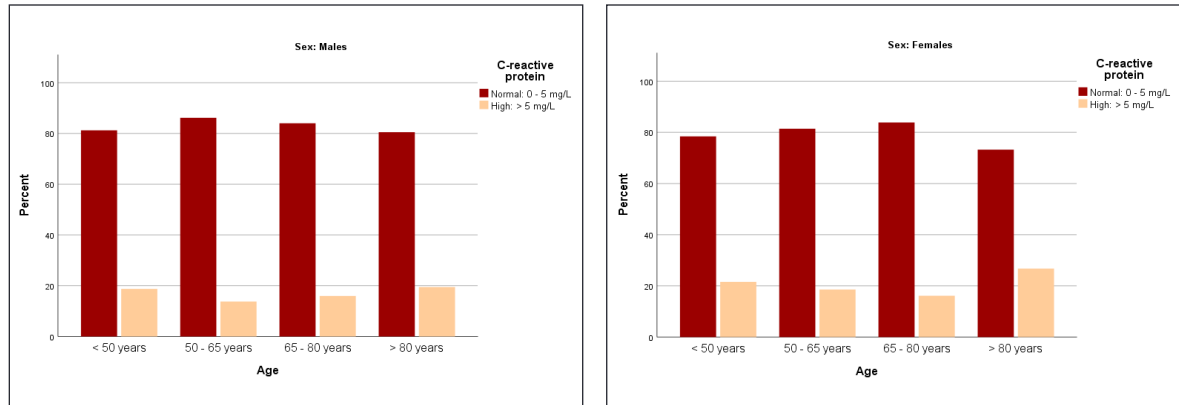## 7.4 Bone and Joint Biomarkers

Musculoskeletal disorders represent ≈17.8% of all causes of the global burden of disease (2), being responsible from 0.22% of all causes of death in 2017, with rheumatoid arthritis (RA) being the single major contributor (1). In fact, RA and osteoarthritis accounted for 20.6 and 303.1 million prevalent cases and 1.2 and 14.9 million incident cases diagnosed globally in 2017 respectively (1,2).

Vitamin D deficiency has classically been associated with musculoskeletal conditions, such as rickets and osteomalacia, although its association with other conditions has also been established (14). Approximately 50% of the UK population have vitamin D insufficiency in spring (15,16), associated with an increased risk of mortality and of several common diseases including CVD, diabetes, cancer and multiple sclerosis (17).

RA is a chronic inflammatory disorder affecting the synovial lining of joints, tendon sheaths, and bursae. Among the many autoantibodies and proteins generated in the course of RA, immunoglobulin M rheumatoid factor (RF) and anti-citrullinated protein antibodies are the two that are most commonly used in clinical practice (18). Both of them are capable of identifying RA in a relatively sensitive and specific way and predict a worse prognosis of the disease (19 – 22).

Alkaline phosphatases are widely distributed enzymes (liver, bile ducts, intestine, bone, kidney, placenta, and leukocytes) that catalyse the release of orthophosphate from ester substrates at an alkaline pH. Serum alkaline phosphatase activity may be increased in liver disease (23), bone disorders such as Paget's disease, osteomalacia and bone metastases, but also in normal processes such as during rapid bone growth in children or in the later stages of pregnancy (24).

Calcium is the most prevalent cation in the body, whose serum concentrations are tightly controlled by Parathyroid Hormone and 1, 25-dihydroxyvitamin D. Estimations of serum levels of calcium are used in the diagnosis and treatment of parathyroid disorders, renal disease, a variety of bone disorders, carcinomas, acromegaly and pancreatitis.

Vitamin D

The median value of serum vitamin D among the NICOLA participants was 19.1 ng/mL. In males, 15% of 50 - 65 year olds, 12% of 65 - 80 year olds and 23% of those aged over 80 years were found to be deficient in vitamin D (< 25 nmol/L) (17). In females, 23% of those aged under 50 years, 17% of 50 - 65 year olds, 14% of 65 - 80 year olds and 31% of those aged over 80 years were deficient in vitamin D.

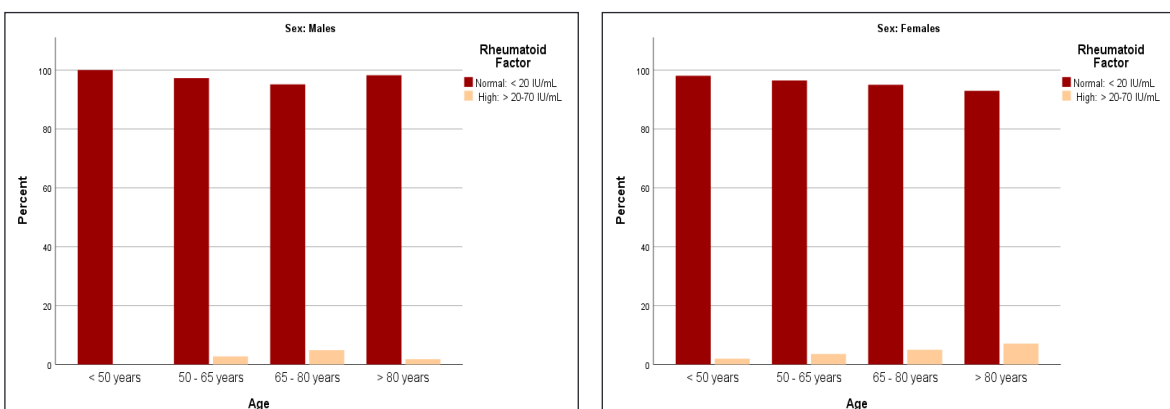**Figure 7.9: Percentage of NICOLA participants with deficient / insufficient / adequate / optimum serum levels of vitamin D, by age group and sex.**
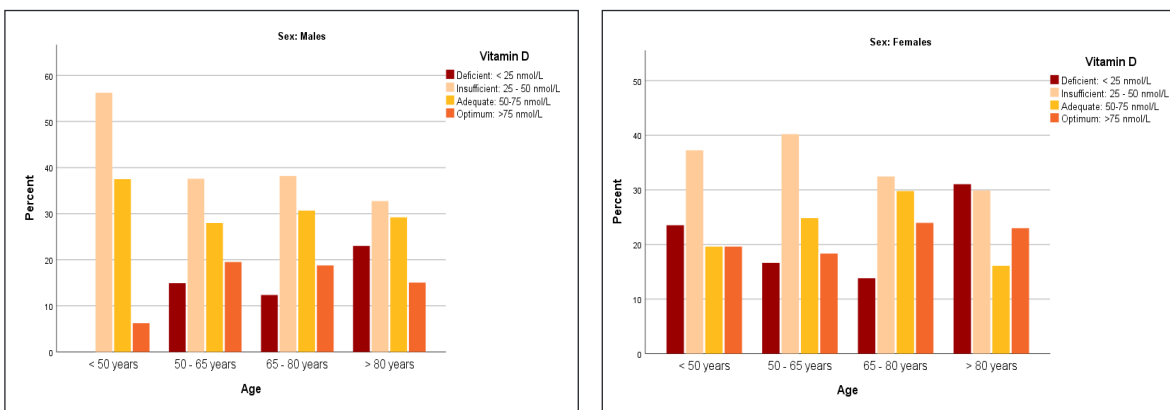
Rheumatoid factor

Serum levels of rheumatoid factor were normal in the majority of the NICOLA participants, median 7.1 IU/mL (Figure 7.10).

Figure 7.10: Percentage of NICOLA participants with serum levels of rheumatoid factor, above / below 20 IU/mL, by age group and sex.

Alkaline phosphatase

The levels of alkaline phosphatase in serum were normal (44 - 147 U/L) in the majority of the NICOLA participants, with median values of 73 U/L (Figure 7.11).

Figure 7.11: Percentage of NICOLA participants with low / normal / high serum levels of alkaline phosphatase, by age group and sex.
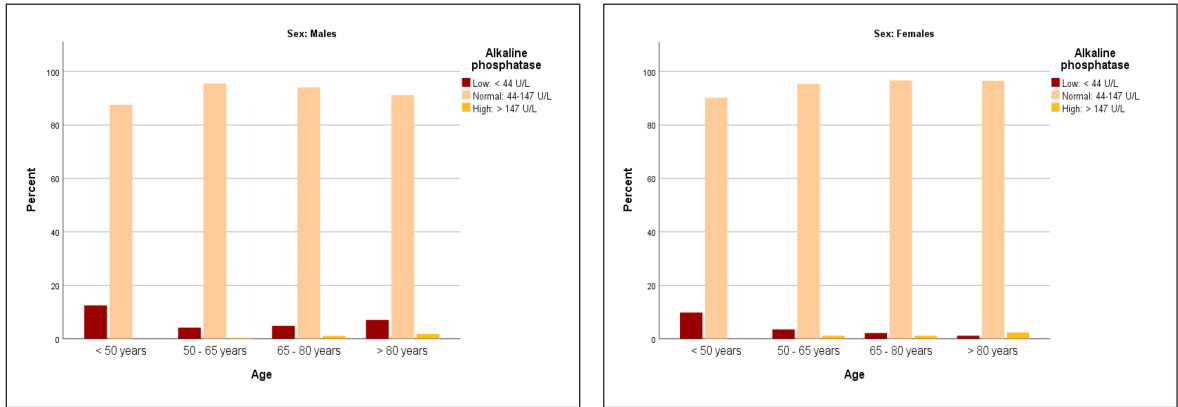
Calcium

Serum levels of calcium were normal in over 80% of the NICOLA participants, across ages and gender (Figure 7.12). Median level of serum calcium was 2.4 g/L.
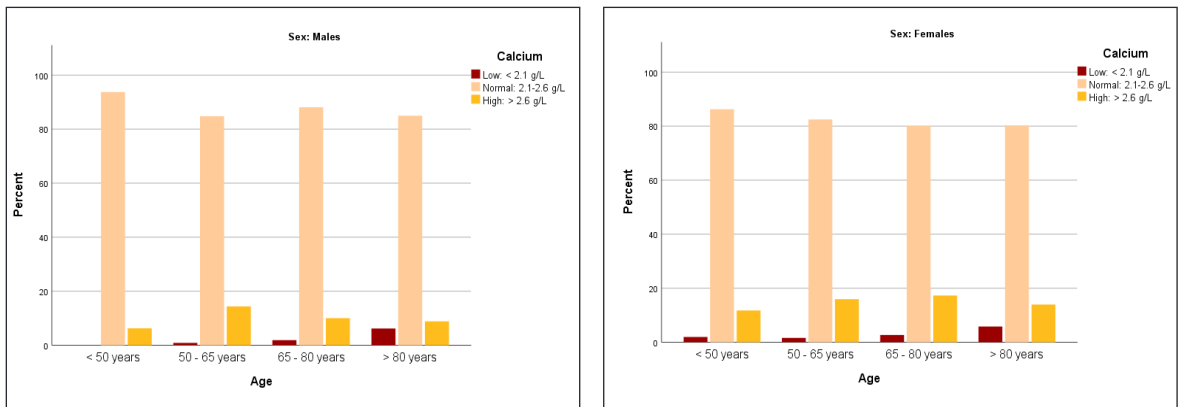
Figure 7.12: Percentage of NICOLA participants with low / normal / high serum levels of calcium, by age group and sex.

7.5 Hormonal Biomarkers

Neoplasms, with a worldwide prevalence of 100.5 million (1.4% of total burden of disease) and an incidence of 24.4 million in 2017, represents one of the major concerns in public health, being responsible of 17.1% of all global deaths (9.6 million) in the same year (1,2).

SHBG is a glycated homo-dimeric plasma transport glycoprotein produced by hepatocytes, which binds and controls the levels of sex-hormones within the circulation (25). Its serum concentration is an indicator of the metabolic clearance of sex steroids and their access to target tissues. Serum SHBG levels have been significantly associated with increased risk of breast and prostate cancer, polycystic ovary syndrome (26), osteoporosis, obesity and metabolic syndrome (27).

Testosterone, the major androgenic steroid hormone, is responsible for the development of secondary sexual characteristics in men. Most of the circulating testosterone is bound to the carrier protein SHBG. In women, high levels of testosterone in serum are associated with polycystic ovaries, ovarian cancer (28), adrenal tumours (29) and adrenal hyperplasia (27).

Oestradiol is a steroid hormone secreted mainly by the ovaries, although small amounts are produced by the adrenals and testis, hence present at low concentrations both in men and in post-menopausal women. Pathologically high values have been associated with neoplasms such as ovarian tumours (30), adrenal tumours (29) and testicular tumours (31), but also with other non-oncological conditions.

SHBG

Serum levels of SHBG in men were 50.3 nmol/L versus 67.9 nmol/L in women. In men, levels of SHBG gradually increased with age, from 43.4 nmol/L in men under 50 years to 66.3 nmol/L in men over 80 years (Figure 7.13).

Figure 7.13: Percentage of NICOLA participants with low / normal / high serum levels of sex hormone-binding globulin, by age group and sex.
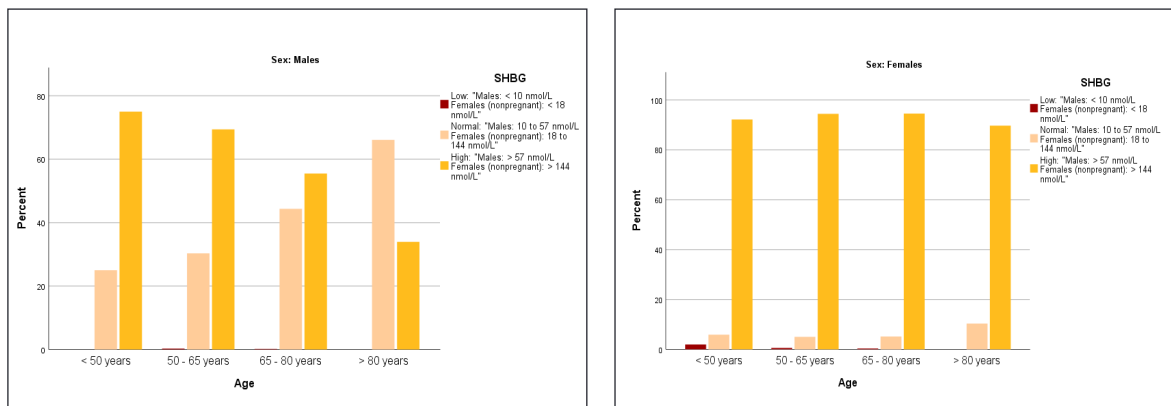
Testosterone

Testosterone levels in participants were normal in over 70% of men and 55% of women (Figure 7.14). Men had median serum levels of testosterone of 15.4 nmol/L, versus 0.75 nmol/L in women.

Figure 7.14: Percentage of NICOLA participants with low / normal / high serum levels of testosterone, by age group and sex.
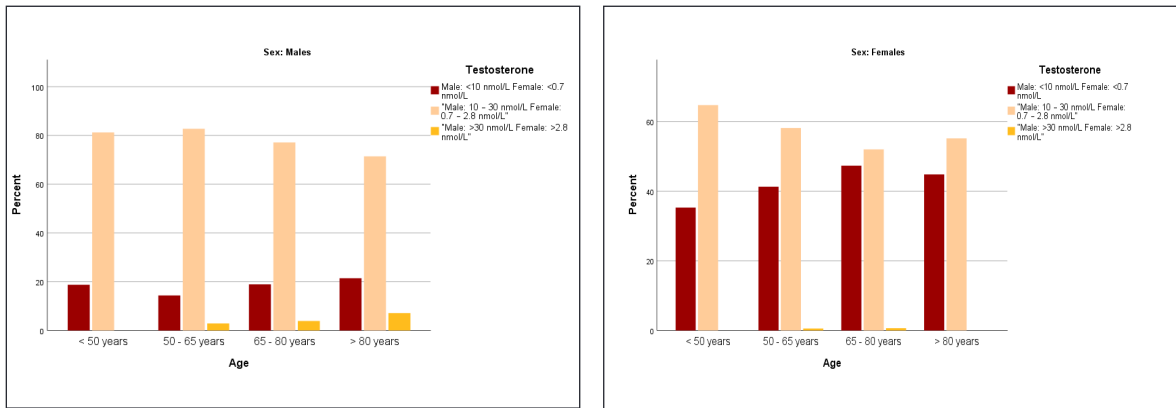
Oestradiol

The majority of men in NICOLA had normal levels of serum oestradiol, across all ages, with a median value of 18 pg/mL (66 pmol/L) (Figure 7.). Women under 50 years showed mostly pre-menopausal levels (47.0 pg/mL or 172 pmol/L) versus post-menopausal levels over 50 years old, stabilised in a median of 10 pg/mL (37 pmol/L) (Figure 7.15).

Figure 7.15: Percentage of NICOLA participants with low / normal / high serum levels of oestradiol, by age group and sex.
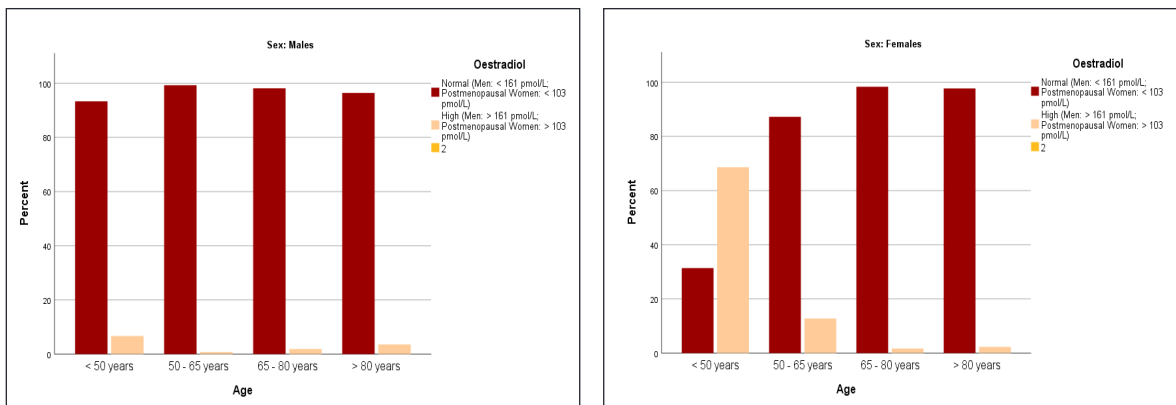
7.6 Renal Biomarkers

Chronic kidney disease (CKD) has a prevalence up to 17.3% in adult European populations (32), and is a global public health problem (33) and a leading cause of death (1). Globally, approximately 697.5 million people had CKD in 2017, and 19.7 million were newly diagnosed. Annually, 11.2 million people die from CKD, which

represents 2.2% of all global deaths (1,2). The worldwide prevalence of individuals with CKD is steadily increasing (2), being predicted to become the fifth leading cause of death worldwide by 2040 (34).

The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline developed by the Kidney Disease Outcomes Quality Initiative (KDOQI) of the National Kidney Foundation (NKF), recommends the use of estimated glomerular filtration rate (eGFR) in the evaluation, classification, and stratification of CKD (35). The most widely used eGFR equation, recommended by the KDOQI guidelines for initial assessment of kidney function (36), is based on serum creatinine, taking account of sociodemographic variables (age, gender and ethnicity). A second equation, based on the measurement of serum cystatin C (36), offers an alternative to the serum creatinine equation in situations where the latter is less accurate, such as in elderly individuals with low muscle mass and in those with extreme body mass index values (37).

Total protein in serum represents a combination of serum albumin (≈60%) and ◻ 1, ◻2, ◻ and ◻ globulins (≈40%). Increased levels of total protein may be an indicator of dehydration but also of disorders that course with abnormally high production of protein, like inflammatory or oncologic conditions. Decreased levels of serum total protein are makers of conditions that interfere with production of albumin or globulin proteins, such as malnutrition or severe liver disease; increase the breakdown or loss of protein, such as kidney disease (nephrotic syndrome) or increase or expand the volume of plasma, such as congestive heart failure.

Urea, formed in the liver, is the nitrogen-containing end product of protein metabolism and the urea cycle. The kidneys eliminate about 85% of urea whereas the rest is excreted via the gastrointestinal tract. Although increased serum urea is usually an indicator of conditions where renal clearance decreases, like acute and chronic kidney disease, it may also increase in other conditions not related to renal diseases such as upper gastrointestinal bleeding, dehydration, catabolic states, and high protein diets. Low-protein diets and severe liver disease may lead to decreased urea concentrations in serum. Despite serum creatinine being a more accurate assessment of renal function, urea is usually increased earlier in kidney disease.

Hyperphosphatemia is associated with significant pathophysiology in CKD, which could contribute to increased mortality (38). Systemic oxidative stress associated with the dysregulation of iron and phosphate is a critical determinant of morbidity and mortality in CKD patients, especially those with concomitant CVD (39). High phosphate levels have been associated with an increased risk for infection in dialysis patients (40).

Hyperuricemia, defined by high concentration of serum urate, is common in people with CKD and is associated with adverse cardiovascular outcomes and progression of CKD (41–44).

Creatinine

Creatinine is the most commonly used endogenous marker for assessment of glomerular function. Serum creatinine levels were within normal range (50 – 120 µmol/L) in over 90% of NICOLA participants across all age groups and sex (Figure 7.16). Median value for serum creatinine was 73.4 µmol/L.

Figure 7.16: Percentage of NICOLA participants with low / normal / high serum levels of creatinine, by age group and sex.
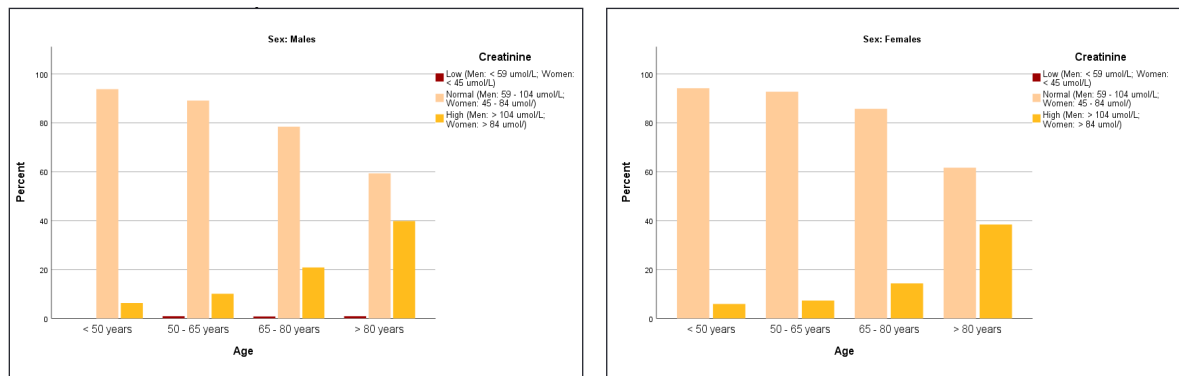
Cystatin C

Cystatin C is a low-molecular-weight protein formed at a constant rate and freely filtered by the kidneys, which functions as a protease inhibitor and is produced by all nucleated cells in the body.

Serum levels of cystatin C steadily increased with age in both men and women, with the majority of those aged 80 years and above having high levels (1 mg/L) (Figure 7.17). Median values in men increased from 1.03 (< 50 years) to 1.40 mg/L (> 80 years) and from 0.91 (< 50 years) to 1.40 mg/L (> 80 years) in women.

Figure 7.17: Percentage of NICOLA participants with low / normal / high serum levels of cystatin C, by age group and sex.

Total protein

The median serum levels of total protein in the NICOLA participants was 74.9 g/L, with around 80% of them within normal levels (60 - 80 g/L) (Figure 7.18).

Figure 7.18: Percentage of NICOLA participants with low / normal / high serum levels of total protein, by age group and sex.

Urea

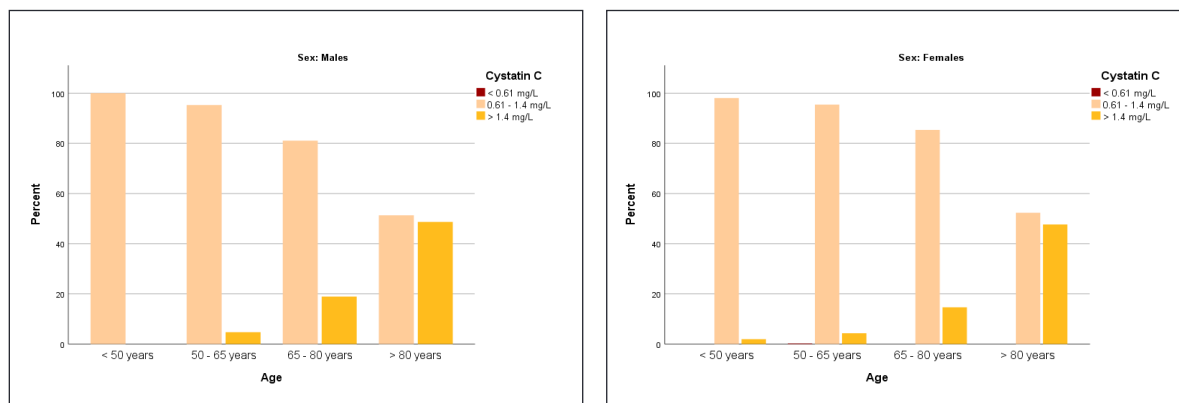The percentage of NICOLA participants who had serum urea within normal levels (2.5 - 7.0 nmol/L) decreased with age in both men and women from 100% to ≈60% (Figure 7.19). The median values in men increased from 5.13 (< 50 years) to 6.80 mg/L (> 80 years) and from 4.47 nmol/L (< 50 years) to 6.35 nmol/L (> 80 years) in women.

Figure 7.19: Percentage of NICOLA participants with low / normal / high serum levels of urea, by age group and sex.
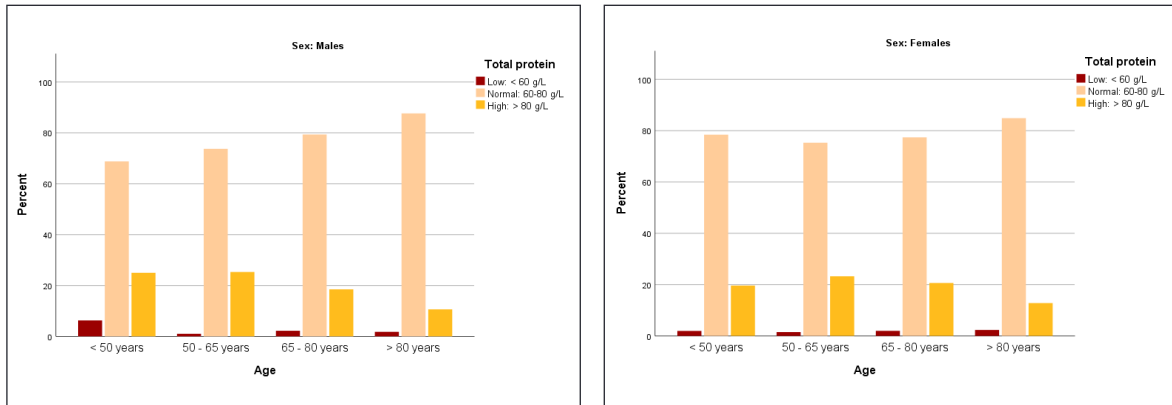

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Phosphate

Over 80% of NICOLA participants had serum levels of phosphate within the normal range (0.74 - 1.4 mmol/L) (Figure 7.20). The median levels were 1.2 mmol/L.

Figure 7.20: Percentage of NICOLA participants with low / normal / high serum levels of phosphate, by age group and sex.

Urate

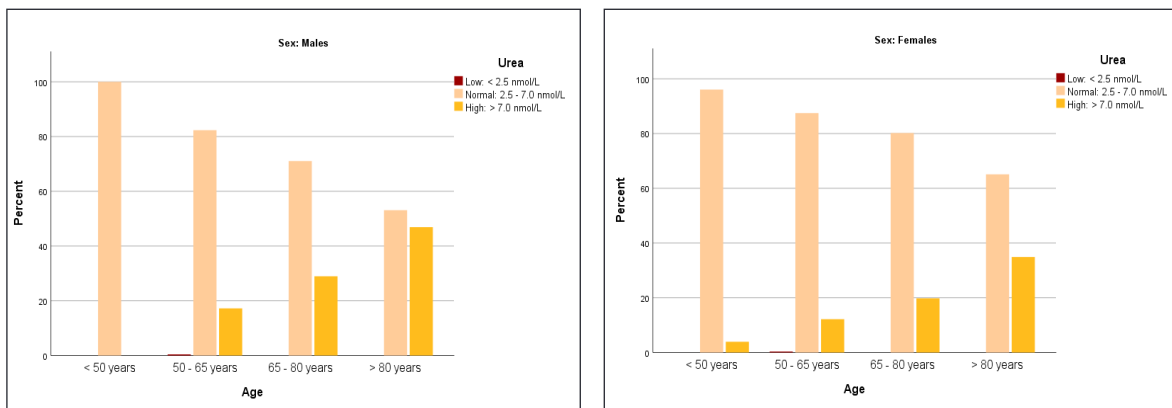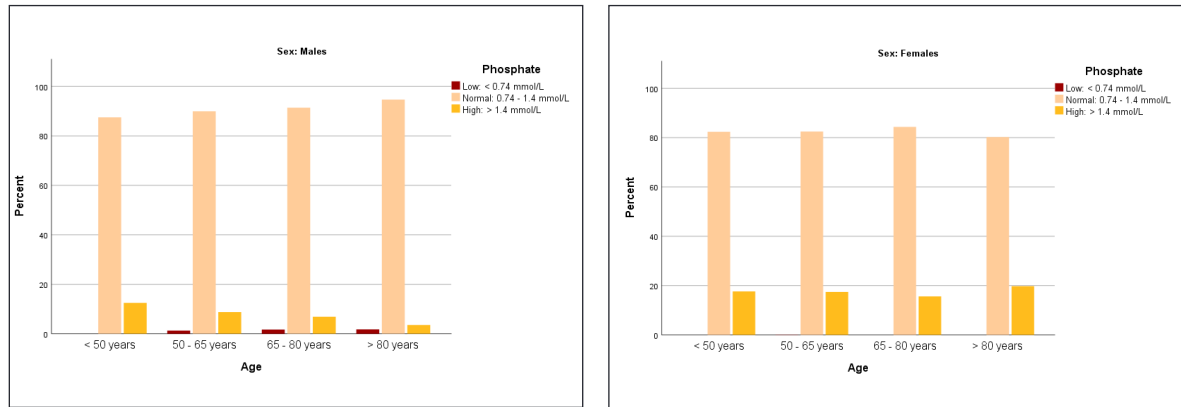Between 60 - 80% of men and women in the NICOLA cohort had serum urate levels within the normal range, with a median value of 0.307 mmol/L (Figure 7.21).

Figure 7.21: Percentage of NICOLA participants with low / normal / high serum levels of urate, by age group and sex.
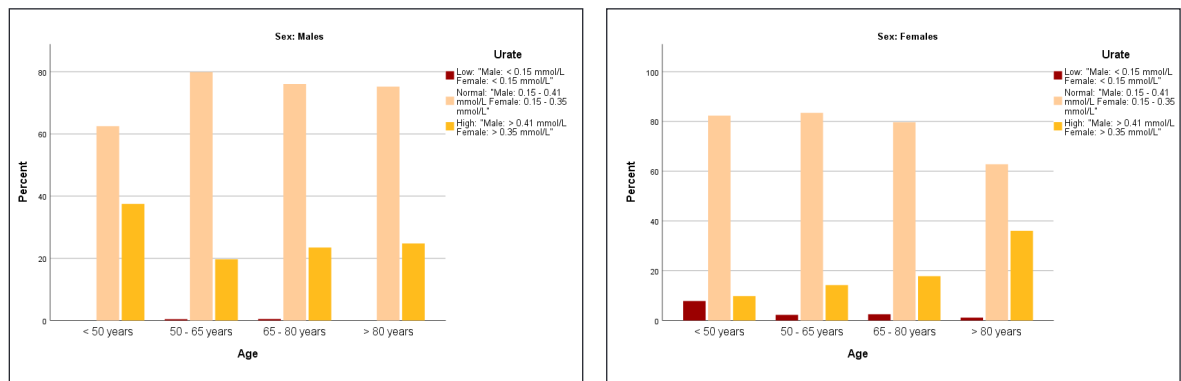
7.7 Liver Biomarkers

Approximately 1500.6 million people were living with cirrhosis and other chronic liver diseases in 2017, 5.2 million new cases were diagnosed and 1.3 million died from the disease, which represents 2.4% of all global deaths (1,2). Human serum albumin accounts for 50% of the plasma proteins, involved in the transport of various metal cations such as copper and zinc as well as poorly water-soluble molecules such as cholesterol, bilirubin, and thyroxine. Lower levels of albumin in serum have been associated with liver disease (45).

Albumin

Most of the NICOLA participants had serum albumin levels within the normal range (35 - 50 g/L) regardless of age and sex, with a median value of 42.6 g/L (Figure 7.22).

Figure 7.22: Percentage of NICOLA participants with low / normal / high serum levels of albumin, by age group and sex.
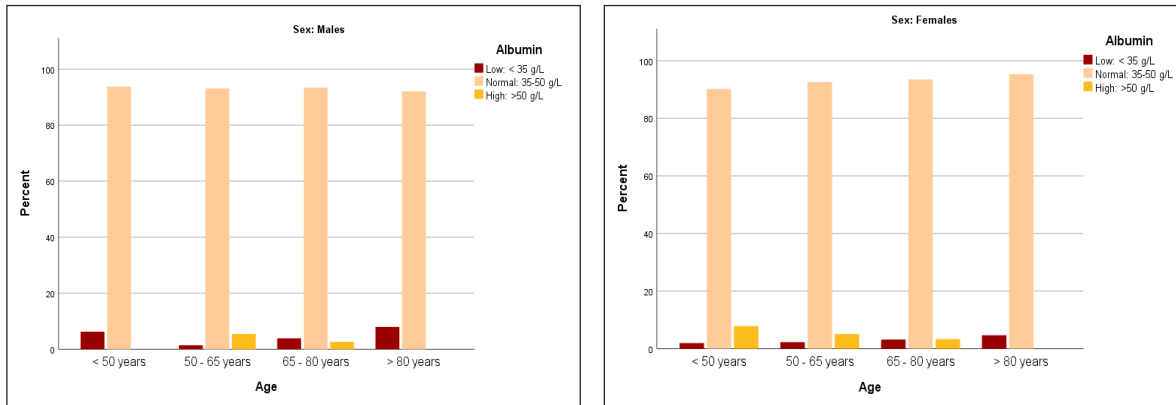
Direct Bilirubin

Most of the NICOLA participants showed normal levels of direct bilirubin (0 - 8 µmol/L), with median levels of 3.53 µmol/L (Figure 7.23).

Figure 7.23: Percentage of NICOLA participants with serum levels of direct bilirubin, above / below 8 µmol/L, by age group and sex.
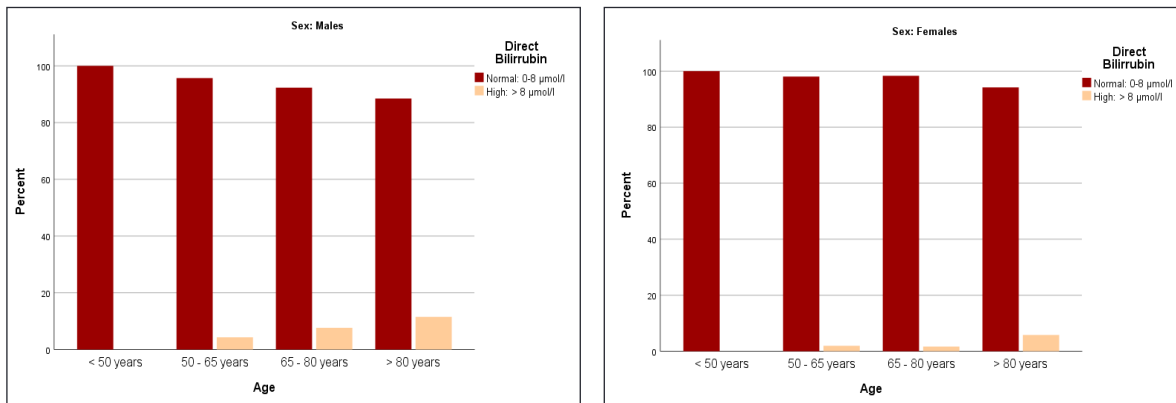
Total Bilirubin

Over 80% of men and almost all women in the NICOLA cohort had serum total bilirubin levels within the normal range (1 - 17 μmol/L) (Figure 7.24) (47). The median levels in men were 10.94 μmol/L and 8.39 μmol/L in women.

Figure 7.24: Percentage of NICOLA participants with serum levels of total bilirubin, above / below 17 μmol/L, by age group and sex.
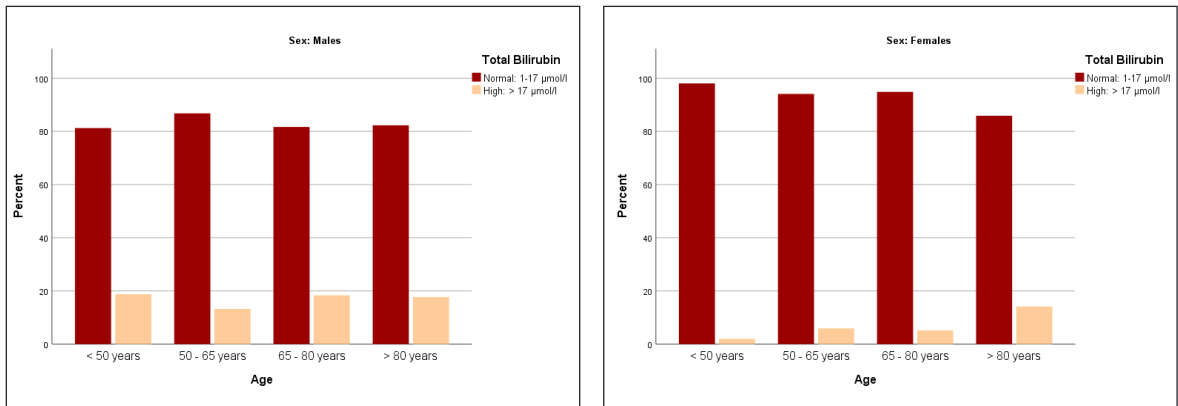
Gamma Glutamyltransferase

Between 80 – 100% of NICOLA participants had normal levels of GGT regardless of sex or age (Figure 7.25). Women had a median GGT of 23.6 U/L versus 31.3 U/L in men.

Figure 7.25: Percentage of NICOLA participants with serum levels of gamma glutamyltransferase (GGT), above / below 78 U/L (men) and 54 U/L (women), by age group and sex.
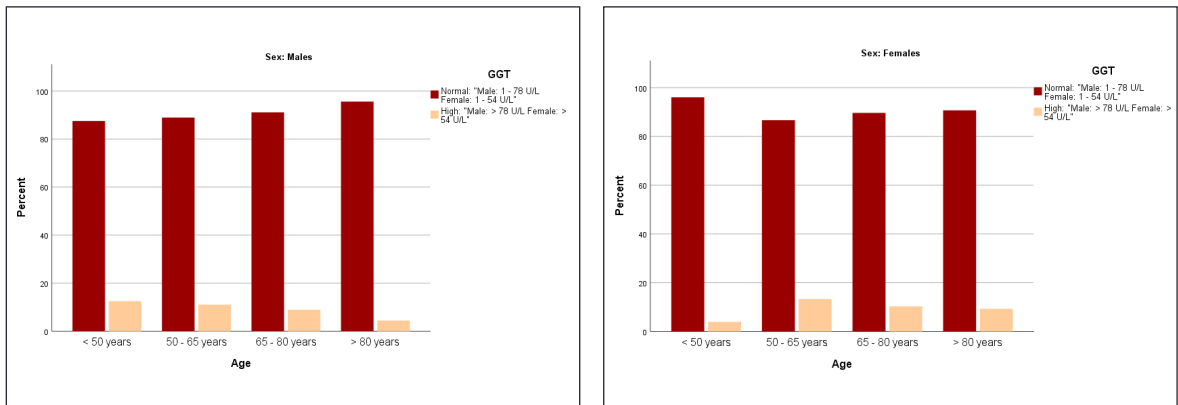
Alanine aminotransferase

Over 80% of NICOLA participants showed normal levels of serum ALT activity, with a median value of 25 U/L (Figure 7.26).

Figure 7.26: Percentage of NICOLA participants with serum levels of alanine aminotransferase, above / below 50 U/L, by age group and sex.
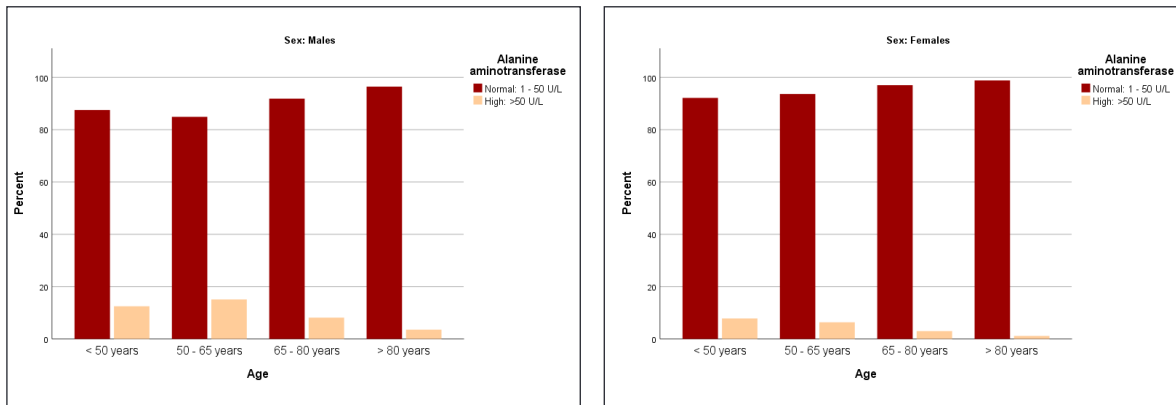
Aspartate aminotransferase

The activity of the AST enzyme in serum was normal (1 - 45 U/L) in the majority of the NICOLA participants with a median value of 27 U/L (Figure 7.27).
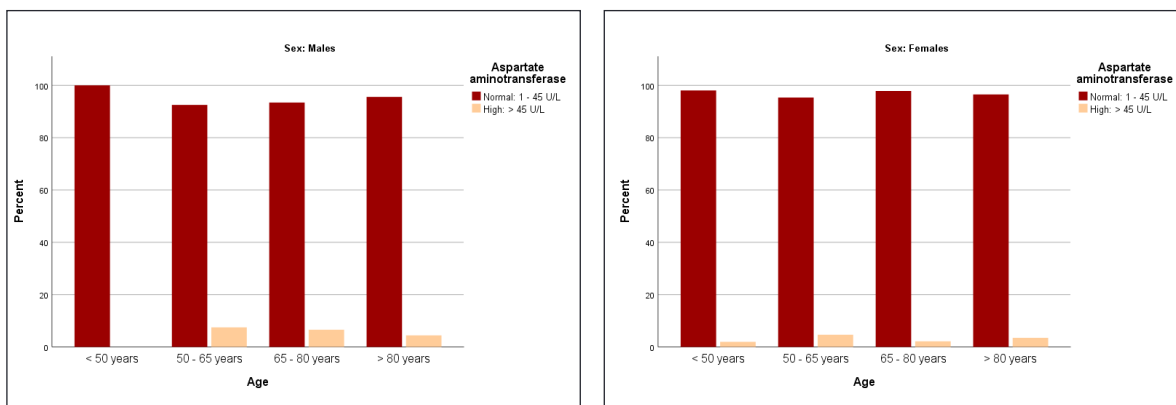
Figure 7.27: Percentage of NICOLA participants with serum levels of aspartate aminotransferase, above / below 45 U/L, by age group and sex.

7.8 Derived clinical variables based on biochemistry data

The eGFR equations derived for serum creatinine, cystatin C and the combined formula, along with CKD, CKD stage and ESRD variables, described in the 7.6 Renal Biomarkers section were calculated by Dr Marisa Cañadas-Garre and Dr Laura Smyth within the QUB Molecular Epidemiology and Public Health research team, funded by the Science Foundation Ireland-Department for the Economy (SFI-DfE) Investigator Program Partnership Award (15/IA/3152) and the Economic and Social Research Council (ES/L008459/1). All equations are based on those defined by the KDIGO2021 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. The values of the eGFR equation based on serum creatinine, serum cystatin C and both serum creatinine and cystatin C are presented in Table 7.2. Both men and women aged under 80 years old in the NICOLA cohort had eGFR in the normal range (over 60 mL/min/1.73m2) (35).

Table 7.2: Estimated glomerular filtration ratio, based on serum creatinine, cystatin C or both, according to the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation, by age and sex. Units in mL/min/1.73m2.

Equation	Age (yrs)	Males	Females
		Median [IQR]	Median [IQR]
eGFR$^{EPI}_{Creatinine}$	< 50	102.1 [94.4-106.0]	95.5 [87.2-103.5]
	50 - 65	91.4 [78.2-98.3]	87.1 [78.9-94.8]
	65 - 80	79.0 [64.8-89.1]	77.2 [68.2-85.6]
	> 80	64.3 [51.0-77.6]	63.8 [46.8-74.5]
eGFR$^{EPI}_{CystatinC}$	< 50	78.4 [66.1-92.8]	86.1 [77.8-93.7]
	50 - 65	73.7 [64.6-84.3]	74.8 [63.6-85.6]
	65 - 80	59.5 [50.3-70.5]	60.1 [49.9-70.3]
	> 80	45.3 [36.9-53.2]	43.0 [33.3-54.1]
eGFR$^{EPI}_{CreatinineCystatinC}$	< 50	87.2 [80.4-99.7]	90.9 [82.3-97.3]
	50 - 65	81.4 [72.1-89.8]	79.7 [69.9-88.6]
	65 - 80	68.8 [58.4-78.8]	67.4 [58.6-76.1]
	> 80	53.3 [44.1-64.0]	51.7 [39.9-61.8]
Abbreviations: eGFR: estimated glomerular filtration rate, according to the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation.			
Values are presented as median [interquartile range]			

CKD

Among the NICOLA participants, 13% of men (n = 194) and 10% of women (n = 159) had CKD, defined as eGFREPI < 60 mL/min/1.73m2, according to the KDIGO guidelines (35).

CKD Stage

The KDIGO guidelines establish the classification for the staging of CKD according to the eGFREPI (35). The distribution of the NICOLA participants according to their CKD stage are presented in Table 7.3.

Table 7.3: Stages of Chronic Kidney Disease (CKD) in the NICOLA participants

Stage	Definition	Males	Females	Total
		n (%)	n (%)	n (%)
G1	eGFR ≥ 90 mL/min/1.73m2	517 (35.3)	450 (27.8)	967 (31.4)
G2	90 > eGFR ≥ 60 mL/min/1.73m2	753 (51.4)	1007 (62.3)	1760 (57.1)
G3a	60 > eGFR ≥ 45 mL/min/1.73m2	142 (9.7)	116 (7.2)	258 (8.4)
G3b	40 > eGFR ≥ 30 mL/min/1.73m2	42 (2.9)	36 (2.2)	78 (2.5)
G4	30 > eGFR ≥ 15 mL/min/1.73m2	8 (0.5)	6 (0.4)	14 (0.5)
G5	eGFR < 15 mL/min/1.73m2	2 (0.1)	1 (0.1)	3 (0.1)
Abbreviations: eGFR: estimated glomerular filtration rate, according to the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation; n: number.				
Values presented are unweighted.				

ESRD

Only two men (n = 2; 0.1%) and one woman (n = 1; 0.1%) from the NICOLA cohort had ESRD according to the KDIGO definition (eGFREPI < 15 mL/min/1.73m^2) (35).

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