# **Biomarker Reference Guide**

A guide for patients and clinicians to understand health through biomarkers

## Contents

Purpose and Background Most Predictive Biomarkers by Disease Risk Ratios by Biomarker Strength Values Our Findings Appendix A. Methods Appendix B. Biomarker Glossary Appendix C. About the Organizations

This guide presents blood biomarker information and related information solely for informational and educational purposes. The information provided is derived by applying data science to a population dataset with limitations regarding the population demographics such as age, race, ethnic background, potential bias in the population, and other factors that influence the data. It is not intended to serve as medical advice, diagnosis, or treatment. The information provided here does not consider your individual health conditions, medical history, or specific circumstances, and should not be used as a substitute for consultation with a qualified healthcare professional. Individuals or entities using this information are doing so at their own risk as the providers do not make claims to its accuracy or the benefits of using such information. For more information on the data set used in preparing this information please visit <u>UK Biobank's website</u>.

# Purpose and Background

#### Introduction

Blood test results can be overwhelming. You're often presented with too much information, yet not enough at the same time. This guide is intended as a resource to aid the interpretation of lab test data by individuals and their care providers. It contains ranges of values for each biomarker and different age-related diseases that can be useful when reviewing your personal results.

The seven common age-related disease-related outcomes explored in this guide are All-Cause Mortality, Major Adverse Cardiac Events (MACE), Type 2 Diabetes (T2D), Dementia, Acute Kidney Disease, Liver Disease, and Chronic Obstructive Pulmonary Disease (COPD). These outcomes were chosen based on their prevalence and individual impacts on aging and mortality.

#### What is a biomarker?

The first step to understanding your bloodwork is recognizing what a blood test is collecting and measuring. A **biomarker**, or biological marker, is a measurable indicator of a biological process or condition in your body.<sup>1</sup> One of the most common ways to measure certain biomarkers is through blood tests, if the biomarker is present in your blood.

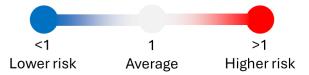
Biomarkers are the key to understanding your health and early detection of diseases. A simple blood test can give you information about your risk for heart disease, liver disease, mortality, and more.<sup>2</sup> Interpreting your blood test results and understanding what each biomarker can tell you about your health is challenging. In this guide, we present this information in the form of risk ratios and Voloridge<sup>™</sup> Modeled Range values or VMR<sup>™</sup> values.

<sup>&</sup>lt;sup>1</sup> Califf, Robert M. "Biomarker definitions and their applications." Experimental biology and medicine 243, no. 3 (2018): 213-221.

<sup>&</sup>lt;sup>2</sup> Kristensen, Michael, Anne Kristine Servais Iversen, Thomas Alexander Gerds, Rebecca Østervig, Jakob Danker Linnet, Charlotte Barfod, Kai Henrik Wiborg Lange et al. "Routine blood tests are associated with short term mortality and can improve emergency department triage: a cohort study of> 12,000 patients." Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine 25 (2017): 1-8.

## What is a risk ratio?

A **risk ratio** is a statistic used to describe your risk for a specific disease relative to other people your age and gender. A risk ratio of one (1) means your risk is exactly average for your age. A risk ratio from zero (0) to one (1) means your risk is lower than the average for your age. This suggests you are doing better than your peers. If your risk ratio is higher than one (1), you have an elevated risk for the disease compared to your peers.



### What is a VMR value?

While risk ratios are great for understanding how you compare to others of your age and gender, they can be misleading if the risk for your age group is very high. For example, you may be looking at the average risk for heart disease for people aged 60 to 70. If you are 63 years old and see a risk ratio of 0.73, you might be pleased to know you are at a reduced risk. However, even if your risk ratio is below 1, this does necessarily mean that your risk ratio is healthy or optimal. People in this age group (60+) have a high risk for heart disease in general, so although you are doing better than the average person your age, there is still room to improve.

Reference ranges provided alongside blood test results can be convenient to use, yet like risk ratios, may not necessarily indicate what is considered optimal. To help address this challenge, we also provide a set of values called the **Voloridge Modeled Range** or **VMR**. The VMR is a set of values that our models associate with the lowest probabilities of adverse outcomes for a given biomarker. Because they are modeled and calculated directly by Voloridge Health's predictive models based on a specific data set and are not designed to be recommendations, these values may differ from what you see as reference ranges on a blood test or online.

## **Predictive Strength**

Another metric used by Voloridge Health when looking at biomarkers as predictors for health is the **predictive strength** value. This metric is used to show how correlated the biomarker is with a certain disease. In the <u>VMR Values by Disease</u> section, the biomarkers

are colored with a gradient like in the graphic below. White represents a lower strength value, while green reprents a higher strength score.



Additionally, you can find all biomarkers and strength values in the <u>Strength Values</u> section.

Please note that findings from Voloridge Health's analysis of UK Biobank data should be interpreted with caution due to the dataset's demographic limitations and potential biases. You can read more in depth about how VMR values and strength values are calculated, as well as population biases and filters, in the <u>Methods</u> section.

## What makes Voloridge Health different?

Most traditional models focus on an individual predictor and its relationship to a single outcome, like cholesterol and heart disease. Furthermore, ranges typical in medical literature are based on clinical recommendations and/or population averages instead of connecting the biomarker with longer term health outcome probabilities. In contrast, we examine many health predictors across multiple potential disease outcomes together. Our VMR values are based on real data associations between biomarker ranges and 15-year disease outcomes. By treating each predictor equally, we give a fully data-driven, longterm view of health risks. This guide is designed to be a tool to help you see patterns that single-variable studies might miss, supporting a proactive and holistic approach to healthcare.

## A Note on Disease Definitions

Some diseases are defined by comparing specific biomarker levels to established thresholds. For example, type 2 diabetes is typically diagnosed if Hemoglobin A1C levels are at or above 6.5 percent.<sup>3</sup> In this case, a risk ratio is no longer meaningful, given that the likelihood someone is diagnosed with such a disease is nearly 100 percent if their

<sup>&</sup>lt;sup>3</sup> Chatterjee, Sudesna, Kamlesh Khunti, and Melanie J. Davies. "Type 2 diabetes." *The lancet* 389, no. 10085 (2017): 2239-2251.

biomarker value passes that threshold. However, for the purpose of this guide, values are provided for such biomarkers regardless of these definitions, to maintain consistency and show data trends.

# Most Predictive Biomarkers by Disease

This section provides VMR values for each of our model's most predictive biomarkers for measuring the likelihood of experiencing a disease. These are provided as a reference for you to compare with your blood test results. The VMR values apply to clinically relevant age ranges for each disease. The table below can be used to link to a specific disease.

Major Adverse Cardiac Events	Type 2 Diabetes
<u>Dementia</u>	Acute Kidney Disease
Liver Disease	Chronic Obstructive Pulmonary Disease
All-Cause Mortality	

## **Reading this Section**

This section provides a two-page report for each of the seven diseases listed above. The first page will include a description of the disease category and a table including the strength values for our model's most predictive biomarkers for that disease, as well as the VMR for that biomarker. **Note that the VMR values in this section are overall ranges, rather than values for a specific disease.** The second page includes disease-specific risk ratios for each of the included biomarkers.

Biomarker	Strength of relation with disease	nship Voloridge M	odeled Range
└	↓	] [	<u> </u> ]
Biomarker	Strength	VMR (Male)	VMR (Female)
Hemoglobin A1C	10	4.72% to 5.48%	4.73% to 5.56%
BMI	9	22.1 to 27.8 kg/m2	20.3 to 26.3 kg/m2
HDL	6	48 to 80 mg/dL	63 to 102 mg/dL

Biomarker	•	Smoke Pack Years		
	Ma	Males		ales
	Range	RR	Range	RR
Г	<10	0.91	<10	0.91
	10-20	1	10-20	1.14
Ranges of values for biomarker	20-30	1.14	20-30	1.3
	30-40	1.26	30-40	1.53
	>40	1.38	>40	1.86
Risk ratios for each range				-

## Major Adverse Cardiac Events (MACE)

A **Major Adverse Cardiac Event** is a heart or blood vessel related event that negatively impacts your health. Examples include heart disease, stroke, heart attack, heart failure, or other adverse cardiovascular outcomes.

Below are suggested target values for the most predictive biomarkers for experiencing MACE in males and females aged 55 to 70 with no prior history of MACE.

Biomarker	Strength	VMR (Male)	VMR (Female)
Hemoglobin A1C	10	4.72% to 5.48%	4.73% to 5.56%
Cystatin C	10	0.72 to 0.95 mg/dL	0.62 to 0.82 mg/dL
Smoke Pack Years	9	0 to 11 years	0 to 9 years
BMI	9	22.1 to 27.8 kg/m2	20.3 to 26.3 kg/m2
HDL	9	48 to 80 mg/dL	63 to 102 mg/dL
LDL/Apolipoprotein B Ratio	8	1.35 to 1.53	1.38 to 1.57
White Blood Cell Count	8	3.9 to 6.4 /µl	3.6 to 6.5 /µl
C-Reactive Protein	8	0.4 to 1.1 mg/L	0.4 to 1.2 mg/L
Neutrophil Count	7	2000 to 3860 /µl	1770 to 3720 /µl
Urate	6	4.4 to 6.3 mg/L	2.9 to 4.9 mg/L
Triglycerides	6	63 to 169 mg/dL	45 to 110 mg/dL
Systolic Blood Pressure*	6	103 to 144 mmHg	99 to 144 mmHg
LDL*	4	113 to 185 mg/L	110 to 181 mg/L

\* LDL and Systolic Blood Pressure are included as they are commonly looked at for MACE. However, they are not top predictive biomarkers.

# Major Adverse Cardiac Events (MACE)

Hemoglobin A1C			
Ма	les	Fem	ales
Range	RR	Range	RR
<4.8	0.85	<4.8	0.9
4.8-5.4	0.88	4.8-5.4	0.86
5.4-5.7	0.98	5.4-5.7	0.94
5.7-6	1.09	5.7-6	1.1
6-6.3	1.25	6-6.3	1.48
6.3-7	1.5	6.3-7	1.69
>7	1.7	>7	2.33

Cystatin C				
Ма	les	Fem	ales	
Range	RR	Range	RR	
<0.8	0.85	<0.8	0.75	
0.8-0.9	0.86	0.8-0.9	0.85	
0.9-1	0.95	0.9-1	0.99	
1-1.1	1.08	1-1.1	1.2	
1.1-1.2	1.21	1.1-1.2	1.4	
>1.2	1.48	>1.2	1.83	

Smoke Pack Years			
Ма	les	Fem	ales
Range	RR	Range	RR
<10	0.91	<10	0.91
10-20	1	10-20	1.14
20-30	1.14	20-30	1.3
30-40	1.26	30-40	1.53
>40	1.38	>40	1.86

BMI			
Ма	les	Fem	ales
Range	RR	Range	RR
<21	0.78	<20	0.77
21-23	0.78	20-22	0.72
23-26	0.87	22-26	0.84
26-29	0.97	26-29	0.97
29-32	1.09	29-33	1.18
32-35	1.3	33-36	1.35
>35	1.45	>36	1.66

HDL			
Ma	les	Fem	ales
Range	RR	Range	RR
<35	1.37	<35	1.93
35-42	1.17	35-42	1.6
42-50	1.02	42-50	1.31
50-60	0.91	50-60	1.06
60-75	0.8	60-75	0.86
>75	0.77	>75	0.73
>15	0.77	~75	0.75

LDL/ApoB Ratio			
Ма	les	Fem	ales
Range	RR	Range	RR
<1.15	1.43	< 1.15	1.84
1.15-1.24	1.17	1.15-1.24	1.41
1.24-1.3	1.06	1.24-1.3	1.14
1.3-1.4	0.92	1.3-1.4	0.96
1.4-1.5	0.78	1.4-1.5	0.81
>1.5	0.86	>1.5	0.8

White Blood Cell Count			
Ма	les	Fem	ales
Range	RR	Range	RR
<4	0.82	<4	0.77
4-6	0.85	4-6	0.83
6-8	0.99	6-8	0.98
8-9.5	1.14	8-9.5	1.2
9.5-11	1.32	9.5-11	1.43
>11	1.42	>11	1.8

Urate			
Ma	Males		ales
Range	RR	Range	RR
<4	0.96	<3	0.93
4-5	0.94	3-5	0.88
5-7	0.97	5-6	1.08
7-8	1.11	6-7	1.29
8-9	1.25	7-8	1.67
>9	1.51	>8	1.85

	LC	DL	
Ма	les	Fem	ales
Range	RR	Range	RR
<90	0.95	<90	1.08
90-100	0.8	90-100	0.89
100-120	0.81	100-120	0.82
120-150	0.86	120-150	0.81
150-175	0.94	150-175	0.89
175-200	1.05	175-200	0.97
>200	1.11	>200	1.09

C-Reactive Protein					
Ма	les	Females			
Range	RR	Range	RR		
< 0.5	0.8	<0.5	0.72		
0.5-1	0.87	0.5-1	0.81		
1-1.7	0.99	1-1.7	0.92		
1.7-3	1.06	1.7-3	1.04		
3-6	1.19	3-6	1.22		
>6	1.24	>6	1.42		

Triglycerides					
Males		Fem	ales		
Range	RR	Range	RR		
<80	0.87	<80	0.75		
80-110	0.92	80-110	0.88		
110-150	0.96	110-150	0.96		
150-200	1	150-200	1.07		
200-300	1.09	200-300	1.26		
>300	1.21	>300	1.36		

Neutrophil Count				
Males		Fem	ales	
Range	RR	Range	RR	
<2000	0.89	<2000	0.84	
2000-3000	0.83	2000-3000	0.8	
3000-4000	0.91	3000-4000	0.89	
4000-5000	1.02	4000-5000	1.02	
5000-6000	1.11	5000-6000	1.19	
>6000	1.26	>6000	1.43	

Systolic Blood Pressure				
Ma	les	Fem	ales	
Range	RR	Range	RR	
<100	0.73	<100	0.68	
100-110	0.74	100-110	0.65	
110-120	0.76	110-120	0.78	
120-130	0.82	120-130	0.82	
130-150	0.95	130-150	0.91	
150-170	1.07	150-170	1.07	
>170	1.18	>170	1.21	

## Type 2 Diabetes (T2D)

**Type 2 Diabetes** occurs when the body develops a resistance to insulin, or your pancreas fails to produce enough insulin. This results in the body being unable to process and use sugar properly.

Below are suggested target values for the most predictive biomarkers for developing Type 2 Diabetes in males and females aged 40 to 70.

Biomarker	Strength	VMR (Male)	VMR (Female)
Hemoglobin A1C	10	4.72% to 5.48%	4.73% to 5.56%
BMI	9	22.1 to 27.8 kg/m2	20.3 to 26.3 kg/m2
HDL	6	48 to 80 mg/dL	63 to 102 mg/dL
SHBG	6	34 to 71 nmol/L	45 to 135 nmol/L
Triglycerides	6	63 to 169 mg/dL	45 to 110 mg/dL
Urate	5	4.4 to 6.3 mg/L	2.9 to 4.9 mg/L
ALT	5	14 to 27 U/L	10 to 20 U/L
GGT	5	13 to 29 U/L	10 to 19 U/L
C-Reactive Protein	5	0.4 to 1.1 mg/L	0.4 to 1.2 mg/L
AST/ALT Ratio	5	1.01 to 1.45	1.17 to 1.57

# Type 2 Diabetes (T2D)

г

Hemoglobin A1C				
Ma	les	Fem	ales	
Range	RR	Range	RR	
<4.8	0.21	<4.8	0.25	
4.8-5.4	0.32	4.8-5.4	0.29	
5.4-5.7	0.77	5.4-5.7	0.68	
5.7-6	2.1	5.7-6	2.04	
6-6.3	5.32	6-6.3	6.01	
6.3-7	9.13	6.3-7	13.02	
>7	11.59	>7	17.6	

	BMI				
Ma	les	Females			
Range	RR	Range	RR		
<21	0.3	<20	0.24		
21-23	0.31	20-22	0.24		
23-26	0.43	22-26	0.4		
26-29	0.77	26-29	0.88		
29-32	1.41	29-33	1.58		
32-35	2.18	33-36	2.43		
>35	3.71	>36	4		

HDL				
Ма	les	Females		
Range	RR	Range	RR	
<35	2.22	<35	4.45	
35-42	1.54	35-42	3.02	
42-50	1.01	42-50	1.85	
50-60	0.65	50-60	1.06	
60-75	0.44	60-75	0.57	
>75	0.36	>75	0.3	

SHBG				
Ма	les	Females		
Range	RR	Range	RR	
<20	2.26	<20	4.36	
20-30	1.37	20-30	2.78	
30-40	0.99	30-40	1.66	
40-60	0.72	40-60	0.85	
60-80	0.5	60-80	0.45	
>80	0.53	80-120	0.37	
		>120	0.42	

Triglycerides				
Ma	les	Fem	ales	
Range	RR	Range	RR	
<80	0.41	<80	0.33	
80-110	0.6	80-110	0.53	
110-150	0.77	110-150	0.85	
150-200	1.03	150-200	1.3	
200-300	1.4	200-300	2.01	
>300	2.01	>300	3.17	

Urate					
Ma	les	Fem	ales		
Range	RR	Range	RR		
<4	0.82	<3	0.39		
4-5	0.71	3-5	0.63		
5-7	0.92	5-6	1.38		
7-8	1.39	6-7	2.39		
8-9	1.79	7-8	3.34		
>9	2.49	>8	4.29		

ALT				
Ма	les	Females		
Range	RR	Range	RR	
<12	0.6	<12	0.49	
12-20	0.55	12-20	0.69	
20-30	0.86	20-30	1.27	
30-45	1.45	30-45	2.1	
45-60	2.17	45-60	2.66	
>60	2.86	>60	3.03	

GGT				
Ма	les	Females		
Range	RR	Range	RR	
<20	0.35	<20	0.42	
20-30	0.6	20-30	0.98	
30-40	0.98	30-40	1.61	
40-60	1.39	40-60	1.91	
60-90	1.66	60-90	2.07	
90-150	1.79	90-150	2.25	
>150	2.14	>150	2.31	

C-Reactive Protein				
Males		Females		
Range	RR	Range	RR	
<0.5	0.4	<0.5	0.29	
0.5-1	0.65	0.5-1	0.47	
1-1.7	0.92	1-1.7	0.69	
1.7-3	1.22	1.7-3	1.09	
3-6	1.66	3-6	1.71	
>6	1.79	>6	2.58	

AST/ALT Ratio				
Ма	Males		ales	
Range	RR	Range	RR	
<0.7	2.2	<0.7	2.99	
0.7-1	1.42	0.7-1	2	
1-1.25	0.84	1-1.25	1.14	
1.25-1.5	0.59	1.25-1.5	0.68	
1.5-2	0.48	1.5-2	0.48	
>2	0.59	>2	0.5	

## Dementia

**Dementia** is an age-related condition resulting from accumulated damage to brain and nerve cells, leading to cognitive and physical decline that interferes with the ability to function in daily life.

Below are suggested target values for the most predictive biomarkers for developing Dementia in males and females aged 60 to 70.

Biomarker	Strength	VMR (Male)	VMR (Female)
Grip Strength (lbs)	10	89 to 133 lbs	48 to 84 lbs
Hemoglobin A1C	9	4.72% to 5.48%	4.73% to 5.56%
Smoke Pack Years	9	0 to 11 years	0 to 9 years
Cystatin C	8	0.72 to 0.95 mg/dL	0.62 to 0.82 mg/dL
LDL/Apolipoprotein B Ratio	8	1.35 to 1.53	1.38 to 1.57
Red Blood Cell Count	7	4.4 to 4.8 million/mcL	3.9 to 4.4 million/mcL
Hemoglobin	7	14.1 to 15.5 g/dL	12.5 to 14.1 g/dL
Urea	6	11.9 to 19.2 mg/dL	11.2 to 18.4 mg/dL
Creatinine	6	0.78 to 1.06 mg/L	0.56 to 0.81 mg/L
LDL	5	113 to 185 mg/L	110 to 181 mg/L

## Dementia

Grip Strength (lbs)			
Males		Females	
Range	RR	Range	RR
<45	2.1	<20	1.81
45-60	1.59	20-30	1.45
60-80	1.09	30-40	1.21
80-100	0.85	40-55	0.93
100-120	0.62	55-65	0.76
>120	0.59	>65	0.71

Hemoglobin A1C				
Ма	les	Females		
Range	RR	Range	RR	
<4.8	0.91	<4.8	1.13	
4.8-5.4	0.89	4.8-5.4	0.95	
5.4-5.7	0.86	5.4-5.7	0.88	
5.7-6	1.03	5.7-6	1	
6-6.3	1.31	6-6.3	1.09	
6.3-7	1.58	6.3-7	1.79	
>7	2.12	>7	2.25	

Smoke Pack Years				
Males		Females		
Range	RR	Range	RR	
<10	0.9	<10	0.93	
10-20	0.86	10-20	1	
20-30	1.02	20-30	1.2	
30-40	1.19	30-40	1.39	
>40	1.63	>40	1.84	

Cystatin C				
Males		Females		
Range	RR	Range	RR	
<0.8	1.08	<0.8	0.92	
0.8-0.9	0.88	0.8-0.9	0.83	
0.9-1	0.84	0.9-1	0.98	
1-1.1	0.97	1-1.1	1.09	
1.1-1.2	1.12	1.1-1.2	1.13	
>1.2	1.64	>1.2	1.79	

	LDL/ApoB Ratio				
Ma	les	Females			
Range	RR	Range	RR		
<1.15	1.65	<1.15	1.79		
1.15-1.24	1.13	1.15-1.24	1.39		
1.24-1.3	1.01	1.24-1.3	1.18		
1.3-1.4	0.83	1.3-1.4	0.94		
1.4-1.5	0.78	1.4-1.5	0.78		
>1.5	0.71	>1.5	0.77		

Red Blood Cell Count				
les	Females			
RR	Range	RR		
1.95	<3.7	1.57		
1.19	3.7-4	1.21		
0.89	4-4.5	0.96		
0.85	4.5-5	0.92		
0.92	>5	0.96		
	RR       1.95       1.19       0.89       0.85	les     Fem       RR     Range       1.95     <3.7		

Hemoglobin				
Males		Females		
Range	RR	Range	RR	
<12.5	2.18	<11.5	1.84	
12.5-13	1.79	11.5-12	1.6	
13-14	1.24	12-13	1.11	
14-15.5	0.91	13-14.5	0.9	
15.5-17	0.89	14.5-15.5	1.02	
>17	1.04	> 15.5	1.06	

Urea					
Ма	les	Females			
Range	RR	Range	RR		
<10	1.84	<10	1.56		
10-12	1.18	10-12	1.15		
12-15	0.95	12-15	0.97		
15-20	0.88	15-20	0.91		
20-24	1.08	20-24	0.99		
>24	1.38	>24	1.51		

Creatinine				
Ma	les	Fem	ales	
Range	RR	Range	RR	
<0.7	1.53	<0.6	1.07	
0.7-0.8	1.15	0.6-0.7	0.96	
0.8-1	0.91	0.7-0.8	0.95	
1-1.2	0.87	0.8-0.9	0.95	
1.2-1.4	1.19	0.9-1	1.08	
>1.4	1.77	>1	1.53	

LDL			
Ма	les	Females	
Range	RR	Range	RR
<90	1.81	<90	1.2
90-100	1.26	90-100	0.91
100-120	0.95	100-120	0.94
120-150	0.81	120-150	0.82
150-175	0.8	150-175	0.86
175-200	0.72	175-200	0.94
>200	0.74	>200	1

## Acute Kidney Disease

Acute Kidney Disease occurs when the kidneys begin to lose their function.

Below are suggested target values for our model's most predictive biomarkers or inputs for developing acute kidney disease in males and females aged 55 to 70.

Biomarker	Strength	VMR (Male)	VMR (Female)
Cystatin C	10	0.72 to 0.95 mg/dL	0.62 to 0.82 mg/dL
Hemoglobin A1C	7	4.72% to 5.48%	4.73% to 5.56%
ВМІ	7	22.1 to 27.8 kg/m2	20.3 to 26.3 kg/m2
Creatinine	6	0.78 to 1.06 mg/L	0.56 to 0.81 mg/L
Urea	6	11.9 to 19.2 mg/dL	11.2 to 18.4 mg/dL
Urate	6	4.4 to 6.3 mg/L	2.9 to 4.9 mg/L
Smoke Pack Years	6	0 to 11 years	0 to 9 years
Glucose	5	63 to 97 mg/L	65 to 95 mg/L
C-Reactive Protein	5	0.4 to 1.1 mg/L	0.4 to 1.2 mg/L
Neutrophil Count	5	2000 to 3860 /µl	1770 to 3720 /µl

# Acute Kidney Disease

Cystatin C			
Ма	les	Females	
Range	RR	Range	RR
<0.8	0.57	<0.8	0.53
0.8-0.9	0.63	0.8-0.9	0.65
0.9-1	0.78	0.9-1	0.86
1-1.1	1.05	1-1.1	1.29
1.1-1.2	1.47	1.1-1.2	1.73
>1.2	2.62	>1.2	3.61

	Hemoglobin A1C				
	Males		Females		
	Range	RR	Range	RR	
	<4.8	0.84	<4.8	1.08	
	4.8-5.4	0.76	4.8-5.4	0.76	
	5.4-5.7	0.88	5.4-5.7	0.85	
	5.7-6	1.11	5.7-6	1.11	
	6-6.3	1.47	6-6.3	1.54	
	6.3-7	1.91	6.3-7	2.42	
-	>7	2.58	>7	3.62	

BMI				
Ма	les	Females		
Range	RR	Range	RR	
<21	0.84	<20	0.78	
21-23	0.72	20-22	0.62	
23-26	0.73	22-26	0.67	
26-29	0.86	26-29	0.88	
29-32	1.13	29-33	1.19	
32-35	1.51	33-36	1.68	
>35	2.25	>36	2.64	

Urate

Females

RR 0.75

0.76

1.06

1.59 2.43

Range

<3

3-5

5-6

6-7

7-8

Male

RR

1.06

0.81

0.89

1.25

1.77

Range

<4

4-5

5-7

7-8

8-9

Creatinine				
Ma	les	Females		
Range	RR	Range	RR	
<0.7	1.11	<0.6	0.92	
0.7-0.8	0.88	0.6-0.7	0.79	
0.8-1	0.83	0.7-0.8	0.86	
1-1.2	1.12	0.8-0.9	1.07	
1.2-1.4	1.79	0.9-1	1.53	
>1.4	3.36	>1	2.91	

Smoke Pack Years				
Ma	les	Females		
Range	RR	Range	RR	
<10	0.83	<10	0.86	
10-20	0.93	10-20	1.07	
20-30	1.17	20-30	1.54	
30-40	1.41	30-40	1.89	
>40	1.73	>40	2.41	

Neutrophil Count				
Ма	les	Fem	ales	
Range	RR	Range	RR	
<2000	0.95	<2000	0.85	
2000-3000	0.72	2000-3000	0.69	
3000-4000	0.81	3000-4000	0.78	
4000-5000	0.96	4000-5000	0.97	
5000-6000	1.21	5000-6000	1.27	
>6000	1.54	>6000	1.98	

Urea				
Ма	les	Females		
Range	RR	Range	RR	
<10	1.35	<10	1.15	
10-12	0.89	10-12	0.86	
12-15	0.83	12-15	0.82	
15-20	0.92	15-20	0.94	
20-24	1.23	20-24	1.36	
>24	2.41	>24	3.2	
		•		

	Glucose						
	Ma	les	Females				
	Range	RR	Range	RR			
	<90	0.87	<90	0.9			
	90-100	0.9	90-100	0.88			
	100-110	1.05	100-110	1.09			
	110-120	1.3	110-120	1.38			
	120-140	1.55	120-140	1.57			
	>140	2.32	>140	3.01			

>9	2.81	>8	4.25
	C-Reactiv	ve Protein	
Ма	les	Fem	ales
Range	RR	Range	RR
<0.5	0.67	<0.5	0.55
0.5-1	0.78	0.5-1	0.69
1-1.7	0.89	1-1.7	0.79
1.7-3	1.05	1.7-3	1.02
3-6	1.35	3-6	1.33
>6	1.61	>6	1.91

## Liver Disease

Liver Disease refers to a set of conditions that prevent the proper function of the liver.

Below are suggested target values for our model's most predictive biomarkers or inputs for developing Liver Disease in males and females aged 40 to 70.

Biomarker	Strength	VMR (Male)	VMR (Female)
GGT	10	13 to 29 U/L	10 to 19 U/L
AST	9	20 to 30 U/L	18 to 29 U/L
ALT	9	14 to 27 U/L	10 to 20 U/L
ВМІ	7	22.1 to 27.8 kg/m2	20.3 to 26.3 kg/m2
IGF-1	6	138 to 242 ng/mL	131 to 246 ng/mL
C-Reactive Protein	6	0.4 to 1.1 mg/L	0.4 to 1.2 mg/L
Cystatin C	6	0.74 to 0.92 mg/dL	0.62 to 0.83 mg/dL
Hemoglobin A1C	6	4.72% to 5.48%	4.73% to 5.56%
ALP	5	43 to 84 U/L	40 to 86 U/L
HDL	5	48 to 80 mg/dL	63 to 102 mg/dL

## Liver Disease

GGT			
Ма	les	Females	
Range	RR	Range	RR
<20	0.61	<20	0.66
20-30	0.71	20-30	0.9
30-40	0.86	30-40	1.16
40-60	1.05	40-60	1.45
60-90	1.39	60-90	1.87
90-150	1.84	90-150	2.25
>150	3.62	>150	4.05

AST			
les	Females		
RR	Range	RR	
1.05	<17	0.93	
0.84	17-20	0.81	
0.78	20-28	0.87	
0.96	28-36	1.15	
1.45	36-45	1.74	
3.29	>45	3.54	
	RR       1.05       0.84       0.78       0.96       1.45	les     Fem       RR     Range       1.05     <17	

ALT				
Ма	les	Females		
Range	RR	Range	RR	
<12	0.92	<12	0.75	
12-20	0.76	12-20	0.77	
20-30	0.82	20-30	1.09	
30-45	1.15	30-45	1.69	
45-60	1.82	45-60	2.5	
>60	3.21	>60	3.62	

BMI				
Ма	les	Females		
Range	RR	Range	RR	
<21	1.03	<20	0.65	
21-23	0.68	20-22	0.62	
23-26	0.72	22-26	0.71	
26-29	0.88	26-29	0.95	
29-32	1.16	29-33	1.3	
32-35	1.53	33-36	1.58	
>35	1.98	>36	2.2	

	IGF-1			
Ma	les	Females		
Range	RR	Range	RR	
<85	3.26	<85	2.04	
85-100	1.84	85-100	1.41	
100-120	1.32	100-120	1.14	
120-150	1.02	120-150	0.99	
150-250	0.83	150-250	0.85	
>250	0.96	>250	1.02	
>250	0.96	>250	1.02	

C-Reactive Protein				
Ма	Males		ales	
Range	RR	Range	RR	
<0.5	0.61	<0.5	0.59	
0.5-1	0.8	0.5-1	0.7	
1-1.7	0.93	1-1.7	0.86	
1.7-3	1.13	1.7-3	1.09	
3-6	1.36	3-6	1.33	
>6	1.54	>6	1.8	

Cystatin C				
Ma	les	Females		
Range	RR	Range	RR	
<0.8	0.78	<0.8	0.74	
0.8-0.9	0.82	0.8-0.9	0.85	
0.9-1	0.93	0.9-1	1.02	
1-1.1	1.1	1-1.1	1.31	
1.1-1.2	1.32	1.1-1.2	1.58	
>1.2	1.85	>1.2	2.27	

	Hemoglobin A1C				
Ma	Males		ales		
Range	RR	Range	RR		
<4.8	1.05	<4.8	1.01		
4.8-5.4	0.83	4.8-5.4	0.86		
5.4-5.7	0.92	5.4-5.7	0.93		
5.7-6	1.09	5.7-6	1.1		
6-6.3	1.49	6-6.3	1.44		
6.3-7	1.8	6.3-7	2.13		
>7	2.08	>7	2.55		

ALP				
Ма	les	Fem	ales	
Range	RR	Range	RR	
<60	0.8	<60	0.71	
60-80	0.86	60-80	0.82	
80-100	1	80-100	0.97	
100-120	1.22	100-120	1.18	
120-140	1.5	120-140	1.42	
>140	2.59	>140	2.29	

HDL				
Ма	Males		ales	
Range	RR	Range	RR	
<35	1.63	<35	2.29	
35-42	1.17	35-42	1.8	
42-50	0.93	42-50	1.38	
50-60	0.79	50-60	1	
60-75	0.8	60-75	0.79	
>75	1.19	>75	0.7	

## Chronic Obstructive Pulmonary Disease (COPD)

**Chronic Obstructive Pulmonary Disease** is a class of progressive lung diseases that results in difficulty breathing.

Below are suggested target values for our model's most predictive biomarkers or inputs for developing COPD in males and females aged 50 to 70.

Biomarker	Strength	VMR (Male)	VMR (Female)
Smoke Pack Years	10	0 to 11 years	0 to 9 years
White Blood Cell Count	5	3.9 to 6.4 /µl	3.6 to 6.5 /µl
Neutrophil Count	4	2000 to 3860 /µl	1770 to 3720 /µl
C-Reactive Protein	4	0.4 to 1.1 mg/L	0.4 to 1.2 mg/L
Cystatin C	4	0.72 to 0.95 mg/dL	0.62 to 0.82 mg/dL
Monocyte Count	3	200 to 540 /µl	200 to 470 /µl
Hemoglobin A1C	3	4.72% to 5.48%	4.73% to 5.56%
Lymphocyte Count	3	1020 to 1950 /µl	1200 to 2150 /µl
RDW	3	12.1% to 13.7%	12.0% to 13.6%
Eosinophil Count	3	0 to 140 /μL	0 to 140 /µL

# Chronic Obstructive Pulmonary Disease (COPD)

Smoke Pack Years			
Ма	les	Females	
Range	RR	Range	RR
< 10	0.5	<10	0.59
10-20	0.97	10-20	1.4
20-30	1.52	20-30	2.34
30-40	2.3	30-40	3.37
>40	3.3	>40	4.65

٦	White Blood Cell Count					
	Ма	Males		ales		
	Range	RR	Range	RR		
	<4	0.6	<4	0.64		
	4-6	0.6	4-6	0.64		
	6-8	0.9	6-8	0.92		
	8-9.5	1.42	8-9.5	1.41		
	9.5-11	1.94	9.5-11	1.96		
_	>11	2.85	>11	3.23		

Neutrophil Count			
Ма	les	Fem	ales
Range	RR	Range	RR
<2000	0.85	<2000	0.74
2000-3000	0.58	2000-3000	0.62
3000-4000	0.7	3000-4000	0.76
4000-5000	0.96	4000-5000	1.01
5000-6000	1.29	5000-6000	1.34
>6000	1.97	>6000	2.08

C-Reactive Protein			
Ма	les	Females	
Range	RR	Range	RR
< 0.5	0.53	<0.5	0.58
0.5-1	0.68	0.5-1	0.72
1-1.7	0.88	1-1.7	0.87
1.7-3	1.1	1.7-3	1.05
3-6	1.49	3-6	1.33
>6	1.94	>6	1.69

Cystatin C					
Ма	les	Females			
Range	RR	Range	RR		
< 0.8	0.65	<0.8	0.65		
0.8-0.9	0.74	0.8-0.9	0.79		
0.9-1	0.9	0.9-1	1.03		
1-1.1	1.14	1-1.1	1.32		
1.1-1.2	1.41	1.1-1.2	1.62		
>1.2	1.9	>1.2	2.16		

Monocyte Count			
Ма	les	Fem	ales
Range	RR	Range	RR
< 300	0.85	<200	1.07
300-500	0.76	200-400	0.77
500-650	0.98	400-550	0.97
650-750	1.27	550-650	1.22
750-850	1.51	650-750	1.5
>850	1.85	>750	1.81

Hemoglobin A1C			
Ма	les	Females	
Range	RR	Range	RR
<4.8	0.66	<4.8	0.88
4.8-5.4	0.77	4.8-5.4	0.83
5.4-5.7	1.01	5.4-5.7	0.98
5.7-6	1.36	5.7-6	1.24
6-6.3	1.52	6-6.3	1.46
6.3-7	1.43	6.3-7	1.52
>7	1.53	>7	1.54

	Lymphocyte Count					
	Ma	les	Females			
	Range	RR	Range	RR		
	<1000	1.05	<1000	1.31		
	1000-1400	0.81	1000-1400	0.82		
	1400-2000	0.88	1400-2000	0.82		
	2000-2600	1.09	2000-2600	0.99		
	2600-3200	1.35	2600-3200	1.34		
	>3200	1.96	>3200	1.86		

RDW			
Ма	les	Fem	ales
Range	RR	Range	RR
<13	0.78	<13	0.75
13-13.5	0.86	13-13.5	0.9
13.5-14	1	13.5-14	1.04
14-14.5	1.27	14-14.5	1.2
14.5-15	1.48	14.5-15	1.42
>15	1.89	>15	1.63

	Eosinophil Count				
	Ma	les	Fem	ales	
Ran	ge	RR	Range	RR	
<10	0	0.72	<100	0.78	
100-2	200	0.86	100-200	0.9	
200-3	300	1.09	200-300	1.17	
300-4	400	1.3	300-400	1.4	
400-5	500	1.49	400-500	1.45	
>50	0	1.73	>500	1.59	

# All-Cause Mortality

**All-Cause Mortality** refers to all forms of death due to any cause. It includes death from the other age-related issues in this guide, but is not limited to them.

Below are the suggested target values for our model's most predictive biomarkers or inputs for experiencing death in males and females aged 55 to 70.

Biomarker	Strength	VMR (Male)	VMR (Female)
Smoke Pack Years	10	0 to 11 years	0 to 9 years
Cystatin C	9	0.72 to 0.95 mg/dL	0.62 to 0.82 mg/dL
RDW	7	12.1% to 13.7%	12.0% to 13.6%
Neutrophil Count	6	2000 to 3860 /µl	1770 to 3720 /µl
Hemoglobin A1C	6	4.72% to 5.48%	4.73% to 5.56%
C-Reactive Protein	6	0.4 to 1.1 mg/L	0.4 to 1.2 mg/L
White Blood Cell Count	6	3.9 to 6.4 /µl	3.6 to 6.5 /µl
Urea	6	11.9 to 19.2 mg/dL	11.2 to 18.4 mg/dL
GGT	5	13 to 29 U/L	10 to 19 U/L
MCV	5	86 to 95 fL	89 to 96 fL

# All-Cause Mortality

Smoke Pack Years				
Ma	les	Females		
Range	RR	Range	RR	
< 10	0.78	<10	0.82	
10-20	0.94	10-20	1.1	
20-30	1.21	20-30	1.48	
30-40	1.4	30-40	1.8	
>40	1.97	>40	2.54	

Cystatin C							
Males		Females					
Range	RR	Range	RR				
< 0.8	0.79	<0.8	0.73				
0.8-0.9	0.77	0.8-0.9	0.82				
0.9-1	0.85	0.9-1	0.93				
1-1.1	1.02	1-1.1	1.14				
1.1-1.2	1.29	1.1-1.2	1.42				
>1.2	1.98	>1.2	2.23				

RDW					
Ма	Males		ales		
Range	RR	Range	RR		
<13	0.78	<13	0.82		
13-13.5	0.85	13-13.5	0.88		
13.5-14	0.98	13.5-14	0.97		
14-14.5	1.18	14-14.5	1.1		
14.5-15	1.41	14.5-15	1.31		
>15	2.01	>15	2.01		

Neutrophil Count				
Males		Females		
Range	RR	Range	RR	
<2000	1.04	<2000	1.03	
2000-3000	0.74	2000-3000	0.8	
3000-4000	0.81	3000-4000	0.84	
4000-5000	0.94	4000-5000	0.95	
5000-6000	1.16	5000-6000	1.19	
>6000	1.61	>6000	1.69	

Hemoglobin A1C							
Males		Females					
Range	RR	Range	RR				
<4.8	0.99	<4.8	1.02				
4.8-5.4	0.81	4.8-5.4	0.88				
5.4-5.7	0.94	5.4-5.7	0.91				
5.7-6	1.13	5.7-6	1.09				
6-6.3	1.37	6-6.3	1.34				
6.3-7	1.52	6.3-7	1.66				
>7	1.95	>7	2.07				

C-Reactive Protein					
Ма	Males		ales		
Range	RR	Range	RR		
< 0.5	0.76	<0.5	0.81		
0.5-1	0.78	0.5-1	0.81		
1-1.7	0.87	1-1.7	0.85		
1.7-3	1.02	1.7-3	0.99		
3-6	1.29	3-6	1.17		
>6	1.68	>6 1.56			

White Blood Cell Count				
Ma	iles	Fem	ales	
Range	RR	Range	RR	
<4	1.05	<4	1.08	
4-6	0.79	4-6	0.84	
6-8	0.92	6-8	0.93	
8-9.5	1.19	8-9.5	1.16	
9.5-11	1.59	9.5-11	1.54	
>11	1.99	>11	2.22	

Urea						
Ма	les	Females				
Range	RR	Range	RR			
<10	1.97	<10	1.4			
10-12	1.14	10-12	1.07			
12-15	0.92	12-15	0.94			
15-20	0.9	15-20	0.92			
20-24	0.99	20-24	1.06			
>24	1.68	>24 1.96				

GGT					
Ма	les	Females			
Range	RR	Range	RR		
<20	0.86	<20	0.85		
20-30	0.86	20-30	0.94		
30-40	0.95	30-40	1.04		
40-60	1	40-60	1.2		
60-90	1.18	60-90	1.33		
90-150	1.39	90-150	1.47		
>150	2.1	>150	1.97		

MCV						
Ма	Males		ales			
Range	Range RR		RR			
<83	1.33	<83	1.28			
83-90	0.93	83-90	0.93			
90-95	0.9	90-95	0.92			
95-100	1.13	95-100	1.16			
>100	2.03	>100	2.13			

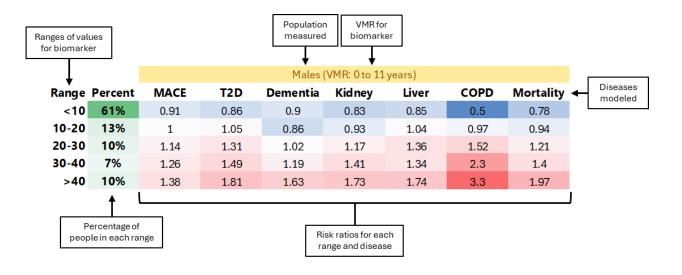
# **Risk Ratios by Biomarker**

Depending on your health goals, it can be more helpful to view risk ratios by each biomarker. The first table below shows each of the biomarkers and inputs included and links you to the associated table of values.

Smoke Pack Years	BMI
Systolic Blood Pressure	Grip Strength
Resting Heart Rate	HDL Cholesterol
LDL Cholesterol	Triglycerides
Lipoprotein (a)	LDL/ApoB Ratio
Alkaline Phosphatase	ALT
AST	AST/ALT Ratio
GGT	Creatinine
<u>Cystatin C</u>	<u>Urate</u>
<u>Urea</u>	Glucose
Hemoglobin A1C	Testosterone
SHBG	IGF-1
Vitamin D	C-Reactive Protein
Red Blood Cell Count	<u>Hemoglobin</u>
Mean Corpuscular Volume	Red Cell Distribution Width
White Blood Cell Count	Neutrophil Count
Lymphocyte Count	Monocyte Count
Eosinophil Count	Lymphocyte Percent

## **Reading this Section**

This section provides ranges for the select biomarkers and inputs shown above. The percentage column shows the prevalence in that range from the UK Biobank for ages 40 to 70, and the following columns show the associated risk ratios for each disease. The VMR values for males and females for each biomarker are shown above the tables as well.



BMI (kg/m²)

	Males (VMR: 0 to 11 years)							
ercent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality	
61%	0.91	0.86	0.9	0.83	0.85	0.5	0.78	
13%	1	1.05	0.86	0.93	1.04	0.97	0.94	
10%	1.14	1.31	1.02	1.17	1.36	1.52	1.21	
7%	1.26	1.49	1.19	1.41	1.34	2.3	1.4	
10%	1.38	1.81	1.63	1.73	1.74	3.3	1.97	
•	61% 13% 10% 7%	61% 0.91   13% 1   10% 1.14   7% 1.26	61%     0.91     0.86       13%     1     1.05       10%     1.14     1.31       7%     1.26     1.49	ArcentMACET2DDementia61%0.910.860.913%11.050.8610%1.141.311.027%1.261.491.19	MACE     T2D     Dementia     Kidney       61%     0.91     0.86     0.9     0.83       13%     1     1.05     0.86     0.93       10%     1.14     1.31     1.02     1.17       7%     1.26     1.49     1.19     1.41	MACE     T2D     Dementia     Kidney     Liver       61%     0.91     0.86     0.9     0.83     0.85       13%     1     1.05     0.86     0.93     1.04       10%     1.14     1.31     1.02     1.17     1.36       7%     1.26     1.49     1.19     1.41     1.34	MACE     T2D     Dementia     Kidney     Liver     COPD       61%     0.91     0.86     0.9     0.83     0.85     0.5       13%     1     1.05     0.86     0.93     1.04     0.97       10%     1.14     1.31     1.02     1.17     1.36     1.52       7%     1.26     1.49     1.19     1.41     1.34     2.3	

#### Smoke Pack Years<sup>4</sup> (years)

		Females (VMR: 0 to 9 years)								
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality		
<10	74%	0.91	0.95	0.93	0.86	0.89	0.59	0.82		
10-20	11%	1.14	1.03	1	1.07	1.15	1.4	1.1		
20-30	7%	1.3	1.38	1.2	1.54	1.45	2.34	1.48		
30-40	5%	1.53	1.69	1.39	1.89	1.66	3.37	1.8		
>40	4%	1.86	2.16	1.84	2.41	2.06	4.65	2.54		

Back to top

		Males (VMR: 22.1 to 27.8 kg/m2)								
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality		
<21	2%	0.78	0.3	1.52	0.84	1.03	1.94	1.5		
21-23	7%	0.78	0.31	1.09	0.72	0.68	1.05	0.96		
23-26	26%	0.87	0.43	0.91	0.73	0.72	0.83	0.85		
26-29	31%	0.97	0.77	0.9	0.86	0.88	0.86	0.89		
29-32	<b>19%</b>	1.09	1.41	0.99	1.13	1.16	1	1.04		
32-35	<b>9%</b>	1.3	2.18	1.21	1.51	1.53	1.31	1.24		
>35	6%	1.45	3.71	1.5	2.25	1.98	1.74	1.69		

			Females (VMR: 20.3 to 26.3 kg/m2)								
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality			
<20	3%	0.77	0.24	1.52	0.78	0.65	1.48	1.42			
20-22	10%	0.72	0.24	0.99	0.62	0.62	0.93	0.95			
22-26	36%	0.84	0.4	0.92	0.67	0.71	0.82	0.87			
26-29	22%	0.97	0.88	0.97	0.88	0.95	0.93	0.9			
29-33	17%	1.18	1.58	0.99	1.19	1.3	1.1	1.05			
33-36	6%	1.35	2.43	1.08	1.68	1.58	1.2	1.21			
>36	6%	1.66	4	1.4	2.64	2.2	1.59	1.72			

Back to top

<sup>4</sup> Smoke Pack Years refers to the number of years a person has smoked if they smoked one pack of cigarettes each day for a year.

### Systolic Blood Pressure (mmHg)

		Males (VMR: 103 to 144 mmHg)							
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality	
<100	3%	0.73	0.62	1.16	0.95	0.94	1.21	1.22	
100-110	11%	0.74	0.58	0.91	0.73	0.78	0.99	0.85	
110-120	22%	0.76	0.65	0.88	0.68	0.81	0.9	0.81	
120-130	25%	0.82	0.76	0.79	0.67	0.81	0.91	0.81	
130-150	30%	0.95	0.9	0.86	0.74	0.9	0.87	0.85	
150-170	8%	1.07	1.05	0.86	0.88	1	0.83	0.91	
>170	1%	1.18	1.36	0.84	1.08	1.07	0.81	1.07	

		Females (VMR: 99 to 144 mmHg)							
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality	
<100	10%	0.68	0.39	0.87	0.64	0.8	1.13	0.95	
100-110	19%	0.65	0.54	0.86	0.66	0.8	1	0.88	
110-120	23%	0.78	0.7	0.88	0.69	0.86	0.94	0.87	
120-130	20%	0.82	0.86	0.86	0.7	0.91	0.91	0.86	
130-150	22%	0.91	0.95	0.91	0.75	0.89	0.87	0.9	
150-170	6%	1.07	1.13	0.93	0.92	0.95	0.82	0.89	
>170	1%	1.21	1.34	0.91	1.14	0.94	0.86	1.02	

<u>Back to top</u>

#### Grip Strength (lbs)

		Males (VMR: 89 to 133 lbs)							
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality	
<45	2%	1.39	1.84	2.1	1.93	1.66	1.78	1.8	
45-60	<b>6%</b>	1.18	1.41	1.59	1.38	1.36	1.34	1.41	
60-80	28%	1.04	1.11	1.09	1.07	1.1	1.1	1.09	
80-100	40%	0.96	0.92	0.85	0.89	0.92	0.92	0.89	
100-120	20%	0.88	0.82	0.62	0.79	0.82	0.76	0.77	
>120	4%	0.97	0.87	0.59	0.71	0.83	0.71	0.71	

		Females (VMR: 48 to 84 lbs)							
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality	
<20	2%	1.68	2.07	1.81	2.06	1.82	1.99	1.64	
20-30	4%	1.3	1.53	1.45	1.48	1.47	1.49	1.34	
30-40	14%	1.11	1.2	1.21	1.13	1.22	1.17	1.12	
40-55	38%	0.97	0.96	0.93	0.93	0.95	0.95	0.96	
55-65	26%	0.87	0.85	0.76	0.8	0.87	0.82	0.85	
>65	16%	0.83	0.83	0.71	0.82	0.83	0.78	0.83	

		Males (VMR: 45 to 70 bpm)							
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality	
<50	4%	1.1	0.7	0.99	0.86	0.68	0.75	0.79	
50-60	20%	0.97	0.73	0.89	0.83	0.77	0.76	0.8	
60-70	34%	0.94	0.83	0.93	0.89	0.89	0.9	0.9	
70-80	25%	1.01	1.15	1.05	1.05	1.1	1.11	1.03	
80-90	11%	1.1	1.48	1.16	1.3	1.37	1.4	1.27	
>90	6%	1.16	1.78	1.35	1.61	1.63	1.54	1.59	

### Resting Heart Rate (bpm)

		Females (VMR: 55 to 73 bpm)									
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality			
<50	1%	1.39	0.76	0.94	1	0.77	0.85	0.96			
50-60	13%	1.11	0.77	1.03	0.9	0.84	0.84	0.84			
60-70	36%	0.93	0.79	0.96	0.84	0.87	0.92	0.88			
70-80	31%	0.96	1.05	0.96	0.97	1.01	1.01	1			
80-90	13%	1.07	1.45	1.11	1.27	1.29	1.23	1.2			
>90	5%	1.15	1.84	1.14	1.61	1.57	1.38	1.45			

Back to top

#### HDL Cholesterol (mg/dL)

		Males (VMR: 48 to 80 mg/dL)								
Range Percent		MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality		
<35	8%	1.37	2.22	1.4	1.69	1.63	1.41	1.45		
35-42	<b>20%</b>	1.17	1.54	1.07	1.2	1.17	1.12	1.1		
42-50	<b>29%</b>	1.02	1.01	0.92	0.94	0.93	0.93	0.93		
50-60	25%	0.91	0.65	0.9	0.82	0.79	0.87	0.87		
60-75	14%	0.8	0.44	0.91	0.73	0.8	0.89	0.85		
>75	3%	0.77	0.36	1.09	0.93	1.19	1.17	1.22		

		Females (VMR: 63 to 102 mg/dL)								
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality		
<35	1%	1.93	4.45	1.94	2.71	2.29	2.18	2.41		
35-42	5%	1.6	3.02	1.44	1.88	1.8	1.54	1.51		
42-50	15%	1.31	1.85	1.12	1.36	1.38	1.21	1.18		
50-60	28%	1.06	1.06	0.93	0.98	1	1.02	0.96		
60-75	33%	0.86	0.57	0.92	0.81	0.79	0.85	0.88		
>75	17%	0.73	0.3	0.98	0.73	0.7	0.81	0.88		

### LDL Cholesterol (mg/L)

		Males (VMR: 113 to 185 mg/L)								
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality		
<90	3%	0.95	0.96	1.81	1.65	1.5	1.48	1.56		
90-100	4%	0.8	0.77	1.26	1.1	1.19	1.23	1.25		
100-120	16%	0.81	0.81	0.95	0.9	0.98	1.03	1		
120-150	38%	0.86	0.79	0.81	0.78	0.85	0.84	0.85		
150-175	25%	0.94	0.82	0.8	0.71	0.79	0.78	0.8		
175-200	10%	1.05	0.83	0.72	0.69	0.76	0.75	0.77		
>200	4%	1.11	0.9	0.74	0.72	0.82	0.73	0.85		

			Females (VMR: 110 to 181 mg/L)							
Range Percent		MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality		
<90	3%	1.08	0.64	1.2	1.64	1.1	1.3	1.56		
90-100	4%	0.89	0.66	0.91	1.07	0.83	1.04	1.21		
100-120	16%	0.82	0.7	0.94	0.94	0.94	0.97	1.04		
120-150	36%	0.81	0.76	0.82	0.79	0.86	0.9	0.89		
150-175	24%	0.89	0.92	0.86	0.8	0.89	0.85	0.88		
175-200	11%	0.97	1.01	0.94	0.72	0.93	0.86	0.84		
>200	5%	1.09	1.14	1	0.83	0.87	0.82	0.9		

<u>Back to top</u>

### Triglycerides (mg/dL)

			Males (VMR: 63 to 169 mg/dL)							
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality		
<80	11%	0.87	0.41	1.18	0.89	0.82	0.97	1.02		
80-110	17%	0.92	0.6	1	0.89	0.86	0.97	0.98		
110-150	22%	0.96	0.77	0.9	0.92	0.91	0.94	0.95		
150-200	<b>20%</b>	1	1.03	1.01	1.01	0.99	0.97	1		
200-300	20%	1.09	1.4	0.9	1.07	1.11	1.04	0.99		
>300	10%	1.21	2.01	1.03	1.31	1.36	1.14	1.09		

		Females (VMR: 45 to 110 mg/dL)							
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality	
<80	20%	0.75	0.33	1.12	0.8	0.68	0.78	0.91	
80-110	24%	0.88	0.53	0.97	0.8	0.8	0.9	0.95	
110-150	23%	0.96	0.85	0.94	0.93	0.94	0.98	0.92	
150-200	16%	1.07	1.3	1.03	1.1	1.15	1.05	1.04	
200-300	12%	1.26	2.01	0.98	1.27	1.37	1.16	1.11	
>300	4%	1.36	3.17	1.04	1.52	1.83	1.43	1.29	

		Males (VMR: 5 to 183 mg/dL)							
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality	
<10	28%	0.92	1.06	1.03	0.99	1.05	0.99	1	
10-20	22%	0.94	0.9	0.97	0.94	0.92	0.96	0.94	
20-40	16%	0.96	0.89	0.91	0.98	0.9	1	0.97	
40-80	13%	1.01	1.02	0.98	1.02	1.01	1.02	1	
80-150	14%	1.15	0.99	0.92	0.93	0.96	0.95	0.96	
>150	<b>6%</b>	1.18	0.88	1.02	1.04	0.91	1.03	1.02	

### Lipoprotein (a) (mg/dL)

		Females (VMR: 4 to 183 mg/dL)							
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality	
<10	25%	0.96	1.01	1	1.01	1.01	1.03	1.02	
10-20	22%	0.9	0.92	0.96	0.94	0.96	0.97	0.97	
20-40	17%	0.95	0.92	0.95	0.95	0.91	0.97	0.97	
40-80	15%	1.02	0.99	1.06	0.98	0.97	0.95	0.98	
80-150	14%	1.02	1.08	0.92	0.97	0.99	0.94	0.94	
>150	7%	1.11	0.99	1.06	1.03	1.02	1.04	1.04	

Back to top

#### LDL/Apolipoprotein B Ratio (LAR)

			Males (VMR: 1.35 to 1.53)							
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality		
<1.15	5%	1.43	2.27	1.65	1.72	1.66	1.47	1.52		
1.15-1.24	17%	1.17	1.63	1.13	1.27	1.3	1.25	1.17		
1.24-1.3	22%	1.06	1.16	1.01	1.01	1.04	1.04	1.02		
1.3-1.4	<b>40%</b>	0.92	0.72	0.83	0.8	0.81	0.84	0.85		
1.4-1.5	14%	0.78	0.44	0.78	0.67	0.7	0.72	0.76		
>1.5	2%	0.86	0.54	0.71	0.88	1.06	0.81	0.98		

		Females (VMR: 1.38 to 1.57)							
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality	
<1.15	2%	1.84	3.37	1.79	2.48	2.27	1.8	1.91	
1.15-1.24	<b>9%</b>	1.41	2.22	1.39	1.63	1.55	1.42	1.35	
1.24-1.3	16%	1.14	1.47	1.18	1.23	1.19	1.17	1.15	
1.3-1.4	45%	0.96	0.85	0.94	0.89	0.91	0.95	0.92	
1.4-1.5	25%	0.81	0.54	0.78	0.7	0.73	0.77	0.82	
>1.5	4%	0.8	0.45	0.77	0.78	0.8	0.75	0.89	

### Alkaline Phosphatase (U/L)

		Males (VMR: 43 to 84 U/L)							
Range Percent		MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality	
<60	13%	0.88	0.72	0.97	0.85	0.8	0.69	0.84	
60-80	39%	0.94	0.85	0.9	0.86	0.86	0.83	0.87	
80-100	31%	1.03	1.05	0.98	1.02	1	1.07	0.98	
100-120	12%	1.13	1.36	1.02	1.21	1.22	1.39	1.25	
120-140	4%	1.2	1.52	1.46	1.47	1.5	1.57	1.48	
>140	2%	1.22	1.68	1.85	1.91	2.59	1.55	2.13	

		Females (VMR: 40 to 86 U/L)							
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality	
<60	14%	0.88	0.52	1.07	0.83	0.71	0.76	0.9	
60-80	32%	0.89	0.75	0.95	0.82	0.82	0.85	0.89	
80-100	30%	0.98	1.05	0.95	0.93	0.97	0.97	0.95	
100-120	15%	1.1	1.33	1.05	1.15	1.18	1.16	1.08	
120-140	5%	1.27	1.59	1.1	1.4	1.42	1.34	1.25	
>140	3%	1.34	1.93	1.2	1.78	2.29	1.43	1.58	

<u>Back to top</u>

#### ALT (U/L)

		Males (VMR: 14 to 27 U/L)							
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality	
<12	3%	1.01	0.6	1.36	1.2	0.92	1.38	1.41	
12-20	<b>29%</b>	0.95	0.55	1.05	0.94	0.76	1.04	1.01	
20-30	38%	1	0.86	0.91	0.94	0.82	0.95	0.92	
30-45	21%	1.05	1.45	0.94	1.07	1.15	0.91	0.96	
45-60	<b>6%</b>	1.11	2.17	0.84	1.16	1.82	1.03	1.1	
>60	3%	1.23	2.86	1.1	1.51	3.21	1.11	1.43	

		Females (VMR: 10 to 20 U/L)							
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality	
<12	13%	0.95	0.49	1.16	1.01	0.75	1.1	1.19	
12-20	<b>50%</b>	0.94	0.69	0.99	0.91	0.77	0.97	0.94	
20-30	25%	1.05	1.27	0.94	1.03	1.09	0.98	0.98	
30-45	8%	1.16	2.1	1.02	1.19	1.69	1	1.06	
45-60	2%	1.17	2.66	1.1	1.39	2.5	1.04	1.11	
>60	1%	1.24	3.03	0.89	1.59	3.62	1.07	1.41	

### AST (U/L)

		Males (VMR: 20 to 30 U/L)							
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality	
<17	2%	1.19	0.94	1.32	1.44	1.05	1.51	1.5	
17-20	8%	1.02	0.79	1.06	1.08	0.84	1.23	1.12	
20-28	51%	0.96	0.82	0.95	0.91	0.78	0.96	0.93	
28-36	27%	1	1.05	0.93	0.95	0.96	0.91	0.9	
36-45	8%	1.06	1.47	1.03	1.2	1.45	0.99	1.12	
>45	4%	1.2	2.37	1.47	1.64	3.29	1.3	1.72	

			Females (VMR: 18 to 29 U/L)							
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality		
<17	7%	1.22	1.02	1.06	1.44	0.93	1.36	1.34		
17-20	18%	0.98	0.85	0.9	0.96	0.81	1.07	0.98		
20-28	55%	0.96	0.87	0.94	0.89	0.87	0.95	0.94		
28-36	15%	1.02	1.2	1.12	1.08	1.15	0.93	1.01		
36-45	3%	1.16	1.8	1.37	1.23	1.74	1	1.23		
>45	2%	1.28	2.58	1.45	1.95	3.54	1.3	1.65		

Back to top

#### AST/ALT Ratio

				Males	(VMR: 1.01 to	0 1.45)		
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality
<0.7	7%	1.15	2.2	0.87	1.14	1.59	0.95	0.96
0.7-1	32%	1.05	1.42	0.87	1.01	1.09	0.93	0.92
1-1.25	<b>29%</b>	0.99	0.84	0.94	0.97	0.88	1	0.96
1.25-1.5	18%	0.95	0.59	1.02	0.95	0.82	0.99	1
1.5-2	11%	0.92	0.48	1.15	1	0.91	1.09	1.13
>2	3%	1.05	0.59	1.41	1.18	1.08	1.2	1.38

			Females (VMR: 1.17 to 1.57)							
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality		
<0.7	2%	1.16	2.99	0.68	1.23	2.24	0.99	0.99		
0.7-1	16%	1.14	2	0.87	1.14	1.46	1.03	1		
1-1.25	26%	1.04	1.14	0.88	0.99	1.03	0.96	0.96		
1.25-1.5	26%	0.95	0.68	0.97	0.93	0.82	0.98	0.97		
1.5-2	24%	0.91	0.48	1.18	0.92	0.73	0.98	1.01		
>2	6%	0.92	0.5	1.39	1.1	0.86	1.07	1.23		

### GGT (U/L)

			Males (VMR: 13 to 29 U/L)							
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality		
<20	14%	0.84	0.35	1	0.82	0.61	0.83	0.86		
20-30	29%	0.93	0.6	0.91	0.85	0.71	0.86	0.86		
30-40	20%	1.01	0.98	0.9	0.94	0.86	0.94	0.95		
40-60	20%	1.09	1.39	1	1.07	1.05	1.08	1		
60-90	10%	1.14	1.66	1	1.2	1.39	1.21	1.18		
90-150	5%	1.14	1.79	1.23	1.35	1.84	1.39	1.39		
>150	3%	1.21	2.14	2.07	2.04	3.62	1.52	2.1		

			Females (VMR: 10 to 19 U/L)						
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality	
<20	44%	0.82	0.42	0.92	0.74	0.66	0.79	0.85	
20-30	28%	1	0.98	0.96	0.94	0.9	1.01	0.94	
30-40	11%	1.13	1.61	1	1.12	1.16	1.14	1.04	
40-60	<b>9</b> %	1.2	1.91	1.13	1.3	1.45	1.2	1.2	
60-90	4%	1.32	2.07	1.2	1.52	1.87	1.26	1.33	
90-150	2%	1.32	2.25	1.29	1.81	2.25	1.3	1.47	
>150	1%	1.39	2.31	1.7	2.28	4.05	1.44	1.97	

<u>Back to top</u>

#### Creatinine (mg/L)

				Males (VMR: 0.78 to 1.06 mg/L)							
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality			
<0.7	4%	1.15	1.42	1.53	1.11	1.71	1.61	1.58			
0.7-0.8	15%	0.98	1.11	1.15	0.88	1.1	1.17	1.09			
0.8-1	55%	0.95	0.92	0.91	0.83	0.9	0.92	0.89			
1-1.2	21%	1.03	0.95	0.87	1.12	0.9	0.89	0.93			
1.2-1.4	3%	1.21	1.22	1.19	1.79	1.18	1.07	1.24			
>1.4	1%	1.68	1.84	1.77	3.36	2.21	1.52	2.25			

			Females (VMR: 0.56 to 0.81 mg/L)							
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality		
<0.6	13%	1.06	1.23	1.07	0.92	1.15	1.15	1.12		
0.6-0.7	32%	0.93	0.92	0.96	0.79	0.94	0.95	0.94		
0.7-0.8	32%	0.94	0.9	0.95	0.86	0.92	0.92	0.91		
0.8-0.9	15%	1.04	0.99	0.95	1.07	0.95	0.95	0.93		
0.9-1	5%	1.06	1.17	1.08	1.53	1.09	1.07	1.11		
>1	3%	1.54	1.63	1.53	2.91	1.63	1.45	1.8		

Cystatin C	C (mg/dL)
------------	-----------

			Males (VMR: 0.72 to 0.95 mg/dL)							
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality		
<0.8	14%	0.85	0.68	1.08	0.57	0.78	0.65	0.79		
0.8-0.9	30%	0.86	0.73	0.88	0.63	0.82	0.74	0.77		
0.9-1	<b>29%</b>	0.95	0.94	0.84	0.78	0.93	0.9	0.85		
1-1.1	16%	1.08	1.24	0.97	1.05	1.1	1.14	1.02		
1.1-1.2	<b>6%</b>	1.21	1.6	1.12	1.47	1.32	1.41	1.29		
>1.2	5%	1.48	1.91	1.64	2.62	1.85	1.9	1.98		

			Females (VMR: 0.62 to 0.82 mg/dL)							
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality		
<0.8	32%	0.75	0.56	0.92	0.53	0.74	0.65	0.73		
0.8-0.9	31%	0.85	0.8	0.83	0.65	0.85	0.79	0.82		
0.9-1	21%	0.99	1.15	0.98	0.86	1.02	1.03	0.93		
1-1.1	10%	1.2	1.47	1.09	1.29	1.31	1.32	1.14		
1.1-1.2	4%	1.4	1.98	1.13	1.73	1.58	1.62	1.42		
>1.2	3%	1.83	2.49	1.79	3.61	2.27	2.16	2.23		

<u>Back to top</u>

### Urate (mg/L)

			Males (VMR:4.4 to 6.3 mg/L)							
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality		
<4	4%	0.96	0.82	1.53	1.06	1.13	1.32	1.3		
4-5	18%	0.94	0.71	1.08	0.81	0.81	0.98	0.98		
5-7	60%	0.97	0.92	0.92	0.89	0.94	0.93	0.92		
7-8	13%	1.11	1.39	0.93	1.25	1.18	1.1	1.05		
8-9	4%	1.25	1.79	1.09	1.77	1.49	1.19	1.3		
>9	1%	1.51	2.49	1.57	2.81	2.15	1.59	1.99		

			Females (VMR: 2.9 to 4.9 mg/L)							
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality		
<3	6%	0.93	0.39	1.22	0.75	0.68	0.97	1.01		
3-5	64%	0.88	0.63	0.96	0.76	0.82	0.92	0.89		
5-6	21%	1.08	1.38	0.98	1.06	1.16	1.03	1.02		
6-7	7%	1.29	2.39	1.04	1.59	1.57	1.19	1.19		
7-8	2%	1.67	3.34	1.09	2.43	2.18	1.46	1.69		
>8	1%	1.85	4.29	1.87	4.25	2.85	1.74	2.45		

		Males (VMR: 11.9 to 19.2 mg/dL)							
Range Percent		MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality	
<10	4%	1.17	1.29	1.84	1.35	1.92	2.24	1.97	
10-12	11%	1	1.09	1.18	0.89	1.03	1.29	1.14	
12-15	32%	0.94	0.97	0.95	0.83	0.93	0.94	0.92	
15-20	42%	0.98	0.94	0.88	0.92	0.91	0.88	0.9	
20-24	<b>9%</b>	1.07	1	1.08	1.23	1.01	0.94	0.99	
>24	3%	1.44	1.35	1.38	2.41	1.51	1.27	1.68	

### Urea (mg/dL)

		Females (VMR: 11.2 to 18.4 mg/dL)								
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality		
<10	8%	1.13	1.13	1.56	1.15	1.21	1.33	1.4		
10-12	16%	0.99	0.98	1.15	0.86	0.96	1.08	1.07		
12-15	35%	0.94	0.93	0.97	0.82	0.94	0.95	0.94		
15-20	34%	0.97	0.97	0.91	0.94	0.95	0.92	0.92		
20-24	<b>6%</b>	1.12	1.2	0.99	1.36	1.09	1.08	1.06		
>24	2%	1.66	1.69	1.51	3.2	1.88	1.44	1.96		

Back to top

#### Glucose (mg/L)

			Males (VMR: 63 to 97 mg/L)							
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality		
<90	53%	0.96	0.66	0.87	0.87	0.89	0.97	0.91		
90-100	<b>29%</b>	0.94	0.87	0.94	0.9	0.92	0.95	0.93		
100-110	<b>9%</b>	1.02	1.63	1.04	1.05	1.09	1.05	1.06		
110-120	3%	1.2	2.79	1.21	1.3	1.41	1.08	1.18		
120-140	2%	1.24	4.03	1.59	1.55	1.57	1.03	1.31		
>140	3%	1.54	7.81	1.91	2.32	2.01	1.36	1.83		

Range Percent		MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality
<90	57%	0.97	0.66	0.94	0.9	0.92	1.02	0.94
90-100	28%	0.96	0.92	0.95	0.88	0.95	0.92	0.95
100-110	8%	0.99	1.87	1.08	1.09	1.06	0.95	1.03
110-120	3%	1.17	2.56	1.18	1.38	1.31	1.15	1.26
120-140	2%	1.28	3.34	1.04	1.57	1.45	1.04	1.29
>140	2%	1.88	7.68	2.09	3.01	2.33	1.31	1.85

		Males (VMR: 4.72% to 5.48%)							
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality	
<4.8	5%	0.85	0.21	0.91	0.84	1.05	0.66	0.99	
4.8-5.4	<b>48%</b>	0.88	0.32	0.89	0.76	0.83	0.77	0.81	
5.4-5.7	26%	0.98	0.77	0.86	0.88	0.92	1.01	0.94	
5.7-6	11%	1.09	2.1	1.03	1.11	1.09	1.36	1.13	
6-6.3	4%	1.25	5.32	1.31	1.47	1.49	1.52	1.37	
6.3-7	3%	1.5	9.13	1.58	1.91	1.8	1.43	1.52	
>7	3%	1.7	11.59	2.12	2.58	2.08	1.53	1.95	

### Hemoglobin A1C (%)

			Females (VMR: 4.73% to 5.56%)							
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality		
<4.8	5%	0.9	0.25	1.13	1.08	1.01	0.88	1.02		
4.8-5.4	<b>50%</b>	0.86	0.29	0.95	0.76	0.86	0.83	0.88		
5.4-5.7	28%	0.94	0.68	0.88	0.85	0.93	0.98	0.91		
5.7-6	11%	1.1	2.04	1	1.11	1.1	1.24	1.09		
6-6.3	3%	1.48	6.01	1.09	1.54	1.44	1.46	1.34		
6.3-7	2%	1.69	13.02	1.79	2.42	2.13	1.52	1.66		
>7	2%	2.33	17.6	2.25	3.62	2.55	1.54	2.07		

Back to top

#### Testosterone (ng/dL)

		Males (VMR: 310 to 582 ng/dL)							
Range Percent		MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality	
<180	3%	1.24	2.33	1.39	1.63	1.5	1.4	1.49	
180-250	14%	1.06	1.62	1.05	1.26	1.16	1.1	1.06	
250-300	18%	1.05	1.2	0.99	1.01	0.98	0.95	0.99	
300-400	37%	0.98	0.85	0.91	0.9	0.9	0.91	0.91	
400-500	19%	0.93	0.63	0.96	0.84	0.89	0.97	0.94	
>500	8%	0.91	0.53	0.98	0.91	1.1	1.13	1.09	

			Females (VMR: 11 to 51 ng/dL)							
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality		
<12	3%	1.11	0.94	1.05	0.99	0.93	1.03	1.07		
12-20	20%	0.98	0.89	0.91	0.92	0.99	0.92	0.94		
20-40	53%	0.96	0.94	0.94	0.94	0.92	0.92	0.94		
40-60	<b>19%</b>	0.97	1.1	0.98	1	1.04	0.89	1.04		
>60	5%	1.07	1.42	1.12	1.2	1.29	1.05	1.18		

### SHBG (nmol/L)

		Males (VMR: 34 to 71 nmol/L)							
Range Percent		MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality	
<20	8%	1.22	2.26	1.13	1.43	1.32	0.91	1.11	
20-30	23%	1.06	1.37	0.97	1.13	1.05	0.95	0.96	
30-40	27%	1.02	0.99	0.86	0.98	0.91	0.94	0.93	
40-60	31%	0.97	0.72	0.98	0.89	0.88	0.99	0.96	
60-80	8%	0.91	0.5	1.09	0.93	1.08	1.12	1.08	
>80	2%	0.96	0.53	1.39	1.17	1.62	1.5	1.52	

			Females (VMR: 45 to 135 nmol/L)							
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality		
<20	3%	1.35	4.36	1.28	1.84	1.99	1.27	1.3		
20-30	<b>9%</b>	1.27	2.78	1	1.28	1.46	1.03	1.07		
30-40	14%	1.15	1.66	0.96	1.19	1.18	0.96	1.04		
40-60	30%	0.98	0.85	0.94	0.94	0.95	0.97	0.94		
60-80	22%	0.91	0.45	1	0.84	0.81	0.95	0.94		
80-120	18%	0.84	0.37	1.02	0.83	0.79	0.99	1.02		
>120	5%	0.97	0.42	1.29	1.09	0.94	1.2	1.18		

<u>Back to top</u>

#### IGF-1 (ng/mL)

		Males (VMR: 138 to 242 ng/mL)							
Range Percent		MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality	
<85	2%	1.33	2.71	1.66	2.04	3.26	1.71	2.03	
85-100	3%	1.16	1.72	1.28	1.42	1.84	1.49	1.37	
100-120	8%	1.05	1.31	1	1.16	1.32	1.3	1.14	
120-150	22%	1	1.04	0.9	0.96	1.02	1.05	0.95	
150-250	63%	0.96	0.86	0.96	0.9	0.83	0.87	0.91	
>250	3%	1.16	1.04	1.51	1.33	0.96	0.93	1.29	

		Females (VMR: 131 to 246 ng/mL)							
Range Percent		MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality	
<85	3%	1.47	1.99	1.36	1.89	2.04	1.68	1.47	
85-100	5%	1.23	1.43	1.17	1.39	1.41	1.36	1.2	
100-120	11%	1.02	1.24	0.95	1.06	1.14	1.12	1.02	
120-150	24%	0.97	1	0.94	0.92	0.99	0.99	0.93	
150-250	55%	0.93	0.85	0.98	0.88	0.85	0.86	0.95	
>250	3%	1.05	0.89	1.44	1.44	1.02	0.9	1.47	

		Males (VMR: 17 to 42 ng/mL)								
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality		
<8	7%	1.22	1.79	1.56	1.55	1.51	1.68	1.67		
8-12	14%	1.08	1.39	1.3	1.3	1.22	1.19	1.27		
12-20	34%	1	1.06	0.98	0.99	1.01	0.98	0.99		
20-30	33%	0.94	0.75	0.86	0.86	0.83	0.87	0.85		
30-40	10%	0.93	0.59	0.91	0.86	0.79	0.87	0.85		
>40	2%	0.87	0.49	0.99	0.95	0.94	1.01	0.86		

#### Vitamin D (ng/mL)

		Females (VMR: 18 to 41 ng/mL)							
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality	
<8	7%	1.35	2	1.4	1.76	1.51	1.58	1.66	
8-12	14%	1.14	1.39	1.24	1.31	1.22	1.2	1.22	
12-20	34%	1.01	1.06	0.99	1	0.99	0.98	0.99	
20-30	34%	0.9	0.72	0.87	0.8	0.85	0.86	0.85	
30-40	10%	0.85	0.51	0.92	0.88	0.83	0.91	0.89	
>40	1%	0.87	0.46	1.09	1.1	0.85	1.14	0.99	

Back to top

#### C-Reactive Protein (mg/L)

		Males (VMR: 0.4 to 1.1 mg/L)							
Range Percent		MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality	
<0.5	16%	0.8	0.4	1.26	0.67	0.61	0.53	0.76	
0.5-1	24%	0.87	0.65	0.89	0.78	0.8	0.68	0.78	
1-1.7	21%	0.99	0.92	0.87	0.89	0.93	0.88	0.87	
1.7-3	<b>19%</b>	1.06	1.22	0.95	1.05	1.13	1.1	1.02	
3-6	13%	1.19	1.66	1.01	1.35	1.36	1.49	1.29	
>6	8%	1.24	1.79	1.18	1.61	1.54	1.94	1.68	

		Females (VMR: 0.4 to 1.2 mg/L)							
Range Percent		MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality	
<0.5	18%	0.72	0.29	1.24	0.55	0.59	0.58	0.81	
0.5-1	21%	0.81	0.47	0.98	0.69	0.7	0.72	0.81	
1-1.7	19%	0.92	0.69	0.87	0.79	0.86	0.87	0.85	
1.7-3	18%	1.04	1.09	0.94	1.02	1.09	1.05	0.99	
3-6	15%	1.22	1.71	0.96	1.33	1.33	1.33	1.17	
>6	10%	1.42	2.58	1.16	1.91	1.8	1.69	1.56	

		Males (VMR: 4.4 to 4.8 million/mcL)							
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality	
<4	2%	1.26	0.96	1.95	2.16	2.02	1.63	2.13	
4-4.5	22%	1.01	0.79	1.19	1.13	1.1	1.09	1.13	
4.5-5	52%	0.96	0.94	0.89	0.88	0.9	0.93	0.88	
5-5.5	22%	1.04	1.29	0.85	0.91	0.97	0.93	0.89	
>5.5	2%	1.16	1.84	0.92	1.13	1.28	1.18	1.11	

#### Red Blood Cell Count (million/mcL)

		Females (VMR: 3.9 to 4.4 million/mcL)								
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality		
<3.7	3%	1.25	0.8	1.57	2.09	1.43	1.47	1.87		
3.7-4	13%	1.02	0.54	1.21	1.17	0.96	1	1.16		
4-4.5	55%	0.96	0.84	0.96	0.92	0.93	0.93	0.93		
4.5-5	27%	1	1.38	0.92	0.92	1.05	1.03	0.94		
>5	2%	1.24	2.58	0.96	1.22	1.42	1.41	1.21		

Back to top

#### Hemoglobin (g/dL)

		Males (VMR: 14.1 to 15.5 g/dL)							
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality	
<12.5	1%	1.46	1.29	2.18	2.66	2.12	1.8	2.36	
12.5-13	1%	1.18	1.14	1.79	2.04	1.43	1.4	1.71	
13-14	12%	1.01	0.87	1.24	1.23	1.04	1.1	1.19	
14-15.5	54%	0.96	0.88	0.91	0.89	0.89	0.92	0.91	
15.5-17	<b>29%</b>	1.02	1.19	0.89	0.88	1.05	0.97	0.9	
>17	2%	1.12	1.82	1.04	1.21	1.51	1.51	1.2	

		Females (VMR: 12.5 to 14.1 g/dL)							
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality	
<11.5	2%	1.61	1.35	1.84	2.83	1.53	1.51	2.32	
11.5-12	3%	1.19	1.06	1.6	1.79	1.17	1.18	1.48	
12-13	22%	1.02	0.82	1.11	1.12	0.92	0.91	1.02	
13-14.5	<b>59%</b>	0.95	0.91	0.9	0.86	0.93	0.92	0.91	
14.5-15.5	12%	1.05	1.43	1.02	0.95	1.17	1.19	1.02	
>15.5	2%	1.25	2.28	1.06	1.46	1.71	1.96	1.48	

### Mean Corpuscular Volume (fL)

		Males (VMR: 86 to 95 fL)							
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality	
<83	3%	1.18	1.65	1.31	1.42	1.22	1.21	1.33	
83-90	33%	1.01	1.13	0.9	0.98	0.91	0.86	0.93	
90-95	<b>46%</b>	0.96	0.91	0.93	0.91	0.87	0.92	0.9	
95-100	16%	1.02	0.89	1.1	1.08	1.24	1.22	1.13	
>100	3%	1.19	0.99	1.88	1.59	2.43	1.95	2.03	

		Females (VMR: 89 to 96 fL)							
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality	
<83	4%	1.33	2.21	1.37	1.57	1.37	1.12	1.28	
83-90	35%	1.03	1.19	0.93	0.99	0.97	0.89	0.93	
90-95	45%	0.93	0.84	0.95	0.89	0.9	0.93	0.92	
95-100	14%	1.02	0.72	1.15	1.07	1.07	1.27	1.16	
>100	2%	1.28	0.96	1.77	1.89	2.09	2.02	2.13	

Back to top

#### Red Cell Distribution Width (%)

		Males (VMR: 12.1% to 13.7%)							
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality	
<13	<b>29%</b>	0.91	0.9	0.91	0.8	0.89	0.78	0.78	
13-13.5	30%	0.97	0.95	0.94	0.86	0.9	0.86	0.85	
13.5-14	22%	1.01	1.01	0.95	0.95	0.96	1	0.98	
14-14.5	11%	1.08	1.08	1.03	1.2	1.11	1.27	1.18	
14.5-15	4%	1.15	1.27	1.25	1.47	1.32	1.48	1.41	
>15	4%	1.24	1.45	1.58	1.95	1.88	1.89	2.01	

		Females (VMR: 12.0% to 13.6%)								
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality		
<13	<b>29%</b>	0.91	0.78	0.97	0.78	0.9	0.75	0.82		
13-13.5	27%	0.93	0.88	0.97	0.84	0.87	0.9	0.88		
13.5-14	21%	0.99	0.99	0.92	0.94	0.99	1.04	0.97		
14-14.5	11%	1.09	1.16	0.99	1.18	1.09	1.2	1.1		
14.5-15	5%	1.2	1.49	1.05	1.49	1.22	1.42	1.31		
>15	6%	1.38	1.84	1.6	2.16	1.59	1.63	2.01		

Back to top

#### White Blood Cell Count (/µl)

		Males (VMR: 3.9 to 6.4 /µl)								
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality		
<4	2%	0.82	0.55	1.23	0.88	0.88	0.6	1.05		
4-6	31%	0.85	0.64	0.85	0.78	0.83	0.6	0.79		
6-8	44%	0.99	0.99	0.98	0.93	0.96	0.9	0.92		
8-9.5	15%	1.14	1.4	1.1	1.23	1.17	1.42	1.19		
9.5-11	5%	1.32	1.77	1.25	1.51	1.42	1.94	1.59		
>11	3%	1.42	1.86	1.47	1.88	1.63	2.85	1.99		

		Females (VMR: 3.6 to 6.5 /µl)									
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality			
<4	2%	0.77	0.5	0.84	0.84	0.86	0.64	1.08			
4-6	32%	0.83	0.58	0.88	0.73	0.79	0.64	0.84			
6-8	44%	0.98	0.93	0.97	0.92	0.96	0.92	0.93			
8-9.5	15%	1.2	1.53	1.13	1.28	1.24	1.41	1.16			
9.5-11	5%	1.43	2.13	1.23	1.79	1.54	1.96	1.54			
>11	2%	1.8	2.91	1.74	2.47	1.65	3.23	2.22			

Back to top

#### Neutrophil Count (/µl)

		Males (VMR: 2000 to 3860 /µl)							
<b>Range Percent</b>		MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality	
<2000	2%	0.89	0.78	1.16	0.95	1	0.85	1.04	
2000-3000	14%	0.83	0.66	0.77	0.72	0.82	0.58	0.74	
3000-4000	31%	0.91	0.79	0.85	0.81	0.87	0.7	0.81	
4000-5000	27%	1.02	1.07	0.99	0.96	1.01	0.96	0.94	
5000-6000	15%	1.11	1.27	1.16	1.21	1.11	1.29	1.16	
>6000	11%	1.26	1.5	1.33	1.54	1.38	1.97	1.61	

		Females (VMR: 1770 to 3720 /µl)							
Range Percent		MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality	
<2000	2%	0.84	0.76	0.93	0.85	0.88	0.74	1.03	
2000-3000	16%	0.8	0.6	0.84	0.69	0.77	0.62	0.8	
3000-4000	32%	0.89	0.76	0.89	0.78	0.87	0.76	0.84	
4000-5000	27%	1.02	0.99	1	0.97	1	1.01	0.95	
5000-6000	14%	1.19	1.37	1.18	1.27	1.2	1.34	1.19	
>6000	10%	1.43	2.02	1.35	1.98	1.44	2.08	1.69	

Back to top

			Males (VMR: 1020 to 1950 /µl)							
Range Percent		MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality		
<1000	3%	1.01	0.68	1.37	1.34	1.2	1.05	1.48		
1000-1400	16%	0.91	0.66	1.07	0.99	0.91	0.81	0.98		
1400-2000	43%	0.97	0.86	0.93	0.92	0.92	0.88	0.92		
2000-2600	26%	1.03	1.19	0.96	0.99	1.03	1.09	0.97		
2600-3200	<b>9%</b>	1.14	1.59	1.01	1.14	1.19	1.35	1.14		
>3200	3%	1.3	1.96	1.09	1.37	1.49	1.96	1.4		

### Lymphocyte Count (/µl)

		Females (VMR: 1200 to 2150 /µl)							
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality	
<1000	2%	1.19	0.79	1.46	1.81	1.25	1.31	1.88	
1000-1400	12%	0.91	0.59	1.09	1.01	0.94	0.82	1.1	
1400-2000	40%	0.91	0.74	0.96	0.88	0.86	0.82	0.91	
2000-2600	31%	1	1.07	0.91	0.95	1	0.99	0.91	
2600-3200	11%	1.17	1.63	1.09	1.1	1.24	1.34	1.07	
>3200	4%	1.4	2.38	1.18	1.48	1.5	1.86	1.36	

<u>Back to top</u>

#### Monocyte Count (/µl)

		Males (VMR:200 to 540 /µl)							
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality	
<300	6%	0.86	0.77	1.09	1.05	0.88	0.85	1.01	
300-500	41%	0.92	0.79	0.96	0.87	0.87	0.76	0.85	
500-650	34%	1.01	1.02	0.97	0.95	0.99	0.98	0.96	
650-750	10%	1.12	1.27	0.98	1.13	1.17	1.27	1.11	
750-850	5%	1.19	1.48	1.08	1.24	1.24	1.51	1.3	
>850	4%	1.27	1.7	1.17	1.56	1.54	1.85	1.62	

		Females (VMR: 200 to 470 /µl)							
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality	
<200	2%	0.9	0.97	1	1.25	0.96	1.07	1.17	
200-400	36%	0.86	0.78	0.96	0.83	0.86	0.77	0.88	
400-550	43%	1	0.97	0.96	0.93	0.98	0.97	0.95	
550-650	12%	1.14	1.24	1.04	1.18	1.19	1.22	1.09	
650-750	5%	1.26	1.55	1.06	1.37	1.23	1.5	1.23	
>750	3%	1.41	1.83	1.44	1.79	1.49	1.81	1.71	

<u>Back to top</u>

		Males (VMR: 0 to 140 /µL)						
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality
<100	18%	0.9	0.73	1.02	0.91	0.96	0.72	1
100-200	<b>40%</b>	0.97	0.95	0.98	0.93	0.94	0.86	0.95
200-300	23%	1.05	1.12	0.96	1.05	1.01	1.09	0.99
300-400	10%	1.08	1.19	0.96	1.09	1.12	1.3	1.03
400-500	4%	1.14	1.17	1.06	1.14	1.12	1.49	1.1
>500	4%	1.09	1.29	1.2	1.33	1.17	1.73	1.21

### Eosinophil Count (/µl)

				Female	s (VMR: 0 to 140 /µL)			
Range Percent		MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality
<100	23%	0.87	0.69	1.01	0.88	0.86	0.78	0.99
100-200	44%	0.98	0.94	0.96	0.91	0.95	0.9	0.95
200-300	20%	1.06	1.26	1.03	1.12	1.08	1.17	1.03
300-400	7%	1.15	1.26	0.96	1.14	1.19	1.4	1.06
400-500	3%	1.13	1.29	1.07	1.41	1.25	1.45	1.12
>500	3%	1.25	1.32	1.21	1.47	1.3	1.59	1.17

<u>Back to top</u>

#### Lymphocyte Percentage (%)

		Males (VMR: 25% to 47%)						
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality
<16	4%	1.14	1.01	1.36	1.58	1.34	1.61	1.65
16-20	<b>9%</b>	1.08	0.99	1.24	1.23	1.11	1.2	1.23
20-28	39%	1	0.97	1.01	1	0.99	1.02	1
28-36	34%	0.96	0.98	0.87	0.87	0.91	0.86	0.84
36-46	12%	0.95	1.11	0.82	0.78	0.98	0.82	0.83
>46	1%	1.11	1.22	0.95	1.2	1.27	1.15	1.22

		Females (VMR: 27% to 44%)							
Range	Percent	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality	
<16	2%	1.42	1.17	1.35	2.24	1.49	1.98	2.08	
16-20	<b>6%</b>	1.14	1.07	1.22	1.51	1.17	1.3	1.43	
20-28	34%	1.04	0.97	1.12	1.09	1.01	1.05	1.07	
28-36	40%	0.95	0.96	0.9	0.86	0.93	0.92	0.88	
36-46	17%	0.95	1.01	0.84	0.78	0.96	0.85	0.81	
>46	2%	0.91	1.4	1.02	0.88	1.09	0.95	1.07	

<u>Back to top</u>

# Strength Values

This section includes all biomarker strength values for each disease.

	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality
Smoke Pack Years	9	3	9	6	6	10	10
BMI	9	9	6	7	7	3	5
Systolic	6	2	1	2	1	1	1
Grip Strength	6	2	10	4	4	2	5
<b>Resting Heart Rate</b>	4	3	3	3	4	2	4
HDL	9	6	6	5	5	2	5
LDL	4	1	5	3	2	1	3
Triglycerides	6	6	3	2	4	1	2
Lipoprotein (a)	3	1	1	0	1	0	1
LDL/ApoB Ratio	8	5	8	5	5	2	5
ALP	5	2	4	3	5	2	5
ALT	3	5	3	2	9	1	3
AST	3	3	4	3	9	1	4
AST/ALT Ratio	3	5	5	1	5	1	2
GGT	6	5	5	4	10	2	5
Creatinine	5	1	6	6	4	2	5
Cystatin C	10	4	8	10	6	4	9
Urate	6	5	5	6	5	1	4
Urea	5	1	6	6	4	2	6
Glucose	6	5	8	5	4	1	4
Hemoglobin A1C	10	10	9	7	6	3	6
Testosterone	3	3	3	2	2	1	2
SHBG	4	6	3	3	4	1	2
IGF-1	4	2	5	3	6	2	4
Vitamin D	4	3	6	3	4	2	5
CRP	8	5	5	5	6	4	6
RBC Count	3	3	7	4	3	1	5
Hemoglobin	4	3	7	5	3	2	5
MCV	3	2	6	3	5	2	5
RDW	4	2	5	5	4	3	7
WBC Count	8	4	5	5	4	5	6
Neutrophil Count	7	3	6	5	3	4	6
Lymphocyte Count	5	3	4	2	3	3	4
Monocyte Count	5	2	3	3	3	3	4
Eosinophil Count	4	2	2	2	2	3	2
Lymphocyte Percent	3	1	6	3	2	2	5

# **Our Findings**

# 1. Closely monitored biomarkers are not top predictors for MACE.

These four common biomarkers are routinely monitored. However, they did not emerge from our models as top predictors for MACE for either gender.

Biomarker	Strength	VMR (Male)	VMR (Female)
Triglycerides	6	63 to 169 mg/dL	45 to 110 mg/dL
Systolic*	6	114 to 159 mmHg	110 to 159 mmHg
Diastolic*	4	62 to 85 mmHg	58 to 80 mmHg
LDL*	4	113 to 185 mg/L	110 to 181 mg/L

\* Individuals are removed from our analysis if they report taking medications intended to directly modify the biomarker, including statins for cholesterol, or anti-hypertensives for blood pressure.

For comparison, below are the most predictive biomarkers among our model inputs for MACE:

Biomarker	Strength	VMR (Male)	VMR (Female)
A1C	10	4.74% to 5.39%	4.83% to 5.54%
Cystatin C	10	0.74 to 0.92 mg/dL	0.62 to 0.83 mg/dL
Smoke Pack Years	9	0 to 12.51 years	0 to 7.84 years
ВМІ	8	21.92 to 27.45	20.83 to 26.4

# 2. Cystatin C is one of the most predictive markers for several diseases.

Cystatin C is a protein that is not commonly monitored and rarely included in standard blood tests.<sup>5</sup> However, our models found it to be among the top ten most predictive biomarkers for every disease analyzed except Type 2 Diabetes.

Below are the six diseases where Cystatin C was a top predictor, ordered by strength of association. The "Rank" column shows where on the list Cystatin C ranks in comparison to the other biomarkers.

<sup>&</sup>lt;sup>5</sup> Cleveland Clinic. 2022. "Blood Tests: Types, Results & How They Work." Cleveland Clinic. December 6, 2022. https://my.clevelandclinic.org/health/diagnostics/24508-blood-tests.

Disease	Strength	Rank
Acute Kidney Disease	10	1
Major Adverse Cardiac Event	10	2
Mortality	9	2
Dementia	8	4
Liver Disease	6	7
COPD	4	5

#### 3. Lipoprotein (a) is not predictive of any major diseases on our list.

Despite being heavily monitored and recommended by physicians, Lipoprotein (a) did not emerge as a top predictor for **any** disease on our list. In fact, our models found it to be especially unpredictive of all diseases, as shown in the table of risk ratios below. Only MACE had an association with the highest values of Lp(a), which was very small in comparison with the associations of other biomarkers.

				Males			
Range	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality
<10	0.92	1.06	1.03	0.99	1.05	0.99	1
10-20	0.94	0.9	0.97	0.94	0.92	0.96	0.94
20-40	0.96	0.89	0.91	0.98	0.9	1	0.97
40-80	1.01	1.02	0.98	1.02	1.01	1.02	1
80-150	1.15	0.99	0.92	0.93	0.96	0.95	0.96
>150	1.18	0.88	1.02	1.04	0.91	1.03	1.02
				E e se e la e			
				Females			
Range	MACE	T2D	Dementia	Kidney	Liver	COPD	Mortality
<10	0.96	1.01	1	1.01	1.01	1.03	1.02
10-20	0.9	0.92	0.96	0.94	0.96	0.97	0.97
20-40	0.95	0.92	0.95	0.95	0.91	0.97	0.97
40-80	1.02	0.99	1.06	0.98	0.97	0.95	0.98
80-150	1.02	1.08	0.92	0.97	0.99	0.94	0.94
>150	1.11	0.99	1.06	1.03	1.02	1.04	1.04

# Appendix A. Methods

## Strength

The prediction strength metric is calculated by applying a non-linear (spline) correlation of each biomarker against a gender and age normalized dependent variable for each disease. The result of the normalization is a dependent variable with the form of a "risk ratio" averaging a value of 1.0 for every age and gender combination. This is achieved by generating a set of weights using a bivariate tensor product spline fitting the relationship between age and each disease outcome for each gender. For each biomarker, the correlation statistic is squared to reflect the percentage of variance explained in a univariate model, then averaged across men and women to create a gender-neutral metric. Next the value is divided by the maximum strength across all biomarkers, and then multiplied by 10, resulting in the final value for the metric where the strength is normalized for each individual disease outcome. The final presentation of the prediction strength metric is the result of sorting the individual biomarker averaged values in descending order, and removing biomarkers that appear redundant in the analysis based on similarity to others (e.g., ApoA, weight, Glucose, Cholesterol).

The normalization method discussed above avoids deceptive correlations with biomarkers that correlate to outcomes simply because they correlate to age, and many of the outcomes also correlate highly to age.

## **VMR** Values

The Voloridge Modeled Range, or VMR value, is the range of values of a marker that yields the lowest overall 15-year association with the seven diseases. This does not necessarily represent a risk category, nor should it be interpreted as a recommendation of any kind. It simply represents associations between biomarker values and 15-year outcomes among the 500,000 participants in the UK Biobank database. To determine a VMR value, we begin by fitting a univariate spline for each of the seven targets against a biomarker. The seven splines are averaged into one final curve with respect to the biomarker. We define the VMR value as the biomarker and model input values that correspond to a risk of no more than 20 percent above the minimum mean risk. Additional constraints ensure that the optimal range does not raise the risk for any individual disease beyond the greater of 1 or 30 percent above that disease's minimum risk. We further restrict the range by placing limits at the top and bottom 1 percent of the biomarker's distribution.

# Population

The values in this report are calculated using data from the UK Biobank. While useful for its large amounts of data, the UK Biobank's generalizability to the greater population is limited due to selection biases. The data comes from primarily White, male and female, and more socioeconomically advantaged populations. However, research suggests that it may still be generalizable to the general population with regards to disease.<sup>6</sup>

In addition to biases inherent in the dataset, a common filter is applied to all disease models. This common filter limits the model inputs to a population between the ages of 40 to 70 that has data for height and weight and is observed in the dataset for at least 12 years. Participant that died within those 12 years will still be included. Additional filters are added to each disease model to exclude people with a prior diagnosis of that specific disease. For example, the MACE model will exclude anyone with prior MACE. Because the age bias for dementia is so strong, there is an extra filter which excludes people who died at any point without getting dementia. Additional age filters are placed on each disease to ensure that the age distribution is balanced between sexes for each disease target.

Age filters are also applied for each disease. The database we used had a uniform distribution of individuals aged 40 to 70. For some disease outcomes, namely liver disease and type 2 diabetes, this entire age range was utilized. For the rest of the disease outcomes, a more limited age range was utilized as risk multipliers would not be as clinically relevant on age groups with lower incidence of the disease. In our analysis of dementia, only 60 to 70 year-olds were included as this subgroup contained 86 percent of all cases in the database. For mortality, we analyzed 55 to 70 year-olds, as this age range included 87 percent of deaths in the database. For MACE, we analyzed 55 to 70 year-olds with no prior MACE, which included 82 percent of MACE events. Similarly, for COPD, we analyzed 50 to 70 year-olds with no prior COPD, which included 92 percent of COPD events. Finally, for acute kidney disease we analyzed 55 to 70 year-olds with no prior acute kidney disease, which included 86 percent of instances of the disease. For Type 2 diabetes, an additional filter requiring Hemoglobin A1C to be less than 6.0 was applied. This is due to the fact that this measure is the primary marker used for diagnosis of the disease. This was done to avoid inclusion of people who may have already had Type 2 diabetes but had not yet been diagnosed.

<sup>&</sup>lt;sup>6</sup> Fry, Anna, Thomas J. Littlejohns, Cathie Sudlow, Nicola Doherty, Ligia Adamska, Tim Sprosen, Rory Collins, and Naomi E. Allen. "Comparison of sociodemographic and health-related characteristics of UK Biobank participants with those of the general population." *American journal of epidemiology* 186, no. 9 (2017): 1026-1034.

# Appendix B. Biomarker Glossary

This glossary is intended to give short descriptions of each biomarker included in this guide. Additional research may be needed to fully understand their effects on your health.

The following definitions are taken from MedlinePlus.<sup>7</sup>

**Hemoglobin A1C (A1C)** reflects your average blood sugar (glucose) level over the past two to three months. Glucose is a type of sugar in your blood that comes from the foods you eat. Your cells use glucose for energy. A hormone called insulin balances glucose in your blood and cells. Glucose in your blood sticks to hemoglobin, a protein in your red blood cells. As your blood glucose levels increase, more of your hemoglobin will be coated with glucose. An A1C test measures the percentage of your red blood cells reflecting glucose-coated hemoglobin. High A1C levels are a sign of high blood glucose from diabetes.

**Alkaline Phosphatase (ALP)** is an enzyme found in many parts of your body. Monitoring this biomarker helps diagnose diseases of the liver or bones and measure how well your liver is working. Each part of your body produces a different type of ALP. Most ALP is found in your liver, bones, kidneys, and digestive system. Abnormal levels of ALP in your blood may be a sign of a wide range of health conditions, including liver disease, bone disorders, and chronic kidney disease.

Alanine Transaminase (ALT) is an enzyme found mostly in the liver. An ALT test measures the amount of ALT in the blood. When liver cells are damaged, they release ALT into the bloodstream. High levels of ALT in your blood may be a sign of a liver injury or disease. Some types of liver disease cause high ALT levels before you have symptoms of the disease. Thus, ALT blood tests may help diagnose certain liver diseases early.

**Aspartate Aminotransferase (AST)** is an enzyme found mostly in the liver, but it is also found in muscles and other organs in your body. When cells containing AST are damaged, they release the AST into your blood. An AST blood test measures the amount of AST in your blood. The test is commonly used to help diagnose liver damage or disease.

<sup>&</sup>lt;sup>7</sup> MedlinePlus. 2019. "MedlinePlus: Medical Tests." Medlineplus.gov. 2019. https://medlineplus.gov/labtests/.

**AST-ALT Ratio** is a simple comparison of two liver enzymes, AST (aspartate aminotransferase) and ALT (alanine aminotransferase), measured in the blood to help assess liver health. In healthy livers, ALT levels are generally higher than AST because ALT is more specific to the liver. When liver damage occurs, both AST and ALT can rise, but the *ratio* between them can hint at the type or severity of liver issues. For example, an AST level that's much higher than ALT (usually a ratio over two) sometimes indicates alcoholic liver disease. A ratio closer to one or below may suggest other liver conditions, such as non-alcoholic fatty liver disease.

**Body Mass Index (BMI)** is quick calculation using a person's height and weight to estimate if they are within a healthy weight range. It doesn't directly measure body fat but gives an idea of whether someone might be underweight, normal weight, overweight, or obese.

**C-Reactive Protein (CRP)** is a protein your liver makes. Normally, you have low levels of CRP in your blood. Your liver releases more CRP into your bloodstream if you have inflammation in your body. High levels of CRP may mean you have a serious health condition causing inflammation. Inflammation is your body's way of protecting your tissues and helping them heal from an injury, infection, or other disease. If inflammation lasts too long, it can damage healthy tissues. This is called chronic (long-term) inflammation. Chronic infections, certain autoimmune disorders, and other diseases can cause harmful chronic inflammation. Chronic inflammation also can happen if your tissues are repeatedly injured or irritated, for example from smoking or chemicals in the environment.

**Creatinine** is a normal waste product in your body. It's made when you use your muscles and some of the muscle tissue breaks down. Normally, your kidneys filter creatinine from your blood and remove it from your body in your urine. If there is a problem with your kidneys, creatinine can build up in your blood and less may be released in urine. If blood and/or urine creatinine levels are not normal, it may be a sign of kidney disease.

**Cystatin C** is protein found in the blood that helps measure kidney function. It's produced at a steady rate by most cells in the body and then filtered out by the kidneys. By measuring how much cystatin C is in the blood, clinicians can estimate how well the kidneys are working. When kidney function is good, cystatin C levels are low because the kidneys filter it out efficiently. High levels can suggest the kidneys aren't filtering well, which may indicate kidney disease. Cystatin C may be especially useful because it's less affected by factors like muscle mass, potentially making it a more accurate measure of kidney health than other tests, like creatinine.

**Eosinophil Count** is a type of white blood cell helping the body fight off infections and react to allergens. Eosinophils are part of the immune system and usually make up a small percentage of the total white blood cells. A higher-than-normal eosinophil count can indicate an allergic reaction, asthma, or a parasitic infection. It also can signal certain inflammatory conditions or autoimmune diseases. A low count is usually normal and not a cause for concern. By checking eosinophil levels, clinicians gain insight into immune activity and better understand symptoms related to allergies or inflammation.

**Gamma-glutamyl Transferase (GGT)** is an enzyme found throughout your body, but it is mainly found in your liver. Enzymes are proteins that speed up certain chemical reactions in your body. Thousands of enzymes play an important role in all of your body functions. If your liver or bile duct is damaged, GGT may leak into your bloodstream. High levels of GGT in your blood may be a sign of liver disease or damage to the bile ducts. Bile ducts are tubes carrying bile in and out of the liver. Bile is an important fluid for digestion made by the liver. While GGT can't diagnose the specific cause of liver disease, levels that are out of range can indicate your liver is being damaged.

**Glucose,** or blood sugar, is the main sugar found in your blood. It is your body's primary source of energy. It originates from the food you eat. Your body breaks down most food into glucose and releases it into your bloodstream. When your blood glucose goes up, it signals your pancreas to release insulin. Insulin is a hormone that helps the glucose get into your cells to be used for energy. Diabetes is a disease in which your blood glucose levels are too high. When you have diabetes, your body doesn't make enough insulin or cannot use insulin as well as it should, or both. Over time, having too much glucose in your blood can cause serious health problems and diabetes complications.

**Grip Strength** is a simple measure of how much force you generate when you squeeze with your hand. It's tested by squeezing a device called a dynamometer, which records the strength of your grip. This measurement isn't just about hand strength; it's also a quick indicator of overall muscle strength and health. Studies show lower grip strength often is linked to a higher risk of certain health issues, like heart disease or mobility problems, especially in older adults. Tracking grip strength helps clinicians assess muscle health, recovery progress, or the risk of future health conditions.

**HDL Cholesterol (high-density lipoprotein)** is often called the "good" cholesterol because it helps remove other forms of cholesterol from the bloodstream. HDL transports excess cholesterol (a waxy, fat-like substance found in your blood) from the arteries back to the liver, where it is processed and eliminated from the body, reducing the risk of

cholesterol buildup which can lead to heart disease or stroke. The ideal HDL levels vary by age and gender.

**Hemoglobin** is an iron-rich protein in your red blood cells. It carries oxygen from your lungs to the rest of your body. Your cells need oxygen to grow, reproduce, and make energy for you to function. Your hemoglobin levels provide information about the health of your red blood cells. If your hemoglobin levels are abnormal, it may be a sign that you have a blood disorder, often referred to as anemia.

**IGF-1 (insulin-like growth factor 1)** is a hormone, a chemical messenger in your bloodstream controlling the actions of certain cells or organs. IGF-1 manages the effects of growth hormone (GH) in your body. Together, IGF-1 and GH promote normal growth of bones and tissues. GH levels in the blood change throughout the day, depending on your diet and activity levels, while IGF-1 levels are more stable. A reliable way to track GH in your body is by measuring the level of IGF-1 in the blood. Levels of IGF-1 and GH change throughout your life. They are normally low when you are a child, increase until they peak during puberty, then decrease once you are an adult. Besides growth, GH also helps control your metabolism, which is the process your body uses to make energy from the food you eat. Some conditions, such as pituitary tumors, can cause your body to make too much or too little GH.

LDL Cholesterol (low-density lipoprotein), or "bad" cholesterol, is one of two types of cholesterol. Cholesterol is a waxy, fat-like substance found in your blood and every cell of your body. Your body needs some cholesterol to make hormones, vitamin D, and substances that help you digest foods. Too much LDL cholesterol in your blood increases your risk for coronary artery disease and other heart diseases. High LDL levels cause the buildup of a sticky substance called plaque in your arteries. This buildup of plaque is known as atherosclerosis. Over time, plaque narrows your arteries or fully blocks them. When this happens, parts of your body may not get enough blood. If the blood flow to your heart is blocked, it can cause a heart attack. If the blood flow to your brain is blocked, it can cause peripheral artery disease.

**LDL-ApoB Ratio (LAR)** compares levels of low-density lipoprotein cholesterol (LDL) with Apolipoprotein B (ApoB), the main protein in LDL particles. This ratio provides additional information on cardiovascular risk by assessing both the cholesterol content and the number of LDL particles, as each ApoB represents an LDL particle. A lower LAR may indicate smaller, denser LDL particles, which are associated with a higher risk of cardiovascular disease.

**Lipoprotein (a)** is a type of LDL (low-density lipoprotein) or "bad" cholesterol. Lipoproteins are particles made of protein and fats (lipids). They carry cholesterol through your bloodstream to your cells. These lipoproteins carry cholesterol to the cells in your arteries. If you have high levels of LDL particles, cholesterol can build up in your arteries and form blockages called plaques. This condition is known as atherosclerosis or "hardening of the arteries." It can lead many serious medical conditions including coronary artery disease (narrow or blocked arteries in your heart), heart attack, stroke, peripheral arterial disease (blocked arteries in your legs or arms), or other blood vessel diseases. Lipoprotein (a) particles are stickier than other types of LDL particles, so they may be more likely to cause blockages and blood clots in your arteries. As a result, high levels of lipoprotein (a) may mean you have a very high risk for heart disease, stroke, and other serious conditions related to blockages and blood clots in your arteries. A lipoprotein (a) blood test gives you a more accurate understanding of your risk than a routine cholesterol tests only measuring your total LDL cholesterol level. This is because a routine cholesterol test may show your LDL cholesterol level is "healthy," but if a large percentage of your LDL cholesterol is carried by lipoprotein (a) particles, your risk for heart disease and stroke could still be high.

**Lymphocyte Count** is part of a complete blood count (CBC) and measures lymphocytes, a type of white blood cell important for immune response. It can be elevated by infections or immune conditions and lowered by certain diseases or treatments. A CBC is a group of blood tests measuring the number and size of the different cells in your blood.

**Mean Corpuscular Volume (MCV)** is part of a complete blood count (CBC). A CBC is a common blood test measuring many parts of your blood, including red blood cells. An MCV blood test measures the average size of your red blood cells. Red blood cells carry oxygen from your lungs to every cell in your body. Your cells need oxygen to grow, reproduce, and stay healthy. If your red blood cells are too small or too large, it could be a sign of a blood disorder such as anemia, a lack of certain vitamins, or other medical conditions.

**Monocyte Count** is part of a complete blood count (CBC) and measures type of white blood cell that helps fight infection. Abnormal monocyte counts can be seen in infections, autoimmune diseases, or bone marrow disorders. A CBC is a group of blood tests measuring the number and size of the different cells in your blood. **Neutrophil Count** is part of a complete blood count (CBC) and measures a type of white blood cell that helps fight infection. Neutrophil count is part of a CBC and can be elevated in bacterial infections or reduced in conditions affecting bone marrow. A CBC is a group of blood tests measuring the number and size of the different cells in your blood.

**Pulse Rate (or resting heart rate)** measures the number of times your heart beats per minute at rest. It provides information on heart health and can vary with activity, stress, and health conditions. Resting heart rate gives insights into cardiovascular fitness and overall health, with lower rates often indicating better fitness and higher rates suggesting potential stress, dehydration, or heart conditions. Sudden changes also may signal early health issues like infection or thyroid changes.

**Red Blood Cell Count (RBC)** measures the number of red blood cells, also known as erythrocytes, in your blood. Red blood cells are made in your bone marrow, the spongy tissue inside your large bones. They contain hemoglobin, an iron-rich protein that carries oxygen from your lungs to every cell in your body. Your cells need oxygen to grow, reproduce, and make energy for you to function. An RBC count higher or lower than normal is often the first sign of an illness.

**Red Blood Cell Distribution Width (RDW)** is a measurement of how much the volume and size of your red blood cells (erythrocytes) vary. Red blood cells are made in your bone marrow (the spongy tissue inside your large bones). They contain hemoglobin, an iron-rich protein that carries oxygen from your lungs to every cell in your body. Your cells need oxygen to grow, reproduce, and make energy for you to function. Normally, your red blood cells are about the same size. Differences in the size of your red blood cells may affect how well they can deliver oxygen through your body. An RDW test uses a special graph called a histogram. If your red blood cells are about the same size, they will be close together on the histogram, and the RDW will be low. A high RDW means the size of your red blood cells varies more than it should. The sizes will be more spread out on the histogram. This may be a sign of a medical condition.

**SHBG (sex hormone binding globulin)** is a protein made mostly in your liver. It binds (attaches) to sex hormones in your blood. SHBG helps control the amount of sex hormones that are actively working in your body. When the SHBG protein binds to sex hormones, your tissues can't use those hormones. Your tissues can only use sex hormones that are "free," which means they aren't attached to proteins, such as SHBG. An SHBG test is usually done if you have signs and/or symptoms of having too much or too little of the sex hormone testosterone. Testosterone is known as a "male" sex hormone, but females have testosterone in smaller amounts. In adult males, testosterone controls sex drive,

maintains muscle mass, and helps make sperm. In adult females, testosterone is important for healthy organs and the growth of bones and muscles. Measuring SHBG levels provides information about how much of your testosterone is active in the tissues of your body.

**Smoke Pack Years** is a measure of smoking exposure calculated by multiplying the number of cigarette packs smoked per day by the number of years the person has smoked. It's a common way to assess the long-term impact of smoking on health, particularly in studies related to lung disease.

**Systolic Blood Pressure** is the top number in a blood pressure reading. It indicates the pressure in the arteries when the heart beats. Each time your heart beats, it pumps blood into your arteries (the blood vessels that carry blood from your heart to the tissues and organs in your body). A blood pressure measurement is a test measuring the force (pressure) in your arteries as your heart pumps. Blood pressure is measured as two numbers: systolic and diastolic blood pressure.

**Testosterone** is known as a "male" sex hormone, but females have testosterone in smaller amounts. Testosterone is made by the testicles (or testes), the part of the male reproductive system that makes sperm; the ovaries, the part of the female reproductive system that makes eggs; the adrenal glands, organs on top of each kidney that make several hormones. During male puberty, testosterone causes body hair, muscle growth, and a deepening voice. In adult life, it controls sex drive, maintains muscle mass, and helps make sperm. In females, testosterone is important for the growth of bones and muscles, and healthy organs. There are different forms of testosterone in your blood that may be measured to help diagnose certain health problems. Most of your testosterone is attached to proteins. The proteins prevent your tissues from using the testosterone right away, which helps control the amount of "active" testosterone in your body. Testosterone not attached to proteins is called free testosterone. Free testosterone acts on your tissues.

**Triglycerides** is the amount of a fat in your blood called triglycerides. High triglycerides may increase your risk for a heart attack or stroke. Your body uses triglycerides for energy. If you eat more calories than you need, your body turns the extra calories into triglycerides and stores them in your fat cells to use later. When your body needs energy, your cells release triglycerides into your bloodstream to provide fuel for your muscles to work. If you eat more calories than you burn off, especially calories from carbohydrates, including sugary foods, and fats, you may have high triglyceride levels in your blood. A high blood

triglyceride level usually doesn't cause any acute symptoms, but over time, may affect your arteries and pancreas and increase your risk of heart disease and pancreatitis.

**Urate** (also known as Uric Acid) is a normal waste product your body makes when it breaks down chemicals called purines. Purines come from your cells when they die. Purines also are found in many foods and beverages. Most uric acid dissolves in your blood. Your kidneys filter the uric acid out of your blood, and it leaves your body in your urine. If uric acid builds up in your blood, it can form needle-shaped crystals in and around your joints. This condition is called gout. Gout is a type of arthritis causing painful swelling in your joints. High uric acid levels also can cause kidney stones, or kidney failure. However, not everyone with high levels of uric acid will have these problems.

**Urea** is a waste product created when the liver breaks down proteins, and it is filtered by the kidneys and excreted in urine. Urea levels help indicate kidney and liver function, and abnormal results may signal health concerns in these areas.

**Vitamin D** is essential for healthy bones and teeth, and for your body to work well. It also helps keep your muscles, nerves, and immune system working normally. Having low levels of vitamin D is a common problem that can lead to bone disorders and other medical problems. Vitamin D testing can let you know if you need to increase your vitamin D levels. You get vitamin D in three ways. Your body makes vitamin D when your bare skin is exposed to sunlight. You get vitamin D from certain foods. Only a few foods, such as egg yolks and fatty fish, naturally contain vitamin D. That's why vitamin D is added to foods, including breakfast cereals, milk, and other dairy items. You can take vitamin D supplements.

White Blood Cell (WBC) Count (also called leukocytes) is a measurement of your white blood cells, which are part of your immune system. They are a type of blood cell made in your bone marrow and found in your blood and lymph tissue (part of your immune system). If you are injured or get sick, the white blood cells travel through your bloodstream and tissues to where they are needed. There, they help your body fight off infections and other diseases. When you get sick, your body makes more white blood cells to fight the bacteria, viruses, or other foreign substances causing your illness. This increases your white blood count. Some diseases can cause your body to make fewer white blood cells than you need. This lowers your white blood count. Diseases can lower your white blood cells. Certain medicines, including chemotherapy, also may lower the number of your white blood cells. There are five major types of white blood cells: Neutrophils, Lymphocytes, Monocytes, Eosinophils, and Basophils.

Version 1.0

# Appendix C. About the Organizations

# About Voloridge Health, LLC

Data is the most powerful tool to understand and enhance human health. Voloridge Healh develops advanced tools to provide predictive insights, giving people the power to take charge of their health and shape a healthier future. Find out more at <a href="https://www.VoloridgeHealth.com">www.VoloridgeHealth.com</a>.

# About VoLo Foundation

VoLo Foundation is a private family organization that exists to accelerate change and global impact by supporting science-based climate solutions, enhancing education, and improving health. Find out more at <u>www.VoLoFoundation.org</u>.

# Authors and Acknowledgements

### Authors

David Vogel, David Hijirida, Monica Vogel, Shannon Maganiezin, Randy Axelrod, M.D., Chris Shnyer, Stephanie Duesing, Aaron Liu, Barry Miller, Jason Kras, Daniel Luis Vera Ph.D. M.B.A.

### Contributions

Conceptualization : DV ; Data Analysis : DV,JK.; Writing : MV,SM; Review & Editing : RA,BM,MK,SD,SM,DLV,CS,DH

### Acknowledgements

We sincerely thank Dr. Eric Topol, Dr. Tommy Woods, Dr. Richard Faro, and Dr. Danine Fruge for their valuable feedback and insightful comments.