The Interpretation of LongevityQuest® For Physicians

A Guide Used By Risk Assessment Experts For Mortality Modeling

The Underwriting Implications of "Normal" Laboratory Test Results and Physical Measurements

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Overview

Life insurers have been routinely screening a substantial portion of applicants with laboratory tests for nearly four decades, and they have been using physical measurements in the assessment of insurability for even longer.

When underwriting lab test and physical measurement findings, we have made a clear distinction between results within the "normal" (reference) range versus those that are either clearly elevated or below the accepted threshold.

With the advent of predictive model scores based on these variables, this approach will change because…

All normal tests are normal – but some normal tests are less normal than other normal tests

The original version of this famous sentence appeared in George Orwell's prophetic fable *Animal Farm*.

By paraphrasing it, we have defined the essence of the paradigm shift ushered in by predictive model scoring.

For nearly all laboratory tests and our three routine physical measurements (build, resting heart rate and blood pressure), high normal and/or low normal findings within the conventional reference range may confer increments of either increased or lesser relative mortality when contrasted to findings in the mid-portion of the "normal" range.

In some cases, the impact of these increments is substantial enough to justify changes in underwriting actions based on these findings alone. In most cases, however, the individual impact of high normal and low normal results is not that great, and it is the interplay of all findings which collectively determine their impact on a given risk.

To facilitate the embrace of risk scoring, insurers need hard evidence demonstrating the insurability implications of test results and physical measurements within traditional reference ranges.

To confer the greatest degree of credibility, such evidence must come from the contemporary medical literature.

By virtue of having this information at hand, insurers using lab/paramedical risk scores will be able to effectively respond to questions and potential challenges from producers, clients, attending physicians, regulatory authorities and others.

Recognizing the importance of providing this resource for insurers, ExamOne retained this underwriter to undertake an extensive review of the medical literature, identifying, assessing and then presenting this evidence in a manner that will best serve the needs of its clients.

This paper is the result of that project.

It reviews all relevant blood and urine profile components, citing clinical and epidemiological findings that underscore the implications of high normal and low normal laboratory test results as they relate to insurability. This paper also addresses similar evidence related to build, resting heart rate and blood pressure.

Findings from 329 clinical studies, meta-analyses of multiple studies, epidemiological investigations and literature reviews were reviewed and analyzed in preparing this paper. All of them are cited in the References section.

This paper will hopefully assist insurers responding to issues arising as a result of the impact of lab/paramedical scores on underwriting actions. At the same time, it should enhance the comfort zone of reinsurers of carriers using these scores.

My thanks to Troy Hartman, Betsy Sears, Dr. James Palmier, Brian Lanzrath and their ExamOne colleagues for entrusting me with this undertaking.

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Section I: Laboratory Tests

Liver-Related Tests

Aminotransferases (ALT and AST)

The aminotransferase enzymes are ALT (alanine aminotransferase) and AST (aspartate aminotransferase). They were formerly known as transaminases and designated SGPT and SGOT, respectively.

Most of this section will be devoted to ALT because far more research has been done to define its relationship to non-liver related disorders.

What is the pattern of mean (average) ALT levels in the general population?

It has a dome-shaped configuration and is lowest in the elderly. [Elinav and Ben-Dov]

Age Range	Mean ALT
< 40	19
40 – 55	19
56 – 72	22
73 – 83	17
> 83	13

In the Rancho Bernardo Study, mean ALT levels in 66-year old male and female subjects were 19 and 16.9, respectively. Their ALT readings decreased progressively over the next 15 years. [Dong]

It is noteworthy in our context that a number of investigators have shown that ALT readings in the 95th percentile of healthy populations may be conspicuously lower than the upper limit of prevailing reference ranges.

Kariv reported a 95th percentile level of 37.5, substantially below the upper limit of normal (52) used by the reporting laboratory. Three other authors have cited similar data. [Harrison, Lee and Shim, Prati]

These revelations support the premise that there is excess insurability risk associated with high normal ALT readings based on prevailing reference ranges.

How do ALT and AST differ in terms of the primary driver of high normal and elevated

readings in the absence of known or suspected liver disease?

For ALT, excess weight is the main consideration, whereas heavier alcohol intake is the most significant issue impacting AST. [Adams, Loomba]

How does clinical medicine view ALT?

"…abnormal ALT activity is often ignored or minimized by practitioners as most patients are asymptomatic. Minor elevations are often construed to be clinically insignificant, in part because of lack of a longitudinal perspective about the impact of abnormal ALT on long-term outcome such as end-stage liver disease or premature mortality."

W. Ray Kim and Steven L. Flamm
American Association for the Study of Liver Disease
Heart
47(2006):1363

How does ALT correlate with weight?

ALT increases significantly within the range held to represent ideal build. [Lee and Ha]

BMI	Odds Ratio for Elevated ALT
< 20	1.0
20 – 21.9	1.2
22 – 24.9	1.6
≥ 25	1.7

This pattern is also found in regard to weight circumference (WC), a marker for abdominal obesity and therefore a greater risk of cardiovascular disease. [Bethel]

ALT Quintile	Mean WC
1	95
2	97
3	99
4	100
5	102

This pattern has been demonstrated in numerous other studies. [Hanley, Schindhelm,

Verrijken]

What is the association between ALT and insulin resistance (a precursor to type 2 diabetes, nonalcoholic fatty liver disease and the metabolic syndrome)?

Hanley and Wagenknecht showed that patients in the top ALT quartile were 3 times more likely to have findings consistent with insulin resistance than those in the lower quartiles.

Cho reported that fasting insulin levels increased linearly across four quartiles of ALT in both men and women. Schindhelm and Marchesini found that high normal ALT correlates directly with elevated fasting insulin readings.

Is ALT within the normal range linked to an increased risk of type 2 diabetes?

Yes.

In a meta-analysis of 10 studies, Fraser showed that ALT in the top quartile doubled the risk of T2DM.

Sattar reported the following in 5974 male subjects:

ALT Quartile (range)	Risk of T2DM
1 (< 17)	1.0
2 (17-21)	1.4
3 (22-28)	1.7
4 (> 28)	3.4

Nguyen had similar results in middle-aged subjects in the Bogalusa Heart Study.

What is the metabolic syndrome?

It is an aggregation of cardiovascular risk factors held by some to constitute a dyslipidemic profile conferring an increased risk of diabetes, coronary artery disease and other atherosclerotic disorders.

There are 5 criteria used for the metabolic syndrome:

- Fasting glucose ≥ 110
- Triglycerides ≥ 150

- HDL-C < 40
- Waist circumference > 102 cm
- Blood pressure ≥ 135/85 or on antihypertensive Rx

The presence of at least 3 of these criteria equates to a diagnosis of metabolic syndrome.

Is there a relationship between ALT and the risk of developing this syndrome?

"ALT could be used to distinguish metabolically healthy patients from metabolically unhealthy patients whether they are lean or obese."

Olusegun A. Mojiminiyi, MBBS, FRCPath; et al.
Journal of Clinic Hypertension
12(2010):301

Olynyk revealed the following relative risks of metabolic syndrome across tertiles of ALT in 3719 subjects without diabetes or CV disease:

	ALT Tertile		
	1	**2**	**3**
Men	1.00	2.30	6.72
Women	1.00	1.62	4.27

Jacobs and van Greevenbroek reported that the mean ALT in subjects diagnosed with the metabolic syndrome was 23.8, as compared to 18.5 in those who did not meet syndrome criteria.

Many other investigations have found similar results linking high normal ALT to a substantially increased risk of the metabolic syndrome. [André, Hanley, Kang and Min, Steinvil, Suh, Xia, Yun]

Why is a relationship between ALT and CRP significant?

CRP is an inflammatory marker strongly associated with increased cardiovascular and all-cause mortality. [Koenig]

Therefore, another aspect of increased mortality risk in high normal ALT is its demonstrated link to elevated CRP. [Cho, Kazumi]

Is high normal ALT a significant risk factor for cardiac events?

"The associations between ALT level and risk of diabetes or CVD seem to follow

a monotonic function (the greater the ALT, the greater the risk). Thus, any threshold of ALT will be relatively arbitrary. However, in most studies quoted the risk seems to increase significantly at ALT levels >20-30 U/L, which is substantially lower than the upper limit of ALT set by most laboratories…"

George Ioannou, MD
University of Washington Medical School
Gastroenterology
135(2008):1851

In a cohort of 50- to 75-year old subjects followed for 10 years, those in the top ALT tertile had a 2-fold increased risk of cardiac events. [Schindhelm]

How do prevailing ALT reference ranges influence the association between ALT and liver disease?

They are not consistently reliable for identifying patients with unsuspected liver disease because there is considerable overlap between ALT readings in healthy subjects and those with potentially serious liver disorders. [Lee and Shim, Neuschwander-Tetri]

For example, Minervini reported that nonalcoholic fatty liver disease (NAFLD) was found in 20% of otherwise healthy young adults with normal ALT.

The risk of NAFLD increases across ALT levels. [Chang]

ALT	Risk of NAFLD
< 16	1.0
16 – 18	1.6
19 – 25	1.7
26 – 34	2.3

Israeli researchers reported the following average ALT readings based on the presence of NAFLD, both alone and with comorbid metabolic syndrome. [Assy]

	Control Subjects	NAFLD Alone	NAFLD & Metabolic Syndrome
Mean ALT	25	31	39

What are the implications of high normal ALT in subjects with known NAFLD?

The likelihood of a positive coronary artery calcium scan increases 82% if ALT is 30 or

higher. [Jung]

The risk of progression from simple fatty liver to advanced fibrosis and NASH is also increased. [Fracanzani, Kang]

Do persons with chronic hepatitis C often have ALT levels in the high normal range?

Yes…and 14-24% of these individuals will have significant fibrosis on liver biopsy. [Calvaruso]

What do we know about the relationship between AST and alcohol abuse?

Whitehead revealed the following association between daily alcohol intake and AST levels in 46,775 non-smoking men:

Daily Alcoholic Drinks	Mean AST
None	22
< 1	22
1 – 2	22
3 – 4	23
5 – 6	25
7 – 8	28
> 8	30

In other words, AST readings well within the normal range are associated with frank alcohol abuse based on admitted daily intake.

Blasco disclosed that cirrhosis-free alcoholics consuming approximately 12 drinks daily had average ALT and AST levels of 24 and 25, respectively.

Conigrave reported a 50% greater likelihood of alcohol-related illness when AST was in the fourth quartile.

In a celebrated autopsy study, fewer than half of all decedents with cirrhotic livers had been diagnosed with cirrhosis *ante mortem* (before death). [Lieber]

This is significant from an underwriting perspective because high normal AST and ALT readings are often seen in the presence of biopsy-proven cirrhosis. [Giannini]

Is there extra mortality risk linked to high normal ALT?

Absolutely.

Schindhelm found that middle-aged subjects with ALT in the highest tertile had 30% higher mortality than those in the first tertile.

Kim and Jee reported that ALT between 20-29 correlated with 20% greater mortality, and readings of 30-39 showed 70% higher risk of death, as compared to persons with ALT < 20. Results were almost identical for AST within the same ranges. These data come from an insurance database consisting of over 142,000 Korean men.

Is low ALT a mortality consideration?

Yes, in the elderly, as revealed by data from a number of investigations:

Elinav found that ALT below the median level (13) was associated with a 2.4-fold higher all-cause mortality after a 12-year follow up. This risk was at least as significant as those associated with cigarette smoking, ischemic heart disease and chronic kidney failure.

Le Couteur followed 1673 elders, mean age 76, and revealed that ALT below the median was linked to more than twice the risk of death as readings above the median.

Hovinen discovered that high normal ALT had roughly half the mortality risk of low normal readings in a cohort of septuagenarians.

Ford followed 5804 subjects, age 70 and over, for 4 years:

ALT Level	% Deceased
< 14	13.6%
14 – 18	10.3%
18 – 22	8.8%
> 22	8.7%

High normal ALT is associated with multiple cardiovascular risk factors. In addition, both high normal and, in the elderly, low normal ALT confer significantly increased mortality risk.

Gamma-Glutamyltransferase (GGT)

> *"Because GGT lacks specificity as a marker and is highly inducible, an extensive evaluation of an isolated GGT elevation in an otherwise asymptomatic patient is not warranted."*
>
> George Aragon MD and Zobair Younossi MD
> George Washington University Medical School
> *Cleveland Clinic Medical Journal*
> 77(2010):195

The context in which elevated GGT is mainly used in the clinical setting is to distinguish bone (GGT normal) from hepatobiliary (GGT elevated) disease in patients with elevated alkaline phosphatase.

Therefore, if elevated GGT is largely dismissed as insignificant by physicians, they are even more likely to ignore high normal readings.

Why do we need to broaden our appreciation of the risk implications of GGT?

> *"Serum gamma-glutamyl transferase (GGT) has long been used as a liver function test and a marker of excessive alcohol use; in recent years our knowledge of GGT's physiological functions has expended and several important epidemiological associations have been reported."*
>
> John B. Whitefield
> Royal Prince Albert Hospital
> Camperdown, New South Wales, Australia
> *Clinical Chemistry*
> 53(2007):1[editorial]

> *"Although GGT is mainly seen as an indicator for hepatobiliary disease and alcohol consumption, several studies have shown its association with morbidity and mortality from other causes, especially cardiovascular disease (CVD)."*
>
> Lili Kazemi-Shirazi MD, et al.
> University of Vienna Medical School
> *Clinical Chemistry*
> 53(2007):940

GGT is now considered a "unique biomarker in the continuum of cardiovascular disease risk," and "subtle gradations in GGT predict the long-term cardiovascular prognosis." [Mason, Turgut]

Is GGT directly linked to an increased circulatory disease risk?

> *"There is evidence that GGT is a potential biochemical marker for the preclinical development of atherosclerosis. GGT was found to play a role in the pathogenesis of atherosclerosis."*
>
> Elfriede Ruttmann MD, et al.
> The Vorarlberg Health Monitoring and Promotion Program Study Group
> *Circulation*
> 112(2005):2130

What evidence supports the argument that GGT has a significant impact in the development and progression of coronary disease and other atherosclerotic disorders?

> *"The pathogenetic mechanism proposed for the role of GGT in promoting the atherosclerotic process should be considered independent, complementary, and synergistic to conventional determinants… Serum GGT activity holds an independent prognostic value within reference level range in all epidemiological studies after adjustment for confounders."*
>
> Michele Emdin MD, PhD, et al.
> Institute of Clinical Pathology
> University of Pisa (Italy) Medical School
> *Circulation*
> 112(2005):2078

In addition:

GGT has been demonstrated within coronary disease plaque lesions. [Paolicchi]

GGT is a recognized marker of oxidative stress, and oxidative stress is a primary disease-induced mechanism. [Fraser and Harris]

GGT levels are impacted by at least four major organic environmental pollutants. [Lee]

GGT levels have been linked to arterial compliance, arterial stiffness and increased systemic vascular resistance. [Patel and Srinivasan, Saijo]

GGT is a proinflammatory marker, as shown by its association with high levels of CRP and white blood cell count. [Kim, Lee, Ryu, Paolicchi and Franzini, Saijo, Wannamethee and Lennon]

And, the relationship between GGT and CRP is particularly important due to the role

of CRP in circulatory disease.

Wannamethee and Lennon reported the following data from the British Regional Heart Study:

GGT	Mean CRP
< 18	1.22
19 – 25.9	1.54
26 – 36.9	1.88
≥ 37	2.20

Is GGT within the normal range related to visceral (abdominal) obesity?

Yes.

Five studies have proven this association. [Cammà, Perlemuter, Shankar, Van Barneveld, Verrijken]

Shankar reported this correlation between waist circumference and GGT:

GGT Quartile	Mean WC
1	88
2	89
3	95
4	99

How does GGT relate to blood pressure?

The likelihood of hypertension increases with GGT levels within the normal range. [Meisinger]

% with High Blood Pressure			
GGT	**Men**	**GGT**	**Women**
< 13	11%	< 8	6%
13 – 19	14%	8 – 9	8%
20 – 34	20%	10 – 15	15%
35 – 55	28%	16 – 24	25%

Stranges found that the incidence of future hypertension was increased at GGT levels within the normal range in both drinkers and nondrinkers.

Miura and Nagakawa demonstrated that GGT of 20 or higher increased the risk of hypertension 4.2-fold, as compared to subjects with GGT readings < 10.

Three additional investigations showed similar findings. [Kim, Nilssen, Shankar]

Does high normal GGT have a relationship to the metabolic syndrome similar to that of ALT?

Yes.

André reported the following association:

Relative Risk of Metabolic Syndrome		
GGT Quartile	**Men**	**Women**
1	1.00	1.00
2	2.06	1.17
3	2.44	1.31
4	4.14	1.27

Five additional investigations found essentially the same relationship. [Devers, Ramesh, Steinvil, Wannamethee and Lennon, Xia]

How does GGT correlate with risk factors for diabetes?

High normal GGT is associated with progressively greater fasting insulin levels. [Akehi, Ryu]

The risk of impaired glucose tolerance (IFG) increases between quartiles of GGT. [Nguyen, Kawamoto]

Mean glycosylated hemoglobin (HbA1-c) readings rise linearly across GGT quartiles. [Shankar]

What is the impact of high normal GGT on the probability of developing type 2 diabetes?

In a meta-analysis of 10 studies, Fraser determined that GGT in the top quartile heightened the risk of T2DM 3-fold.

Ford and Thamer showed that men were 3 times more prone to diabetes in the 4th quintile of GGT, whereas women in the 5th GGT quintile had twice the risk of peers in the 1st through 3rd quintiles.

Sato reported that nondrinkers in the 3rd GGT tertile were twice as likely to become diabetic as those in the first 2 tertiles.

The link between high normal GGT and type 2 diabetes is also shown in 8 other investigations. [Kim, Lee and Gross, Nakanishi, Nguyen, Sabanayagam, Shankar, Simó, Wen]

What other evidence links high normal GGT to circulatory disease?

Many investigators have shown that high normal and elevated uric acid (UA) is a powerful predictor of diabetes, metabolic syndrome, coronary disease, CVD mortality and all-cause mortality. [Baker, Fang, Jee, Kodama, Milionis, Obermayr, Santos] Because we do not screen applicants with uric acid, it is highly significant that UA levels rise progressively within GGT's normal range. [Lee, Ryu]

In a 52-country study, apolipoprotein B was superior to all other lipid markers as a risk factor for heart attacks, and APO B elevation doubles the risk of CAD mortality. [McQueen, Sierra-Johnson] Perlemuter showed that GGT correlates independently and positively with APO B.

Men with GGT readings in the 4th quartile have more than 4 times the risk of peripheral arterial disease (PAD) as those in the lowest quartile. [Shankar and Li]

Poelzl found *"a stepwise increase in GGT levels according to decreased categories of LVEF"* (left ventricular ejection fraction) and a close correlation between GGT and NT-proBNP.

In patients screened for obstructive sleep apnea with polysomnography, apnea-hypopnea index score increases paralleled rising GGT within the normal range. [Kanbay]

Two studies pinpoint an inverse relationship between GGT and physical activity. Both male and female subjects with lesser degrees of activity had higher GGT readings within the normal range. [Lawlor, Meisinger]

In a cohort of 13,188 adults of all ages, those with GGT readings in the 4th quartile had a more than 40% increased likelihood of developing chronic kidney disease, as compared to peers with GGT readings below the midpoint. [Targher]

Through all of these mechanisms, high normal GGT is confirmed as a powerful predictor of circulatory disease.

Have there been studies directly correlating GGT with coronary artery disease?

Yes.

Khan found that subjects age 45 and younger with high normal GGT had a significantly increased probability of angiographic CAD.

In the Framingham Offspring Study, Lee and Evans showed a direct correlation between GGT and the development of CAD after 20 years' follow up:

GGT	% Developing CAD
Male 1-11; Female 1-6	10.5%
Male 12-16; Female 7-9	12.1%
Male 17-24; Female 10-13	16.7%
Male > 24; Female > 13	23.8%

Ruttmann followed 163,944 adults for 17 years. They found this association between fatal cardiac events in males:

GGT	Relative Risk of Fatal Events
< 14	1.00
14 – 27	1.17
28 – 41	1.28
42 – 55	1.39
≥ 55	1.64

Two additional studies demonstrate a similarly strong connection between high normal GGT and CAD. [Fraser and Harris, Meisinger and Döring]

Is GGT a marker for increased risk of NAFLD (nonalcoholic fatty liver disease)?

Yes.

In one study, this risk increased from 22% in subjects with GGT readings between 2 and 20 to 38% when GGT was between 27 and 35. [Kim]

High normal GGT also correlates with the presence of hepatitis C antibodies, with a 5-fold higher probability in the top GGT quartile. [Targher]

Does GGT have to be elevated to reflect excessive alcohol consumption and its consequences?

No.

Brenner looked at a large group of male workers, ages 25 to 64:

Admitted Daily Alcohol Intake	Mean GGT
None	14.4
1 – 49 grams	18.9
50 – 99 grams	28.8
≥ 100 grams	39.6

Of those consuming at least 100 grams (approximately 8 drinks), 63% had GGT readings within the normal range.

Five other investigators documented a progressive rise in GGT, within the normal range, despite consuming as many as 9 or more alcoholic drinks per day. [Breitling, Nyström, Stranges and Freudenheim, Tsuboya, Whitehead]

Daeppen showed that high normal GGT is associated with a greater risk of bingeing.

Blasco reported a mean GGT of 40 in clinically alcoholic patients averaging 10 or more drinks daily.

Conigrave discovered that subjects with GGT in the top 2 quintiles had more than 50% more alcohol-related illnesses than the other 60% of subjects.

Is there any association between GGT and cancer?

Yes.

Strasak and Rapp reported that GGT readings in the top 20% correlated with a significantly increased cancer risk and that the association between cancer and GGT showed a clear dose-response relationship.

In an epidemiological investigation, Tsuboya and coworkers discovered a linear increase in cancer risk by GGT quartile:

GGT Quartile	Relative Cancer Risk
1	1.00
2	1.21
3	1.45
4	1.62

Three other studies document a significant relationship between GGT and specific malignant neoplasms. [Hu and Tuomilehto, Strasak and Goebel, Van Hemelriick]

Is there robust evidence that GGT within the normal range is a marker for increased all-cause mortality?

Yes.

There are at least 8 investigations documenting this association. [Brenner, Karlson, Kazemi-Shirazi, Lee and Evans, Ruhl, Stojakovic, Strasak, Wannamethee and Ebrahim]

For example, Stojakovic found this relationship between GGT and all-cause mortality after following subjects for almost 8 years:

GGT Quartile	Relative Mortality Risk
1	1.0
2	1.2
3	1.4
4	1.9

In the aforementioned assessment of male workers ages 25-64, followed for 6 years: [Brenner]

GGT Range	Relative Mortality Risk
< 15	1.00
15 – 19	1.46
20 – 29	1.78
30 – 49	2.09
≥ 50	3.44

Extensive evidence proves that high normal GGT readings are a powerful predictor of chronic disease and excess mortality.

Alkaline Phosphatase (AP)

How often is alkaline phosphatase elevated or below normal in insurance applicants?

Compared to other liver-related tests, alkaline phosphatase is less frequently outside the reference range.

Based on recent ExamOne data, 0.59% of tests are below the normal range and 1.82% of AP test results are elevated. [Sears; personal communication]

What are the more prevalent causes of low alkaline phosphatase? [Williamson]

- Hypothyroidism
- Vitamin B-12 deficiency and pernicious anemia
- Celiac disease
- Malnutrition

What are the two main mechanisms accounting for most high normal and elevated levels?

- Hepatobiliary disease
- Bone disorders

Do AP readings within the normal range correlate with increased risks of diabetes and cardiovascular disease?

Yes.

Abramowitz found the following association between AP and the likelihood of both conditions:

AP	% with DM	% with CVD
< 67	5.1%	5.3%
67 – 82	8.1%	8.3%
83 – 103	9.7%	9.4%
> 103	11.4%	10.3%

Cheung reported similar results by quartile of AP.

Is there any association between AP levels and cognitive function in elders?

Yes.

Kellett showed that AP is higher in persons with mild cognitive impairment, the primary precursor of dementia. There was a strongly inverse association between AP readings and cognitive function scores.

How does AP relate to excess mortality?

Abramowitz followed 10,743 subjects, mean age 51, for nearly 7 years. Among those who had no other liver-related findings and no history of hepatobiliary disease, high normal AP was a marker for greater all-cause mortality:

AP Quartile	Relative Mortality Risk
1	1.00
2	1.02
3	1.25
4	1.52

Three additional studies link minimally elevated AP – at levels we would not typically rate as isolated findings – with increased all-cause and especially liver-related mortality. [Fleming, McLernon, Pinkham]

Low, high normal and modestly elevated alkaline phosphatase readings have significant insurability implications.

Total Bilirubin (TB)

How often is total bilirubin elevated or below normal in insurance applicants?

In males, 5.06% are 0.3 or lower and 2.96% are ≥ 1.6. In females, 17.88% are ≤ 0.3 and 2.33% are 1.3 or higher. [Sears, personal communication]

Because bilirubin is reported as the sum of the direct (conjugated) and indirect (unconjugated) fractions for underwriting purposes, we will confine this review to total bilirubin (TB).

How has the perception of bilirubin changed in a clinical setting?

> *"Bilirubin, once considered simply the metabolic end product of heme degradation, has emerged as a potential endogenous inhibitor of atherosclerosis."*
>
> Todd S. Perlstein MD, et al.
> Harvard Medical School
> *Arteriosclerosis, Thrombosis and Vascular Biology*
> 28(2008):166

What are the pathophysiologic mechanisms by which relatively higher bilirubin levels are thought to lower disease risk?

- It is a potent antioxidant, more efficient in squelching free radicals than vitamins C and E. It also suppresses oxidation of lipids, which is the process by which they are made atherogenic. [Ajja, Djoussé, Sedlak, Yesilova]
- It inhibits endothelial dysfunction inflammation and thrombus formation. [Perlstein]
- It is inversely correlated with CRP levels. [Perlstein, Tapan]
- Bilirubin ≥ 1.1 lowers the risk of hypertension by 29%, as compared to readings < 1.1. [Chin]

Is there an association between bilirubin and the metabolic syndrome?

Yes, and that association is inverse (lower bilirubin equates to greater risk). [Giral, Kwon]

In a cohort of female subjects, Kwon found that the risk of developing this syndrome decreased by quartile of bilirubin:

Quartile	% Developing Metabolic Syndrome
1	48%
2	42%
3	34%
4	33%

Is low bilirubin also a risk factor for type 2 diabetes?

Yes, as shown in 4 studies. [Cheriyath, Han and Na, Inoguchi, Ohnaka]

Cheriyath and Srouji looked at the risk of T2DM and found that 9.8% of subjects with

bilirubin < 0.64 became diabetic, as compared to 6.98% with higher bilirubin readings.

How significant is the impact of low bilirubin on the risk of cardiovascular disease?

"Many studies have reported that low serum bilirubin concentrations are associated with an increased risk of coronary heart disease (CHD) events. The strength of the association was similar to that of smoking, elevated systolic blood pressure, and low levels of high-density lipoprotein (HDL) cholesterol."

Jing-Ping Lin MD, PHD, et al.
National Institutes of Health
Circulation
114(2006):1476

Troughton found the following relationship between bilirubin levels and coronary disease:

Bilirubin	Observed Risk
< 0.4	1.00
0.4 – 0.49	0.60
0.5 – 0.59	0.36
0.6 – 0.81	0.57
> 0.81	0.55

While the risk is U-shaped, TB< 0.4 correlates with a greater CAD risk as compared to higher levels. Similar findings emerged from the Framingham Study. [Djoussé]

Hopkins found a 60-90% reduction in early onset CAD in subjects in the top 3 bilirubin quintiles as compared to those with lower readings.

Which other associations have been established between low bilirubin and cardiovascular risk?

Tanaka found that TB levels were inverse to the likelihood of high coronary artery calcium (CAC) scores in both genders.

Three studies correlate lower bilirubin levels with greater risk of peripheral arterial disease in middle-aged and older subjects. [Krijgsman, Perlstein, Rantner]

Perlstein and Pande reported that the risk of stroke was 42% lower in the 3rd tertile and 24% lower in the 2nd tertile, as compared to the 1st tertile of TB.

Kimm demonstrated a similar relationship between TB levels and stroke risk.

Shin showed that bilirubin was inversely associated with 24-hour urinary protein levels, whereas eGFR was progressively higher as bilirubin readings increased.

Does low bilirubin have a significant association with any other diseases?

Yes.

When Horsfall followed more than 500,000 UK subjects, mean age 54, for a median of 8 years, he found that the incidence of new COPD diagnoses declined steeply with increasing bilirubin levels. The risk at readings < 0.34 was 2.5-fold greater than when bilirubin was 1.11 or higher.

Low normal bilirubin is also related to the risk of cancer.

Wei showed a 56% lower malignancy risk in the highest quartile of bilirubin. Horsfall and Zucker both reported similar findings implicating low and below normal bilirubin with a greater likelihood of cancer.

What is the association between low bilirubin and all-cause mortality?

Ajja observed 1279 subjects, average age 52, for a period of 17 years:

Bilirubin Quartile	Relative All-Cause Mortality
1	1.00
2	0.86
3	0.86
4	0.73

Temme tracked 10,502 individuals between ages 25 and 74 for 10 years, finding a similar relationship.

Three additional investigations confirm this association. [Han, Horsfall, Wei and Schwertner]

Is elevated bilirubin – in the absence of evidence of hepatobiliary disease – a favorable prognostic factor?

Yes.

Wei and Schwertner followed 17,322 men free of liver disease for 11 years:

Bilirubin	Relative Mortality Risk
< 0.5	1.00
0.5 – 1.0	0.68
1.1 – 1.4	0.64
> 1.4	0.24

When Pinkham and Krause (Swiss Re) examined the association between total bilirubin and mortality in life insurance applicants, they found no excess risk even when bilirubin was > 3.2

It is likely that primary care physicians are largely unaware of the associations between bilirubin and disease risk outside of the context of liver disease.

Nevertheless, it is clear that low/low normal levels substantially increase risk, whereas higher readings (including elevated bilirubin) are somewhat protective against chronic disease and mortality.

Serum Albumin

When is serum albumin an issue in underwriting?

Both abnormally low and low normal are significant. Elevated albumin, on the other hand, is virtually always due to dehydration. [Williamson]

What are the 5 main pathological factors linked to low normal and below normal serum albumin? [Shah, Williamson]

- Nutritional deficiencies
- Decreased or ineffective protein synthesis
- Decreased functional liver capacity
- Greater oxidative stress
- Increased inflammation

Is there an association between low normal serum albumin and cardiovascular risk?

Yes.

Djoussé and Rothman followed 4506 subjects, mean age 38, for 22 years:

Relative Risk of Heart Attack		
Albumin Quartile	**Men**	**Women**
1	1.49	2.12
2	1.25	1.79
3	1.00	1.00

Nelson showed a 60% greater risk of CV events in men with serum albumin in the lowest quartile.

Gupta documented a linear inverse relationship between serum albumin and risk of heart failure.

Which major geriatric risk domains are strongly impacted by serum albumin?

It has an imposing relationship with premature frailty and physical disability.

Le Couteur evaluated 1673 elders, mean age 76, to assess the connection between serum albumin and frailty:

Frailty Status	Mean Serum Albumin
Robust	44.3
Prefrail	43.8
Frail	42.6

Despite the fact that these readings are relatively close to one another, the findings reported here were highly significant on a statistical basis ($p < 0.001$).

Okamura showed that the risk of impaired Activities of Daily Living (ADLs) was substantially higher when serum albumin was < 45 in men and < 40 in women.

Landi found that women with abnormally low mid-arm circumference had lower serum albumin, and this was linked to ADL and IADL disability as well was slower walking speed.

Is low serum albumin a marker for excess mortality?

Yes, in virtually every study.

Corti found a graded increase in mortality from low normal to progressively lower readings.

An Austrian study encompassing 285,930 subjects, mean age 50, revealed the following association between deciles of serum albumin and all-cause mortality. [Grimm]

Serum Albumin Decile	Relative Mortality Risk Ratio
1	2.98
2	2.21
3	1.77
4	1.57
5	1.47
6	1.36
7	1.22
8	1.08
9	1.05
10	1.00

Here we see that mortality increases progressively as serum albumin declines, and it

is already 22% higher in the 7th decile, as compared to subjects with the top 10% of readings.

Grimm and his associates concluded that serum albumin is *"…a very sensitive prognostic marker for an increased risk of death."*

In the Cardiovascular Health Study of persons age 65 and over, relative 5-year mortality was substantially influenced by serum albumin. [Fried]

Serum Albumin	Relative 5-Year Mortality Risk
< 37	1.00
38 – 38	0.71
39 – 40	0.83
41 – 42	0.63
> 42	0.54

Singer calculated mortality ratios for serum albumin based on the British Regional Heart Study and reported his findings in the *Journal of Insurance Medicine.*

Serum Albumin	Mortality
30 – 39.9	220%
40 – 41.9	126%
42 – 43.9	124%
44 – 45.9	95%

Carriere followed 60-year old subjects for 9 years and compared average serum albumin levels in those who died to those in survivors:

Mean Serum Albumin		
	Men	Women
Alive	42.3	41.1
Dead	40.4	39.8

Four more investigations support these findings. [Darne, Le Counteur, Reuben, Sullivan]

Serum albumin is a powerful mortality marker, and even seemingly modest diminutions within the normal range exert a significant risk impact in late middle-aged and elderly applicants.

Blood Glucose

Which significant conditions are linked to low levels of blood glucose? [Williamson]

- Malnutrition
- Alcohol abuse/dependency
- Diffuse liver disease
- Various cancers

Fasting hypoglycemia should always be regarded as a **RED FLAG** and fully evaluated clinically.

Which specific risk considerations have been linked to lower glucose levels within the normal range?

- NAFLD [Rhee]
- Hyperuricemia [Obermayr]
- Left ventricular hypertrophy [Patel]

What is the association between fasting glucose within the normal range and the risk of cardiovascular disease?

Investigators at Kaiser-Permanente followed 46,578 plan participants, average age 56, for 7 years. [Nichols]

Fasting Glucose	% Developing CV Disease
< 86	9.7%
85 – 89	8.3%
90 – 94	11.9%
95 – 99	11.7%

Iribarren found that patients manifesting early-onset CAD had significantly higher mean fasting glucose readings (99) than those who did not develop coronary disease (88).

Is there excess mortality linked to low normal fasting glucose?

Yes.

Wei and Gibbons observed 40,069 healthy individuals, mean age 43, for 8 years. After excluding all subjects under age 50:

Fasting Glucose	Relative Mortality Risk
≥ 80	1.0
70 – 79	1.9
< 70	3.2

Impaired Fasting Glucose (IFG)

> *"Epidemiologic evidence suggests that the relationship between diabetes and cardiovascular disease begins earlier in the progression from normal glucose tolerance to impaired glucose tolerance and impaired fasting glucose to diabetes."*
>
> Prakash C Deedwania MD and Vivian A. Fonseca MD
> University of California-San Francisco Medical School
> *The American Journal of Medicine*
> 118(2005):939

What is impaired fasting glucose (IFG)?

The American Diabetic Association defines IFG as fasting glucose between 100 and 125.

Are there specific CV risk factors linked to IFG, as compared to patients with normal fasting blood sugar?

Yes.

- Abnormal ECG findings [Sui]
- Later onset of metabolic syndrome [Abdul-Ghani, Sui]
- Future need for antihypertensive Rx [Yeboah]
- Abdominal obesity [Chowdhury, Faech]
- Elevated cystatin C kidney disease marker [Donahue]
- Elevated CRP [Rekeneire]

In addition, IFG is associated with a 3.5-fold increased risk of chronic hepatitis C. [Mavrogiannaki] Many of these cases will have normal liver enzymes and not be identified during the underwriting process.

What is the nature of the correlation between IFG and circulatory disease?

In a review of 17 studies, Ford and Zhao found an aggregate 20% increased relative risk of adverse CV outcomes in subjects with IFG, as compared to normal blood glucose levels.

Sui showed that IFG raised the risk of stroke 32% over a 19-year period in 43,933 male subjects.

Yeboah reported that IFG, as compared to normal fasting glucose, increased the probability of angina 95% and the risk of coronary events by 41%

Is IFG also a marker for excess mortality?

Yes.

Barr showed that IFG heightened the mortality risk 60% when contrasted to fasting normoglycemia.

This risk was 71% higher in another study. [Rijkelijkhuizer]
In the Framingham Study, mortality in males age 60 and over with IFG was nearly as high as in subjects with a diagnosis of type 2 diabetes. [Port]

Low normal, high normal and modestly elevated (IFG) fasting blood glucose all have strong links to excess disease risk and greater mortality.

Lipids

Low Total Cholesterol (TC)

"…physicians may want to regard very low levels of cholesterol as potential warning signs of occult disease or signals of rapidly-declining health."

Sonia Brescianni MD, et al.
National Research Council on Aging (Italy)
Journal of the American Geriatric Society
51(2003):991

What adversities have been linked to lower levels of total cholesterol within the normal range?

In elderly subjects, Tuikkala showed the following correlations:

Total Cholesterol			
	< 193	**193 – 228**	**>228**
Mean MMSE Cognitive Score*	23.3	25.3	25.4
Diabetes Mellitus	26%	20%	13%
Atrial Fibrillation	27%	15%	8%
COPD	18%	11%	9%
Self-Reported "Poor Health"	22%	19%	15%

* The lower the MMSE score, the higher the risk of dementia

Wannamethee found these associations in late middle-aged males:

Total Cholesterol			
	< 185	**185 – 228**	**229 – 274**
Anemic	13%	7%	4%
BMI < 20	10%	5%	2%
Mean Serum Albumin	43.1	44.1	44.7

Volpato reported that the risk of diabetes was 24% when TC was 160 or lower, as compared to 16% when TC was between 161 and 239.

NT-proBNP is inverse to TC level. [deFilippi, Wannamethee and Welsh]

In 2975 subjects, mean age 73, deFilippi documented this statistically significantly relationship between total cholesterol and NT-proBNP:

NT-proBNP Quintile	Mean TC
1	215
2	216
3	213
4	209
5	206

The likelihood of weight loss in the elderly decreases by increasing TC quartile. [Brescianni]

The risk of CAD onset and events in the elderly has a U-shaped relationship with cholesterol. [Curb]

Total Cholesterol	Relative Risk
< 160	1.5
160 – 179	1.1
180 – 219	1.0
220 – 239	1.7
> 239	1.9

TC < 178 is associated with a 2.7-fold greater risk of hemorrhagic stroke at ages 65 and over. [Iribarren and Jacobs]

Is low cholesterol related to the risk of frailty in elders?

Yes.

Le Couteur showed that the mean TC in robust septuagenarians was 180, as compared to 174 and 164 in those who were deemed pre-frail or overtly frail.

In the Italian Longitudinal Study on Aging, there was a strong relationship between TC and likelihood of ADL disability. [Brescianni]

TC Quartile	% ADL Disability
1	34%
2	27%
3	21%
4	20%

When Schalk considered cholesterol and albumin together, there was a 2-fold greater likelihood of ADL disability in both genders when TC was < 200 and serum albumin was < 43.

What is the association between TC and cancer?

Iso evaluated the risk of cancers in 33,368 subjects followed for 12 years, showing that men with TC < 160 were 24-29% more likely to develop a malignancy than peers with higher readings.

In the ABTC Study: [Ahn]

TC Quartile	Cancer Risk
1	1.00
2	0.92
3	0.89
4	0.89
5	0.86

Two other studies further underscore this relationship. [DiAgostino, Rywik]

Is there a strong relationship between cholesterol and mortality?

Yes.

This issue has been well studied from various perspectives.

In a 46-year follow up of 3277 healthy males, Hvttinen observed that *"…a graded highly significant association was seen between both total mortality and cholesterol…"*

A 15-year assessment of the link between cholesterol and mortality in more than 65,000 men yielded the following findings by age group: [Ulmer]

Relative Mortality Risk			
	Age Group		
Total Cholesterol	**20 – 49**	**50 – 64**	**≥ 65**
< 187	1.28	1.28	1.26
187 – 248	1.00	1.00	1.00
> 248	1.24	1.04	1.01

The risk is U-shaped under age 50 and then associated solely with lower cholesterol in older subjects.

In the Peoples Gas Company Study and the Chicago Heart Association Study, both of which followed young males through mid-life, all-cause mortality was significantly greater when cholesterol was < 160. [Stamler]

In an evaluation that followed middle-aged subjects at baseline for 23 years, TC < 180 showed a 23% higher mortality than readings between 180 and 239. [Iribarren and Reed]

Is the mortality associated with cholesterol in the elderly mainly related to with low normal and below normal readings?

Yes.

For example, in the Cardiovascular Health Study: [Psaty]

Total Cholesterol	Mortality Rate/1000 Person-Years
< 160	37
160 – 199	26
200 – 239	22
> 239	23

After 7 years follow up, Hu showed that TC < 169 conferred a 1.9-fold increased mortality risk in elders, as compared to those with higher readings.

When total cholesterol and serum albumin were considered together in terms of 7-year mortality at ages 70-79, Reuben and Ix found this mortality association:

	Relative Mortality Risk
Both Tests Normal	1.0
Cholesterol Below Normal	2.1
Both Tests Below Normal	3.5

There are 5 more investigations that support the relationship between both below normal and low normal cholesterol, and all-cause mortality in elders. [Brescianni, Carriere, Palma, Petersen, Schupf]

The risk implications of below normal, low normal and borderline elevated total cholesterol at all ages, and especially in the elderly, are convincingly documented in the medical literature

High-Density Lipoprotein Cholesterol (HDL-C)

In what ways is low HDL-C linked to extra risk?

It is one of the 5 criteria for the metabolic syndrome and a major risk factor for circulatory disease. It is also associated with chronic liver disease, impaired nutrition, lack of exercise and cigarette smoking. [Williamson]

Which key CV risk factors are associated with HDL-C readings that are within the low normal range?

Oxidized LDL-C is the portion of total LDL-C associated with atherosclerosis. Holvoet found this relationship between oxidized LDL-C and HDL-C.

Oxidized LDL-C Quintile	Mean HDL-C
1	57
2	54
3	54
4	51
5	49

There is also a strong correlation between low normal HDL-C and HbA1-c in non-diabetics free of known CV disease. [de Goma, Rubin, Selvin]

Selvin reported these findings in 11,092 subjects:

HbA1-c	Mean HDL-C
5.0 – < 5.5	53
5.5 – < 6.0	50
6.0 – < 6.5	47
≥ 6.5	44

HDL-C has been shown to be inverse to uric acid readings in 4 studies. [Hu, Obermayr, O'Reilly, Zoppini]

Obermeyr's data demonstrate this link between HDL-C and uric acid:

Uric Acid	Mean HDL-C
< 7	62
7 – 9	51
> 9	48

In what we consider the finest clinical laboratory test handbook, the threshold at which HDL-C is considered an adverse CV risk factor is < 40.

Nevertheless, these studies show that an applicant with an HDL-C of 44 would be at high risk for major elevations of oxidized LDL-C and uric acid, as well as for having glycosylated hemoglobin at or near the threshold for a diagnosis of type 2 diabetes.

Is low normal HDL-C predictive of CV disease?

Yes.

Blankstein followed 2263 subjects, mean age 65, for 8 years. All were healthy and free of known CAD at baseline:

Developed CAD	Mean HDL-C
Yes	50.1
No	54.1

This difference, while appearing modest, was highly significant ($p < 0.001$).

A similar relationship between CAD and HDL-C was revealed in 3 other studies.

[Harchaoui, Iribarren, Kotecha]

In a study of patients age 65 and older, Volpato and Ble documented these relationships between low normal HDL-C and a range of findings associated with high risk of CAD:

	HDL-C Tertile		
	1	**2**	**3**
Peripheral Arterial Disease	17%	14%	9%
Diabetes Mellitus	14%	11%	9%
Waist Circumference	95.9	93.4	88.8
CRP (mg/dL)	3.21	2.34	1.83
IL-6* (pg/mL)	1.55	1.16	1.09

* Interleukin 6 (IL-6) is one of the main markers of inflammation

Low normal HDL-C is also associated with high levels of both NT-proBNP and cystatin C. [Wannamethee and Welsh, Wu]

Is low normal HDL-C a marker for excess coronary disease mortality?

Reflecting on 61 studies encompassing 900,000 adults of all ages, experts directing the Prospective Studies Collaboration concluded that *"…there was a strong negative (i.e., inverse) association with IHD [ischemic heart disease] mortality in every age group, with no evidence of a threshold."*

Two more studies concur with this assessment. [Barter, Haier]

What is the nature of the relationship between low normal HDL-C and anemia in elders?

Low normal readings correlate with a 50% greater risk of significant anemia, as reflected in this analysis of 4188 subjects, ages 65 and over: [de Goma]

HDL-C Quartile	% with Hemoglobin < 10
1	16%
2	9%
3	10%
4	10%

This degree of anemia has protean mortality and morbidity implications in the elderly.

Is low normal HDL-C a marker for higher mortality?

Absolutely.

Stensvold tracked 47,115 subjects, ages 40 to 54, over 7 years. Mortality was consistently inverse to HDL-C at readings of 57 and under.

In another investigation, mortality was 37% higher when HDL-C was 43 to 51, as compared to 62 and higher. [Upmeier]

The mortality implications of low normal HDL-C even affect octogenarians in a variety of ways: [Landi and Russo]

- Mean HDL-C in male survivors was 43.4 as compared to 36.7 in those who died over the course of the study.
- In women, the readings were 49.3 and 42.2, respectively.
- Overall mortality was markedly higher in the 1st tertile of HDL-C.
- Average ADL disability score was 3 times higher in the 1st tertile.
- Cognitive scores were lowest in the 1st tertile.

Do we have data corroborating the relationship between high HDL-C and heavy drinking?

Yes.

The first illustrates the linear correlation between admitted weekly alcohol intake and HDL-C. There were 5769 persons, ages 35 to 75, in this assessment. They were asked about alcohol use and their answers were matched to their HDL-C levels: [Foerster]

Drinks per Week	Mean HDL-C
0	61
1–6	63
7–13	64
14–20	67
21–27	68
28–34	71
≥ 35	73

The second reveals a J-shaped association between HDL-C and likelihood of being diagnosed with an alcohol use disorder. This study was limited to subjects age 65 and over: [de Goma]

HDL-C Quartile	% Alcohol Abuse/ Dependency
1	14%
2	11%
3	11%
4	26%

HDL-C in the low normal range is associated with many CV risk factors we do not routinely assess, and it correlates with excess mortality.

High normal and elevated HDL-C correlated with higher levels of alcohol intake as well as increased risk of alcohol abuse and dependency.

Triglycerides

Does it matter whether triglycerides are reported on a fasting basis?

The notion that only fasting triglycerides should be considered in the context of circulatory disease risk is little more than an "old wives' tale"!

Many investigators have provided evidence that postprandial readings are *at least* as significant. [Bansol, Freiberg, Iso and Naito, Nordestgaard, Roche, Warnick]

What is generally considered the threshold for elevated triglycerides?

160 mg/dL in males and 143 in females. [Pagana]

Are high normal triglycerides a risk factor for the metabolic syndrome?

Yes.

For example, Hanley found that the mean reading in subjects who progressed to this diagnosis was 117, as compared to 93 in those who did not develop the metabolic syndrome.

Which other CV risk factors have been linked to high normal triglycerides readings?

The relationship between HDL-C and oxidized LDL-C is also found in triglycerides. The mean reading in the top quintile of highly atherogenic LDL-C was 116, as compared to 68 and 77 in the 1st and 2nd quintiles. [Holvoet]

There is also a linear association between elevated uric acid and high normal triglycerides. [Zoppini]

Insulin resistance is an essential step in the development of metabolic syndrome, nonalcoholic fatty liver disease and type 2 diabetes. Tenenbaum showed that the odds of insulin resistance were proportional to triglyceride levels within the normal range.

Selvin compared triglyceride readings and HbA1-c. The average reading in persons having glycosylated hemoglobin at the diabetic threshold (6.5%) was 139.

Two investigations have documented an increased likelihood of eventual type 2 diabetes in subjects with high normal triglycerides. [Akehi, Mykkänen]

A great deal of attention is now being focused on the association between low vitamin D and the risk of various chronic diseases. These associations are so consistently strong that many physicians recommend the use of supplements to patients with low blood levels of vitamin D.

Hutchinson discovered that patients in the lowest vitamin D quartile had a mean triglycerides reading of 147, as compared to 119 in the top quartile. They also reported a 30% increase in mortality for the 1st quintile.

Is there a connection between high normal triglycerides and circulatory disease events?

After reviewing the literature, we believe that triglycerides are every bit as relevant in this context as total cholesterol.

Onset of coronary disease events in midlife is a particularly unfavorable insurability scenario. Therefore, it is noteworthy that the mean triglycerides reading in subjects developing CAD by age 45 was 128, as compared to 93 in those who did not experience a CAD event or require coronary revascularization. [Iribarren]

High normal triglycerides were also shown to be associated with an increased risk of ischemic stroke after following 13,951 subjects for 33 years. [Varbo]

Are high normal triglycerides predictive of nonalcoholic fatty liver disease?

Yes.

Rhee found that the mean triglycerides level in patients developing NAFLD was 134, as compared to 101 in subjects who did not manifest this metabolic liver disorder.

How do high normal triglycerides relate to mortality?

In a 27-year follow up of 86,261 persons, ages 20 to 50 at study onset, there was a statistically significant link between high normal readings and mortality: [Lindman]

	Relative All-Cause Mortality Risk	
Triglycerides Quintile	**Men**	**Women**
1	1.00	1.00
2	0.95	1.15
3	1.04	1.34
4	1.12	1.48
5	1.28	1.87

Ho and Cannuday tracked 30,365 male subjects for 14 years and found this association:

Outcome	Mean Triglycerides Reading
Alive	113
Deceased; CV Disease	140
Deceased; All-Causes	129

Similar findings were reported in a 15-year follow up study of 24,535 middle-aged females. [Stensvold]

High normal triglycerides, whether fasting or postprandial, are consistently associated with greater risks of other cardiac risk factors, development of circulatory and metabolic disease, and excess mortality.

Kidney-Related Tests

Albuminuria

Is there a threshold level at which albuminuria becomes significant to mortality and morbidity risk?

No.

We found 5 investigations demonstrating that urinary albumin readings below the cutoff from microalbuminuria are significantly predictive of increased cardiovascular disease. [Cerasola, Danziger, Glassock, Polonsky, Solbu]

In addition, Hillege found that high normal albumin excretion correlated with a 1.8-fold greater risk of type 2 diabetes and a 20% increased likelihood of developing hypertension.

Does this association between "normal" quantities of urinary albumin influence mortality as well?

Yes.

Klausen showed that albuminuria within the normal range strongly predicted for coronary disease and all-cause mortality. This association was independent of age, gender, renal function, lipids and the presence of diabetes or hypertension.

In underwriting, our attention is focused on urinary albumin that is consistent with micro- and macroalbuminuria. Nevertheless, urinary albumin excretion below the threshold level for microalbuminuria confers increments of added risk for the development of major circulatory disease risk factors and excess mortality.

Blood Urea Nitrogen (BUN)

Is BUN within the high normal range of much value in risk assessment?

No.

BUN is readily increased by functional dehydration, so we defer to creatinine as the significant kidney-related screening blood test in this setting.

Is this also true for low and below normal BUN?

No, because these findings, while uncommon in a screening context, have major insurability implications: [Pagana, Williamson]

- Chronic liver disease
- Alcohol use disorders, especially alcoholism
- Malnutrition
- Malabsorption

Low, borderline low and steadily decreasing BUN are RED FLAGS, doubly so if there is any other reason to suspect liver disease or abusive drinking. They are also markers for frailty due to inadequate nutrition in the elderly.

Creatinine

What is the typical normal range for serum creatinine?

One leading reference handbook uses 1.1 in females and 1.2 in males. [Pagana] Another prominent source uses 1.2 and 1.3 respectively, and we have seen thresholds as high 1.5 in males. [Williamson]

Mean creatinine levels are generally lower at older ages.

Is high normal creatinine linked to significant CV risk factors not used in insurance screening?

Yes – uric acid and homocysteine.

Three studies show a relationship between high uric acid levels and high normal creatinine in healthy subjects. [Afzali, Hu, Tamariz]

Tamariz recently documented this association in 15,382 adults, ages 45-64:

Uric Acid Quartile	Mean Creatinine
1	0.98
2	1.06
3	1.14
4	1.25

Homocysteine is a powerful independent predictor of CV and all-cause mortality. [Blacher, Robinson, Vollset, Wald]

It is therefore significant to insurability risk that increased homocysteine levels are often found in subjects at creatinine levels within the reference range. [Refsum]

Is there a relationship between cystatin C and high normal creatinine?

Yes.

Cystatin C is superior to creatinine as a mortality marker, as we demonstrated in our white paper several years ago.

Wu measured cystatin C and creatinine in 2990 individuals with normal eGFR levels:

Cystatin C	Mean Creatinine
< 10th percentile	0.92
> 90th percentile	1.08

High normal creatinine has also been linked to increased risk of peripheral arterial disease. In one study, the average creatinine level in patients diagnosed with PAD was 1.09, versus 0.91 in those free of this disease. [Selvin and Köttgen]

What is sarcopenia?

It is excessive loss of skeletal muscle. Sarcopenia occurs mainly in the elderly (6-15%) and is strongly associated with slower gait speed, physical frailty and more frequent falls and fractures. [Chapman]

How do creatinine levels correlate with sarcopenia?

Creatinine is a byproduct of muscle metabolism. For this reason, sarcopenia leads to relatively lower creatinine levels. The net effect is that elderly persons often have high normal creatinine despite substantially impaired renal function.

This phenomenon is reflected in the association between high normal creatinine vs. readings < 0.9, and excess mortality in the Cardiovascular Health Study (subjects age 65 and over, followed for 5 years): [Fried]

Serum Creatinine	Relative Mortality Risk
< 0.9	1.00
0.9 – 1.1	1.68
1.1 – 1.2	1.60
1.2 – 1.5	2.55
> 1.5	5.77

Note that mortality is 68% higher when creatinine is well within the normal range and 2.55-fold greater with borderline/minimally elevated readings.

High normal serum creatinine is associated with cardiovascular risk factors. It is also a marker for chronic kidney disease in elderly individuals due to the effects of sarcopenia.

Estimated Glomerular Filtration Rate (eGFR)

How do eGFR readings relate to the stages of chronic kidney disease? [Tonelli]

eGFR	No Proteinuria	Proteinuria Present
≥ 90	Normal	Stage 1
60 – 89.9	Normal	Stage 2
30 – 59.9	Stage 3	Stage 3
15 – 29.9	Stage 4	Stage 4
<15	Stage 5	Stage 5

Based on these criteria, eGFR of 60 or greater in the absence of proteinuria or other evidence of chronic disease is considered a “normal” finding.

Does eGFR decline with age?

Yes.

The rate of decline is broadly estimated at 1% per year. [Graves]

Is low normal eGFR linked to any prominent mortality risk markers?

Yes, cystatin C and NT-proBNP.

Spanaus reported the following relationship between eGFR and cystatin C:

eGFR	Mean Cystatin C
≥ 90	0.91
60 – 89	1.26
30 – 59	2.06

Wu found that mean eGFR in the lowest cystatin C decile was 79.4, as compared to 68.8 in the top decile.

In a cohort of 2975 healthy community-dwelling subjects, mean age 73, there was a direct correlation between NT-proBNP and eGFR > 60. [deFilippi]

NT-proBNP Quintile	Mean eGFR
1	83.7
2	81.7
3	79.5
4	77.4
5	70.1

In a second study involving 3649 elderly males free of CV disease, mean eGFR in the top NT-proBNP quartile was 69.8. [Wannamethee and Welch]

These studies affirm that cystatin C and NT-proBNP correlate significantly with eGFR determinations deemed insignificant to insurability.

Do we have evidence that low normal eGFR relates directly to circulatory disease?

Yes.

In the Cardiovascular Health Study, mean eGFR was 71 in patients with an ankle-brachial index (ABI) diagnostic of peripheral arterial disease, as compared to 77 in subjects with a normal ABI. [Ix]

In 589 subjects referred for angiography, eGFR averaged 80.2 in those with proven obstructive coronary artery disease, versus 87.2 when significant CAD was not present. [Kotecha]

Does a similar relationship exist between low normal eGFR and increased mortality?

Yes.

In 4358 consecutive patients enrolled in a Cleveland Clinic preventive care program, there was higher mortality in subjects with eGFR < 79, as compared to participants whose eGFR was 79 or higher. [Shishehbor]

Another study with 14,971 subjects, ages 45 to 64, also showed excess all-cause mortality where eGFR was in the low normal range. [Astor]

eGFR	Deaths/1000 Person-Years
75 – 89	8.0
60 – 74	9.5

Low normal estimated glomerular filtration rate (eGFR) is associated with elevated NT-proBNP and cystatin C. It is also linked to atherosclerotic circulatory disease and excess mortality.

Section II: Physical Measurements

Body Mass Index (BMI)

What are the conventional BMI ranges and how do they correlate with weight status?

BMI	Weight Status
< 18.5	Underweight
18.5 – 24.9	Normal Weight
25 – 29.9	Overweight
30 – 34.9	Stage I Obesity
35 – 39.9	Stage II Obesity
≥ 40	Stage III/Morbid Obesity

Overweight

Which risk factors are associated with overweight at younger ages?

As compared to normal weight, overweight relates directly to increased risks of high blood pressure, hyperlipidemia, hyperuricemia and the metabolic syndrome. [Afzali, Hanley, Kannel, Suadicani]

Is GGT higher in overweight than in normal weight?

Yes. [Lawlor]

BMI	Mean GGT
15.3 – 24.2	25.8
24.3 – 26.9	26.2
27.0 – 30.3	30.2

High normal GGT and overweight combine to double the incidence of type 2 diabetes diagnoses. [Lim]

Is there higher mortality in overweight individuals?

Yes.

In one study, mortality was increased 40% in nonsmokers with a BMI between 27 and 30. [Seidell]

In another investigation, overweight conferred a 20% increase in mortality in nonsmoking subjects aged 18-39, followed for 16 years. [Ma]

Several other reports demonstrate that overweight is the threshold for CV and all-cause extra mortality in young and middle-aged persons. [Allison and Zhu, Padwal, Pischon, Yan]

Based on these findings, overweight will adversely impact multivariate risk scores, mainly at ages 50 and under.

Underweight

Does underweight exert an unfavorable impact on mortality across all age groups?

Yes. [Magnusson, Romero-Corral, Tice, Weitoft]

In a review of 40 studies encompassing over 250,000 adults of all ages, BMI < 20 correlated with 37% greater all-cause mortality. [Romero-Corral]

Tice reported 2.4-fold higher mortality among underweight subjects in a cohort of 17,748 postmenopausal women followed for 9 years.

At what threshold does lower BMI begin to confer increased mortality in elders?

There is some degree of added risk when BMI is < 25, and this becomes progressively greater at < 20 and < 18, respectively. [Mové, Østbye, Schooling, Sergi]

For example, when Sergi assessed 4-year mortality in 3110 persons age 65-84, the BMI 20-22 subset had 60% higher all-cause mortality. If BMI was > 20, the mortality escalated steeply to 2.9-fold increased.

Is class I obesity associated with reduced survival rates in elders?

No.

It has been repeatedly shown that less severe degrees of obesity in older individuals are associated with relatively favorable mortality. [Bender, Grabowski, Stevens]

In an assessment of 1673 subjects, mean age 76, underweight doubled mortality (as compared to normal weight), whereas overweight and obese subjects had 50% lower mortality than normal weight study participants. [Le Couteur]

Mazza followed 3282 persons, ages 65 and older, and found that cancer mortality was inverse of BMI:

BMI	Relative Risk of Cancer Death
< 22.8	1.63
25.2 – 27.1	1.00
> 29.9	0.91

How does BMI affect other aspects of geriatric risk?

Cognitive dysfunction and walking speed are both inverse to BMI. [Cattin, Newman]

The risks of pre-frailty and frailty are steeply U-shaped in relation to BMI in elders. [Blaum]

BMI Range	Relative Risk	
	Pre-Frailty	Frailty
18.5 – 19.9	1.94	2.26
20.0 – 24.9	1.00	1.00
25.0 – 29.9	0.48	1.25
≥ 30	2.61	2.53

The same is true for the risk of functional limitations. [Freedman]

In addition, BMI < 20 heightens the probability of sustaining a hip fracture 2.5-fold, as compared to BMI of 25. [De Laet]

Overweight young and middle-aged applicants have a greater likelihood of adverse cardiovascular risk factors as well as some degree of increased mortality.

Underweight confers an adverse impact on mortality at all adult ages, and additional significant risks in the elderly.

Resting Heart Rate (Pulse)

"Heart rate is a pivotal variable that is precisely regulated in health but disrupted in disease. Elevated heart rates can influence the development of cardiovascular disease through a multitude of actions that can be classified both as long-term and acute effects."

Richard L. Verrier, PhD and Alex Tan, MD
Beth Deaconess Medical Center at Harvard University
Heart Rhythm
6, Supplement 2(2009):S68

This segment of our review of the risk implications of "normal" findings is especially important because underwriters seldom pay much attention to the applicant's resting heart rate (pulse) except in 4 specific contexts:

- Marked bradycardia (< 50 beats per minute)
- Tachycardia (100+ beats per minute)
- Extrasystoles reported
- Heart rate decrease with exercise

What are the mechanisms by which resting heart rate in the high normal range impacts risk?

- As a marker of sympathetic nervous system overactivity it has been implicated in the development of hypertension and diabetes. [Ho]
- It contributes to imbalance between oxygen supply and demand. [Tardif]
- It is a template for arrhythmia induction. [Verrier]

What is the association between resting heart rate and CV risk factors?

Nauman found that resting heart rates ≥ 70 directly correlated with the following mortality risk factors:

- Current cigarette smoking
- Less formal education
- Sedentary lifestyle
- Alcohol use abstinence

Julius divided subjects into quintiles of resting heart rate and demonstrated that high normal pulse rates predisposed to greater incidences of major risk factors:

	Heart Rate Quintiles				
	1	**2**	**3**	**4**	**5**
Mean HR (beats per minute)	**56**	**63**	**68**	**74**	**85**
Diabetes	19%	25%	30%	36%	45%
Elevated Cholesterol	28%	30%	34%	36%	38%
Urinary Protein	18%	22%	22%	24%	27%

Gupta and Okin both showed that the risk of heart failure increases substantially when one's rest heart rate is ≥84.

What is the relationship between resting heart rate and mortality?

It is best characterized as J-shaped, with excess risk when the pulse rate is < 50 or > 70. Overall, the most favorable mortality outcomes occur when the resting pulse is between 60 and 70 beats per minute. [Bangalore]

In 29,325 men, mean age 52 and followed for 12 years, Nauman reported the following data:

Resting HR	All-Cause Mortality	CV Mortality
< 70	1.0	1.0
70 – 85	1.2	0.9
> 85	1.5	1.9

Cooney and Tice reported similar findings in large studies over follow up intervals of 12 years and 9 years, respectively.

In an assessment of 15,193 patients on antihypertensive therapy, Julius found a strong correlation between quintiles of resting heart rate and relative risks of various undesirable 5-year events:

Heart Rate Quintile	Heart Attack	Stroke	All-Cause Mortality	Sudden Death
1	1.00	1.00	1.00	1.00
2	0.94	1.15	1.10	1.02
3	1.19	1.41	1.18	1.04
4	1.20	1.73	1.45	1.28
5	1.40	1.49	2.00	1.48

Legeai followed 9294 community-dwelling persons age 65 and over for 6 years and reported all-cause mortality by pulse rate quintiles:

Quintile	Beats per Minute	Relative All-Cause Mortality Risk
1	< 62	1.00
2	62 – 67	1.00
3	68 – 72	1.29
4	73 – 79	1.11
5	> 79	1.85

There is considerable evidence that high normal resting heart rates are harbingers of greater cardiovascular risk as well as higher likelihood of circulatory events and mortality.

Blood Pressure

Prehypertension

"The continuous relations of rising BP with increasing cardiovascular risk have been demonstrated consistently… Furthermore, these investigations have highlighted the lack of a distinct threshold at which risk escalates: the greater vascular risk with higher BP is evident for levels down to at least 115/75 mmHg."

Kayalar Atilla, MD, et al.
Boston University School of Medicine
Expert Reviews in Cardiovascular Therapy
4(2006):111

"Prehypertension is associated with subclinical vascular disease, including both microvascular and macrovascular pathology."

Eduardo Pimenta, MD, et al.
University of Queensland Medical School
Nature Reviews Nephrology
6(2010):21

What is prehypertension?

By convention, it is defined as systolic BP 120-139 or diastolic BP 80-89.

This concept was added to guidelines for blood pressure management in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. [Chobanian]

Is prehypertension considered a candidate for antihypertensive Rx?

Yes.

The benefits of treating prehypertension have been documented in several clinical trials. [Chalmers, Gaede, Nissen] Nevertheless, it is likely that nearly all applicants with prehypertension will not be taking blood pressure medication.

Which risk factors for cardiovascular disease and all-cause mortality have been linked to prehypertension?

- Chronic inflammation [Chrysohoou]

- Elevated homocysteine [Refsum]
- Elevated uric acid [Fang]
- Positive coronary artery calcium scores [Allison, Pletcher]
- Pathological echocardiographic findings in the left ventricle [Markus, Patel]
- Atrial fibrillation [Conen]
- Metabolic syndrome [Hanley]
- Type 2 diabetes [Zhang]
- Microvascular eye disease [Ikram]
- Early onset of overt high blood pressure [Gray]

Is prehypertension an independent risk factor for circulatory disease events?

Yes, even after adjustment for all other risk factors. [Atilla, Hanse, Hsia, Vasan]

Allen followed 61,585 subjects, age 55 and older, for 10 years and found that the adjusted risk for onset of CAD was significantly higher in prehypertensive individuals, as compared to those with lower blood pressure levels.

What is the relationship between high normal blood pressure and mortality?

In an assessment of more than 1.2 million subjects spanning 24 years, Sundström showed that systolic BP has a U-shaped association with mortality.

This U-shaped relationship is clearly shown in a 35-country study of 20,330 persons age 50 and over, followed for 2.5 years: [Ovbiagele]

Systolic BP	% Deceased
< 120	9.2%
120 – 129	6.9%
130 – 139	5.8%
140 – 149	7.5%
≥ 150	9.2%

Lewington reported a 2-fold increase in CV mortality for each 20 mmHg increase in systolic blood pressure > 115. There was an equivalent increase for every 10 mmHg rise in diastolic blood pressure > 75.

Mainous followed 9706 subjects, ages 30-74, for 12 years. Subjects were said to have been specifically selected to mirror the general population:

Blood Pressure	Relative Mortality Risk	
	All-Cause	Cardiovascular
Normal	1.00	1.00
120-129/80-84	1.09	1.42
120-139/85-89	1.50	1.97
≥ 140/90	2.71	4.45

In the San Antonio Heart Study, all-cause mortality increased 53% when systolic BP was 107-117, as compared to < 107, and there was a further 25% increase between 118 and 139. [Lorenzo]

In two major large population investigations (Chicago Heart Association Study and University of Glasgow Alumni Study), prehypertension increased mortality 37% and 65%, respectively, when compared to normal BP. [McCarron, Miura]

The following data were reported in the Harvard Alumni Study. This unique investigation tracked 18,881 graduates for 45 years. It is important to bear in mind that these subjects enjoyed high socioeconomic status and, by inference, continuous access to high quality medical care and superior health maintenance, as compared to the general population. [Gray]

Baseline Systolic Blood Pressure	Relative All-Cause Mortality
< 105	0.99
105 – 114	1.00
115 – 124	1.04
125 – 134	1.04
135 – 144	1.16

Wannamethee and Shaper found that 5-year cancer mortality was significantly higher in subjects with prehypertension.

At what age group does prehypertension no longer impact mortality risk?

Age 55 and over. [Mainous]

Low Blood Pressure in the Elderly

What is the low diastolic blood pressure threshold linked to increased cardiovascular disease risk?

Depending on the study, it ranges from < 80 to < 55. [Sesso]

In the Honolulu-Asia Aging Study, diastolic BP < 80 and systolic BP < 120 in subjects aged 71-93 were related to increased coronary disease, stroke and physical frailty. [Fujikami]

Both heart failure and stroke risk are increased by low diastolic BP. [Casiglia, Guichard]

Is there credible evidence of excess mortality with low BP at older ages?

Yes.

In a study involving participants age 75 and over, systolic BP < 120 and diastolic BP < 70 conferred significant excess mortality. [Hakala]

When treated hypertensive patients age 60 and older were followed for 3.8 years, the death rate was 3-fold higher at diastolic BP < 80, as contrasted to levels between 90 and 95. [Ungar]

After surviving an acute coronary event, mortality was markedly greater in patients whose diastolic blood pressure was < 70, as compared to readings between 80 and 100. [Bangalore and Qin]

What other adversities are associated with low blood pressure in the elderly?

Compared to readings of ≥ 80, subjects with diastolic blood pressure < 70 have a 2.2-fold greater risk of cognitive dysfunction. [Haan]

Three additional studies demonstrate similar findings. [Cattin, Ingerslev, Paran]

Depression is significantly more prevalent in those with diastolic BP < 75 and systolic BP < 120. [Stroup-Benham]

Okumiya found that low systolic blood pressure correlated with excess deaths from both respiratory disease and cancer. Furthermore, most of the extra mortality was manifested within 3 years of onset of systolic BP < 120.

Prehypertension increases mortality on an incremental basis in persons age 50 and under.

In the elderly, low systolic and diastolic blood pressure are harbingers of functional decline, cardiovascular disease and excess mortality.

Closing Observations

The studies cited in this paper affirm the substantial insurability implications of high normal, low normal and below normal laboratory test and physical measurements.

They clearly show why the incremental additive effects of these findings will often result in a high lab/paramedical score in applicants whose findings fall within the low and high ends of the conventional reference ("normal") ranges.

Because it is based on clinical and epidemiological research, this paper should provide support for insurers called upon to explain these risk scoring systems to producers, applicants' physicians and other inquiring parties.

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What to do with *myLQAnalysis*

It is important to remember that we are measuring mortality—how long someone is likely to live—rather than trying to assess what disease or disorder may be contributing to the mortality expectation. We leave the diagnostic work to the physician.

Statistically, most of our customers should generally be in normal ranges, and their interaction with their physician will simply be a heightened willingness to keep an eye on their health. However, some will have mortality analysis results that are concerning and they will want to engage their physician to dig deeper to find what may be underlying the contributing factors in the *Analysis*. The physician is to use best judgment in determining what additional tests or analysis would be helpful.

About LongevityQuest®

LongevityQuest® encourages and empowers people to pursue a long, good life. LongevityQuest's innovative *myLQAnalysis*® provides individuals with a personal longevity projection, valuable ranking against others, and comprehensive analysis of risk factors that may be subtracting from or adding to longevity—all from the convenience and confidentiality of home. For more information please email ***info@mylongevityquest.com.***