MarinBio Blog

How Lifestyle Changes Prevent Progression to Lethal Diseases

Diabetes / Liver Cirrhosis & Cancer / Obesity / Dementia

This blog will emphasize lifestyle diseases and their considerable interrelatedness among various disorders. This interrelatedness is especially relevant given the substantial clinical burden borne by the U.S. population, as described in our prior blogs (Blog 1 and Blog 2), and the commonalities in diagnoses as well as shared preventive strategies. These relationships also inform health care providers of the essential elements required to prevent lifestyle-related morbidity and mortality. Shifting clinical focus from late-stage treatment to early detection, risk-factor reduction and prevention offers the greatest opportunity to reduce morbidity, mortality, and societal burden from these interconnected chronic diseases.

Lifestyle and Disease Nomenclature and Risk

1. **Prediabetes**
   Prediabetes is a dysglycemic condition that first becomes clinically apparent with a hemoglobin A1c threshold equal to or > 5.7%. HbA1c is the percentage of hemoglobin molecules that are glycated by glucose, and in a blood test shows your average blood glucose (sugar) level over the previous 2–3 months. Dysglycemia is also determined by a fasting blood glucose threshold exceeding 85-90 mg/dL(1). The thresholds for diabetes are a fasting blood glucose >200mg/dL or a hemoglobin A1c equal to or >6.5%. Prediabetes is unique among the other early lifestyle disorders in that it is potentially fatal itself registering a US death rate of 2.4 percent attributable fraction, whereas diabetes registers 11.2 and is the third leading cause of US deaths (1). It appears that about one third of individuals with prediabetes will revert back to having normal blood glucose and A1c values, another one third will remain prediabetic without advancing to diabetes in the near term and the final one third will progress to diabetes. Since over 100 million U.S. citizens have prediabetes, these epidemiological findings are of substantial

importance. The factors that advance prediabetes to a fatal or diabetic outcome are independent cardiovascular death risk factors detailed below. Given these serious outcomes, it follows that a subclass of prediabetes - subclinical prediabetes becomes relevant, when blood glucose and A1C values are approaching the thresholds of prediabetes itself (1). At this point, especially for those with family members already having these same disorders, several lifestyle changes are indicated as preventive treatment, such as diet and exercise.

2. **Pre-obesity**

Pre-obesity is an isolated overweight condition, which importantly differs from prediabetes above, in that it is neither an independent death risk factor, nor directly associated with a fatal outcome. Pre-obesity becomes obesity when the excess body fat is associated with substantially increased disease risk including cardiovascular death risks such as sleep apnea, impaired physical activity, and various liver conditions associated with increased lipid deposits and inflammation (2). Although there are various methods to measure the overweight condition quantitatively, the most common determination is the body mass index or BMI. The 58 co-authors of an article published in the journal Lancet could not agree that the BMI is a method to determine obesity for a number of reasons. For example, individuals with increased muscle mass can have elevated BMI levels. Unfortunately, there is no normal BMI level, and obesity must be "clinically determined" without physical body metrics until future research is more definitive.

The current ambiguity necessitates a return to earlier BMI classifications. Previously, a BMI of less than 25 kg/m² was considered normal, 25–30 was classified as overweight, and greater than 30 as obese. It therefore seems reasonable to incorporate the clinical features described above for individuals with a "normal" BMI (<25) who do not have excessive muscle mass. Preclinical obesity (pre-obesity) can be defined as a BMI below 40 without the additional clinical abnormalities noted above, while clinical obesity refers to a BMI above 25 accompanied by these additional clinical and laboratory abnormalities.

3. **Steatotic Liver Disease (also known as Fatty Liver Disease)**

Steatotic Liver Disease is a group of liver diseases defined by excess fat in the liver, most commonly driven by metabolic dysfunction, and associated with increased cardiometabolic and liver-related risk. The most specific early warning blood test for Steatotic Liver Disease is the alanine aminotransferase (ALT) assay. In 2017 the American College of Gastroenterology guidelines lowered the ALT high normal range for men from the 40 to 60 international units/Liter (IU/L), currently used by the various US national laboratories performing these tests, down to a new threshold of < 33 IU/L for men and for women < 25 IU/L. The rationale for lowering diagnostic thresholds to enable earlier diagnosis arises from the recognition of a continuing increase in liver cancer mortality in the United States, while mortality from most other cancers is declining. The increase in liver cancer deaths is largely secondary to slowly progressive liver disease that leads to cirrhosis. Therefore, early liver disease must be identified in order to prevent the fatal outcomes of liver cirrhosis and/or cancer. These liver disorders

represent another category of lifestyle-associated conditions and should therefore be included alongside other lifestyle conditions in prevention and treatment frameworks.

Table 1. Classifications to help guide clinicians in managing liver disorders.

Abbreviation	Full Name	Definition / Criteria	Diagnostic Methods
SLD	Steatotic Liver Disease	Presence of fat in the liver, often associated with mildly elevated ALT (alanine aminotransferase) levels	Liver ultrasound; ALT blood test
MASLD	Metabolic Dysfunction-Associated Steatotic Liver Disease	SLD plus at least one metabolic dysfunction risk factor (obesity, hypertension, hypertriglyceridemia, prediabetes or T2D)	Liver ultrasound; ALT; assessment of metabolic risk factors
MASH	Metabolic Dysfunction-Associated Steatohepatitis	MASLD with liver inflammation and fibrosis	Non-invasive liver elastometry/elastography or liver biopsy
METALD	Metabolic and Alcoholic Liver Disease	MASLD in combination with history of excessive alcohol intake	Clinical history; liver imaging; liver function tests; possibly elastography or biopsy

4. **Mild cognitive impairment (MCI)**

Mild cognitive impairment is the earliest clinical stage of dementias, including Alzheimer's disease, and can be considered a "predementia" condition. Evidence from randomized, controlled trials (FINGER and POINTER) shows that Mild cognitive impairment is strongly influenced by lifestyle factors. It is especially important in individuals with cardiovascular risk factors combined with conditions such as prediabetes, pre-obesity or obesity, depression, traumatic brain injury, physical inactivity, excessive alcohol use, social isolation, air pollution exposure, and sensory impairment. Together, these factors account for nearly half of the potentially modifiable risks for dementia (3), while non-modifiable risks include age and biological sex.

The Independent Cardiovascular Death Risk Factors

It must be appreciated that the leading cause of US deaths is cardiovascular disease affecting about 950,000 Americans annually. The irony is that cardiovascular death risk factors are easily prevented and treatable. The “independent” definition of the risk factors is that each risk *alone* can lead to death, and if several coexist the death risks appear additive. Since these risk factors are so important in each of these epidemic and pandemic lifestyle disorders, we must *understand* how to determine the clinical thresholds which require medical attention for prevention and treatment. Usually, the *thresholds* will also be the clinical treatment *targets*. Understanding thresholds is critical because fewer than 10% of Americans meet the target goals for dysglycemia, dyslipidemia, and hypertension. This remains true despite U.S. guidelines, which are often too lenient for these three independent risk factors for cardiovascular death.

The following risks are presented in the order according to clinical significance related to cardiovascular events and deaths.

SMOKING: This long-standing risk factor has been removed from many Americans lifestyles but still needs substantial attention to remove it from the 20% of Americans who continue to smoke.

HYPERTENSION: The thresholds for abnormal blood pressure have been decreasing over the last 2-3 decades. Whereas a blood pressure of 140/90 was considered normal, more modern recommendations have substantially lowered that threshold especially when associated with conditions such as prediabetes, diabetes, obesity and MCI. Currently, blood pressure recommendations for individuals with subclinical and clinical prediabetes, diabetes, obesity, and mild cognitive impairment should be <120/80 in those patients who can tolerate this target (4-6). For patients with multiple cardiovascular risks and/or kidney disease, that threshold is lowered to <120/70. Because many patients have nocturnal hypertension, the best time to measure the blood pressure is first thing in the morning before becoming physically or mentally active. Thus, home monitoring of blood pressure is essential.

DYSLIPIDEMIAS: Major considerations for dyslipidemias are circulating LDL cholesterol and more importantly elevated serum triglyceride levels and Lipoprotein(a) (Lp(a)). Lp(a)) is a LDL-like lipoprotein particle that is an independent cardiovascular risk factor. Lp(a) is genetically determined and is not a lifestyle disorder. A review article published in 2000 states, triglyceride thresholds should be < 115-120 mg/dL (5). Recent changes to the European guideline indicate values should be < 135 mg/dL with multiple risk factors (5,6), whereas current 2026 values from major US clinical laboratories indicate “normal” values of 150 or 200 mg/dL. The rationale for lowering triglyceride levels is based on their role in increasing small, dense LDL cholesterol, the primary LDL particle type responsible for cardiovascular disease and related mortality. Mass spectrometry assays for small, dense LDL cholesterol are presently available in clinical test laboratories.

Total LDL cholesterol level clinical thresholds, above which medical attention is advised, vary depending on the presence of other cardiovascular and/or other risk factors such as prediabetes, obesity and/or mild cognitive impairment. The higher the cardiovascular risk, the lower total LDL cholesterol should be, with a prevention or treatment target of 50 mg/dL if two or more risks exist. Interestingly, if the serum triglyceride level is lowered by statin medications to the acceptable (110-120 mg/dL range), the total LDL cholesterol and small, dense LDL

cholesterol will both automatically be reduced to the recommended target of 50 mg/dL. Due to several genetic randomization studies, circulating HDL should not be considered a protective factor (6). Additional information clinical therapeutic thresholds and targets as well as mechanisms can be found in more detail in the *American Journal of Cardiology, and Nature: Chemical Biology* (8, 9).

Although Lp(a) has been identified as a substantial independent risk factor for cardiovascular death, many U.S. clinicians remain unaware of its importance. Most major clinical laboratories are able to perform an Lp(a) detection test. Therefore, individuals aged 40–50 who have multiple independent cardiovascular risk factors, lifestyle-related diseases, and/or a family history of premature cardiovascular death should be tested for Lp(a). Importantly, as of 2026, Niacin is the only specific therapy available for this form of dyslipidemia, in addition to managing other independent cardiovascular risk factors. Several new injectable RNA-based oligonucleotide therapies appear promising and are expected to become available within the next few years.

In summary, dyslipidemias can be characterized as follows. In 2000, among men with coronary artery disease, only 10% had elevated total LDL cholesterol, whereas 30% had elevated Lp(a) and 50% had elevated small, dense LDL cholesterol (5). This latter 50% group, by definition, also had elevated serum triglyceride levels above 115–120 mg/dL, since elevated triglycerides are the primary metabolic mechanism leading to increased small, dense LDL cholesterol. As noted above, many cardiovascular clinicians have progressively lowered target thresholds for total LDL cholesterol from approximately 130–150 mg/dL to near 50 mg/dL, thereby obscuring the clinical importance of small, dense LDL cholesterol and serum triglyceride levels. These dyslipidemias are also more difficult to treat in patients with diabetes (8).

MICROALBUMINURIA: Microalbuminuria is a clinical term for a small but abnormal increase in the amount of albumin excreted in the urine, indicating early damage to the kidney's glomerular filtration barrier. Microalbuminuria is important because it is an early marker of diabetic nephropathy, predicts progression to chronic kidney disease, and is also a strong independent risk marker for cardiovascular disease, reflecting generalized vascular and endothelial injury (5). It is unfortunate that microalbuminuria remains cryptic in the U.S., because it is easy to treat and serves as an early warning marker in diabetic patients. The microalbuminuria assay was developed in 1979, and by 1990 the assays were generally available, however most US clinicians caring for diabetic patients remain unaware of the test and its significance. Microalbuminuria is defined as a 24-hour urinary albumin excretion of 30–300 mg/day, or alternatively as an albumin-to-creatinine ratio >30 mg/g on a 'spot' urine assay. These thresholds are substantially lower than those used for total urinary protein. Critical interrelationships exist among hypertension, dysglycemia, and dyslipidemia that create renal–cardiac vicious cycles, causing further damage to the kidney and heart, leading to end-stage renal disease, and cardiovascular death (5,10).

Cardiovascular Risks Associated with Menopause and Estrogen Therapy

Although menopause is unlikely to be an independent risk factor for cardiovascular death, it is strongly associated with increased cardiovascular mortality. Normal female physiology

illustrates how readily U.S. clinicians discontinue an important therapy, estrogen, while simultaneously struggling to identify and appropriately manage independent cardiovascular risk factors. Following the 2002 NIH Women's Health Initiative report, which linked postmenopausal estrogen therapy to serious adverse events such as stroke, thromboembolism, and cancer, estrogen use was rapidly abandoned in the United States. Subsequent reanalysis revealed that these cardiovascular events primarily occurred 10–15 years after menopause onset, yet estrogen therapy was not reinstated for eligible women.

As outlined in 2000, cardiovascular complications can be largely avoided by assessing and adequately treating established cardiovascular risk factors; women without these risks, or in whom they are well controlled, should therefore be candidates for estrogen therapy regardless of age or years since menopause. Cardiovascular deaths increase with age, but they are primarily driven by cumulative exposure to modifiable cardiovascular risk factors rather than by aging itself; effective identification and treatment of these risk factors substantially reduce cardiovascular morbidity and mortality even in older adults. Importantly, cardiovascular disease causes approximately approximately 500,000 deaths annually among postmenopausal women, far exceeding deaths from estrogen-associated breast and uterine cancers, estimated at 35,000 and 13,000, respectively, both of which continue to decline due to improved screening and treatment. A substantial body of literature supports estrogen use for the prevention of cardiovascular disease and hip fractures, and these conclusions are consistent with both the 2000 guidelines cited here and current North American Menopause Society recommendations.

Conclusion

Preobesity, prefatty liver disease, and mild cognitive impairment should no longer be viewed as benign or isolated findings but rather as early clinical warning states that signal progression toward far more lethal lifestyle-related diseases. These conditions reflect underlying metabolic, inflammatory, and vascular disturbances that, if unrecognized and untreated, predict the development of prediabetes and diabetes, obesity, advanced liver disease including cirrhosis and hepatocellular carcinoma, cardiovascular disease, and dementia. Recognizing these early states provides a critical window for intervention, during which lifestyle modification, risk-factor reduction, and targeted clinical management can meaningfully alter disease trajectories.

This prevention-oriented framework is particularly relevant in midlife and postmenopausal women, in whom the loss of estrogen is associated with a marked rise in cardiovascular mortality driven largely by cumulative, modifiable risk factors rather than menopause itself. Evidence indicates that appropriate identification and control of cardiovascular risk factors, and judicious use of estrogen therapy in well-selected women, can substantially mitigate cardiovascular risk, which far exceeds mortality attributable to estrogen-associated malignancies.

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