



Projected Increase in Obesity and Non-Alcoholic-Steatohepatitis-Related Liver Transplantation Waitlist Additions in the United States

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Nonalcoholic steatohepatitis (NASH) cirrhosis is the fastest growing indication for liver transplantation (LT) in the United States. We aimed to determine the temporal trend behind the rise in obesity and NASH-related additions to the LT waitlist in the United States and make projections for future NASH burden on the LT waitlist. We used data from the Organ Procurement and Transplantation Network database from 2000 to 2014 to obtain the number of NASH-related LT waitlist additions. The obese population in the United States from 2000 to 2014 was estimated using data from the U.S. Census Bureau and the National Health and Nutrition Examination Survey. Based on obesity trends, we established a time lag between obesity prevalence and NASH-related waitlist additions. We used data from the U.S. Census Bureau on population projections from 2016 to 2030 to forecast obesity estimates and NASH-related LT waitlist additions. From 2000 to 2014, the proportion of obese individuals significantly increased 44.9% and the number of NASH-related annual waitlist additions increased from 391 to 1,605. Increase in obesity prevalence was strongly associated with LT waitlist additions 9 years later in derivation and validation cohorts ($R^2 = 0.9$). Based on these data, annual NASH-related waitlist additions are anticipated to increase by 55.4% (1,354-2,104) between 2016 and 2030. There is significant regional variation in obesity rates and in the anticipated increase in NASH-related waitlist additions ($P < 0.01$). **Conclusion:** We project a marked increase in demand for LT for NASH given population obesity trends. Continued public health efforts to curb obesity prevalence are needed to reduce the projected future burden of NASH. (HEPATOLOGY 2019; 70:487-495).

SEE EDITORIAL ON PAGE 459

Nonalcoholic steatohepatitis (NASH) cirrhosis is the fastest growing indication for liver transplantation (LT) in the United States.^(1,2) Whereas hepatitis C infection is currently

the most common indication for LT in the United States, the proportion of patients who require LT for hepatitis C is projected to decrease in coming years, primarily attributed to increased hepatitis C screening efforts among at-risk groups and the advent of highly effective antiviral therapies for hepatitis C.⁽³⁾ In con-

Abbreviations: BMI, body mass index; BRFSS, Behavioral Risk Factor Surveillance System; CI, confidence interval; HCC, hepatocellular carcinoma; HS, hepatic steatosis; LT, liver transplantation; MetS, metabolic syndrome; MSE, mean square error; NASH, nonalcoholic steatohepatitis; NHANES, National Health and Nutrition Examination Survey; OPTN, Organ Procurement and Transplantation Network; rMSE, root mean squared error; UNOS, United Network for Organ Sharing.

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trast, given the historic rise obesity in the United States, the incidence of NASH is expected to increase; however, we lack granular projections of the future burden of NASH cirrhosis and NASH-related complications in the United States.

Obesity is highly prevalent in the United States, with recent estimates indicating 38% of adults with a body mass index (BMI) greater than 30.⁽⁴⁾ Obesity is associated with the development of the metabolic syndrome (MetS), which includes dyslipidemia, hypertension, insulin resistance, and hepatic steatosis (HS).⁽⁵⁾ Those with HS can develop NASH, which is characterized by necroinflammation, which, in turn, leads to hepatic fibrosis and increased risk of development of hepatocellular carcinoma (HCC).^(6,7) Thus, NASH will become a leading indication for LT both in the United States and internationally in other countries with rising obesity prevalence.^(3,4,8) This has several health care resource implications, as the population of patients with NASH-related cirrhosis grows and subsequently develops cirrhosis-related complications (i.e., hepatic decompensation and HCC) that require high-resource care and consideration of LT.

Duration of obesity and presence of MetS in an individual patient can increase the risk of development of NASH-related cirrhosis and HCC.^(9,10) From an epidemiological perspective, however, the temporal relationship between obesity prevalence in the population and the rise in NASH-related cirrhosis and decompensation is unclear. Several developed and developing countries worldwide are seeing increases in obesity prevalence⁽¹¹⁾; however, the lag in years between development of obesity in the population and increases in the proportion of patients that present for LT attributed to NASH remains poorly characterized. Thus, in this analysis, we aimed to determine the population-based temporal relationship between obesity and NASH-related cirrhosis requiring LT listing in the United States. We also aimed to project the

future burden of NASH-related cirrhosis requiring LT waitlist addition in the United States based on historical and projected U.S. population obesity prevalence.

Materials and Methods

DATA SOURCES

Waiting List Data

We analyzed data from the Organ Procurement and Transplantation Network (OPTN) database from 2000 to 2014 to obtain the historical number of additions to the waiting list per year attributed to NASH.⁽¹²⁾ From 2000 to 2003, there were no primary codes attributed to NASH, thus we relied on the “other” field in identifying NASH diagnoses. If the primary diagnosis was “other,” we included those individuals who had “NASH” or “NAFLD” included in the text field. Previous analyses have shown that a significant proportion of patients diagnosed with cryptogenic cirrhosis likely represented undiagnosed NASH cirrhosis, so we used a modified definition of NASH that includes obese cryptogenic patients, based on a previously published algorithm.⁽¹⁾ We included all adult waiting list additions between 18 and 74 years of age whose body mass index (BMI) was less than 60 kg/m². The 60-kg/m² cutoff was used because of the low likelihood of transplant of extremely obese individuals. For our regional analyses, NASH additions to the waiting list per year were categorized into 11 regions established by the United Network for Organ Sharing (UNOS).

Historical National Population Obesity Prevalence Data

Data from the Continuous National Health and Nutrition Examination Survey (NHANES) from 1999 to 2014 were used to obtain estimates of national

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obesity prevalence per year.⁽¹³⁾ The Continuous NHANES data on BMI are directly measured and collected in 2-year cycles, thus we divided each cycle according to the time period the data was collected. We assumed data collected from November 1 through April 30 were representative of the first year of the cycle and data collected from May 1 to October 31 were representative of the second year of the cycle. NHANES entries with any missing BMI data were excluded for this calculation ($n = 869$; 2.1%). We stratified the data from the Continuous NHANES data according to obesity categories based on the following obesity strata (class I-III): 30 to <35, 35 to <40, and 40+ kg/m².⁽¹⁴⁾

Because Continuous NHANES data does not contain geographical information regarding the individuals enrolled, and there is significant geographical variation in obesity prevalence, we used data from the Behavioral Risk Factor Surveillance System (BRFSS) from 2000 to 2014 to estimate obesity prevalence by year and regional division instituted by the UNOS.⁽¹⁵⁾ The BRFSS is a self-reported survey that allows analysis of regional variation in obesity prevalence. Entries with any missing data were excluded for this calculation. To account for missingness in height and weight variables in the BRFSS data set (4.9%) through the years 2011-2014, we imputed the missing values using MissForest imputation method.^(16,17) We conducted imputation with the BRFSS data to maximize the number of values in the regional data.

The national and regional U.S. population was obtained aggregating the U.S. population by state using two U.S. Census Bureau data sets: (1) Intercensal Estimates of the Resident Population by Single Year of Age, Sex, Race, and Hispanic Origin for the United States: April 1, 2000 to July 1, 2010 and (2) Monthly Population Estimates by Age, Sex, Race, and Hispanic Origin for the United States: April 1, 2010 to July 1, 2014.⁽¹⁸⁾ The historical population data were stratified by year, race/ethnicity, sex, BMI, and age group. We first applied obesity proportions, including BMI categories, from Continuous NHANES data to the U.S. Census Bureau population estimates to obtain an estimate of the national obese population. We then estimated the regional obese population by applying obesity estimates obtained from the BRFSS data to the regional population estimates from the U.S. Census Bureau.

MODEL SELECTION

We used scatter diagrams to visualize the relationship between obese population estimates and NASH-

related additions to the transplant waiting list at 0- to 10-year lags (i.e., a rise in obesity led to a rise in NASH-related waitlist additions 0-10 years later.) The range of lag times was limited by the availability of data on NASH-related waitlist additions data. The scatter diagrams showed a linear association between obesity and NASH additions to the waiting list at all time lags considered, so a linear regression model was used for analyses.

NATIONAL ANALYSIS

We examined the association between obesity and NASH additions to the waiting list using a linear regression model. To choose the lag time that best correlated obesity estimates and NASH-related waitlist additions, we evaluated predictive performance using leave-one-out cross-validation methodology under different lag times (0-10 years). We chose the lag time that minimized the internal validation root mean squared error (rMSE).⁽¹⁹⁾

Based on our historical analysis, we observed the U.S. adult obese population increased linearly from 2000 to 2014 with excellent fit, so we assumed time is a predictor for obesity. However, recently published data suggest that the obesity epidemic has plateaued in recent years and it may stabilize over the coming decade. Thus, we modeled an increase and then plateau in obesity prevalence based on published estimates.⁽²⁰⁾ We accomplished this by adding a quadratic term to our regression model of obese population as a function of time.

Sensitivity Analysis on Obese Population Growth

Given the rise in obesity, we also performed a sensitivity analysis where the obese population was modeled as a function of time for future projections using linear regression.

REGIONAL ANALYSIS

Given regional variability in obesity prevalence, we performed a secondary analysis by each UNOS region. We visualized the relationship between obesity estimates and NASH-related additions in each of the 11 UNOS regions using scatter diagrams and observed a linear relationship as in the national analysis, again allowing linear regression analysis. Future regional obesity estimates were then forecasted using time as

the predictor. The linear regression model was based on regional obesity estimates as a continuous predictor and the region from which the estimates belonged as a categorical predictor.

Because each UNOS region was coded as a level in a categorical predictor, the regional differences were expressed as differences in the intercept and slope of a linear model. The changes in the intercept of the model were represented by adding the value of the region to the original intercept of the model. Changes in the slope of the model were made by including an interaction term between the obese population and the region. We chose region 1 to be the reference level because it had the smallest estimated total obese population. In addition, the estimates of the obese population were divided by 1×10^6 to obtain easily legible coefficient estimates. We used the Wald test to assess whether the pair-wise difference between the coefficients of the levels of the categorical predictor were statistically different from zero.⁽²¹⁾ The significance of the categorical predictor and the interaction among the categorical and numerical predictor in the regression model were tested using the likelihood ratio test.⁽²¹⁾

CATEGORICAL OBESITY ANALYSIS

To better understand the impact of each BMI category on projected additions to the waitlist, we performed an analysis that stratified the general population and NASH additions to the waitlist by BMI. The obese population by obesity class I-III (30 to <35, 35 to <40, and 40+ kg/m²) was estimated using linear regression with time as the predictor. We developed univariate and multivariate models to examine the relationship of each obesity category predicting NASH-related waitlist additions.

PROJECTIONS AND STOCHASTIC SIMULATION

NASH additions to the waiting list for those lagged years where data on obesity estimates were available were forecasted using linear regression. Prediction intervals were then obtained using a standard regression methodology.⁽²²⁾ However, in the years where we estimated the obese population by linear regression, we could not calculate prediction intervals of NASH-related waitlist additions using standard regression methodology. Therefore, point estimates and prediction intervals of NASH-related waitlist additions in

these cases were estimated using stochastic simulation. This method is described in the Supporting Methods section of the appendix.

Evaluation of Model Performance

We evaluated the model performance in two ways: the rMSE, which evaluated the derivation and internal validation models, and the R², which evaluated the derivation model. The mean square error (MSE) is the average squared difference between an estimator (our estimates for NASH-related waitlist additions) and the true value of the parameter (historical NASH-related waitlist additions). The squared root of this measure yields the rMSE, which scales the MSE so the units in which it is expressed are NASH-related waitlist additions. We measured the performance of our models in terms of the derivation and internal cross-validation rMSE. The derivation rMSE evaluates the performance of our models in predicting additions to the waiting list at years that were used to fit the models. The internal cross-validation rMSE assesses the performance of our models in predicting the leave-out year of waitlist additions during our leave-one-out cross-validation scheme.

In addition, we assessed how well the model fit the derivation set using the adjusted coefficient of determination R². The coefficient of determination R² is a measure of how much variability in the data is accounted by the model. This statistic is defined as the squared of the correlation coefficient between the estimates and the true values. The adjusted R² is a modification of the coefficient of variation to consider the number of predictors in the model.⁽²³⁾ It only increases if the addition of a new predictor improves the fit of the model more than would be expected by chance and it decreases if the new predictor improves the fit of the model less than expected by chance. The adjusted R² was only used to evaluate how well our models fit the data, and not how well our models predicted out-of-sample data.⁽²³⁾

All statistical analyses were performed with R (v3.2.1; The R Foundation for Statistical Computing, Vienna, Austria).

Results

TRENDS IN OBESITY

A total of 40,694 records from the Continuous NHANES data set were included for calculation of

obesity prevalence. The historical trend of estimates for obesity in the United States is included as Supporting Fig. S1. Although there are minor fluctuations, the population of obese individuals shows a steady increase between 2000 and 2014, increasing 44.9% over that time period.

NASH related additions to the waitlist also increased dramatically over the study period, from 391 in 2000 to 1,605 in 2014 (410%). From 2000 to 2003, the majority of patients defined as having NASH were coded obese cryptogenic patients (~98%); however, from 2012 to 2014, approximately 86% of patients were coded as NASH rather than cryptogenic.

LAG TIME SELECTION

NASH-related waitlist additions were best predicted by the prevalence of obesity 9 years previously. For example, NASH-related transplant waitlist additions in 2009 were associated with the proportion of obese individuals in 2000. A scatter plot describing the relationship between NASH-related waitlist additions and obesity estimates from 9 years previously is shown in Fig. 1.

This preferred model had an excellent adjusted R² value of 0.9 (meaning 90% of variability in NASH-related waitlist additions could be explained by obesity estimates from 9 years previously) and excellent average rMSE of 50.49 in the derivation cohort and 86.49 in the validation cohort. Model performance under all considered time lags is included in Table 1. Coefficient estimates with 95% confidence intervals (CI) and

TABLE 1. National Model Performance Under Different Time Lags

Time Lag (Years)	rMSE Training	rMSE Validation	Adjusted R-Squared
0	199.56	227.31	0.74
1	177.23	199.27	0.78
2	184.11	223.60	0.75
3	204.32	257.25	0.63
4	182.39	218.48	0.63
5	102.66	125.05	0.85
6	141.98	184.41	0.64
7	179.15	274.42	0.28
8	117.14	168.35	0.62
9*	50.49	86.49	0.90
10	52.72	83.78	0.82

*That 9-year time lag is the preferred model given lowest rMSE and highest R-squared.

corresponding *P* values are included in Supporting Table S1.

NATIONAL PROJECTION OF OBESITY AND NASH-RELATED WAITLIST ADDITIONS

The point estimates and 95% prediction intervals for obesity in the United States from 2016 to 2030 are depicted in Fig. 2. The obese population is expected to continue increasing, with an estimate of over 92 million obese adults aged 18-74 in the United States by 2025. The number of NASH-related waitlist additions is also expected to increase by 55.4% (1,354–2,104) between 2016 and 2030 (Fig. 3A,B).

To assess the robustness of our model, we predicted NASH-related waitlist additions using different time

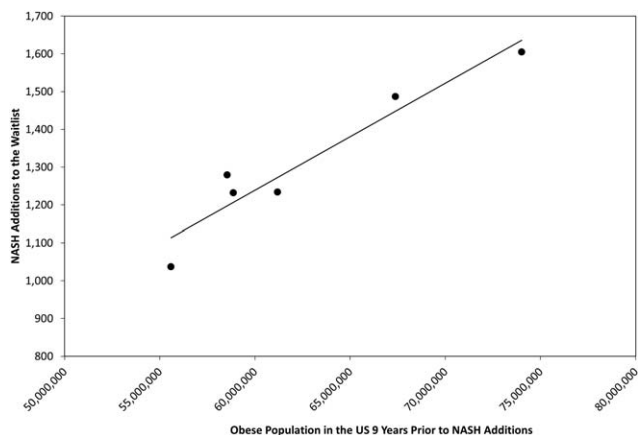


FIG. 1. Relationship between NASH-related transplant waitlist additions and obesity in the United States using a 9-year time lag.

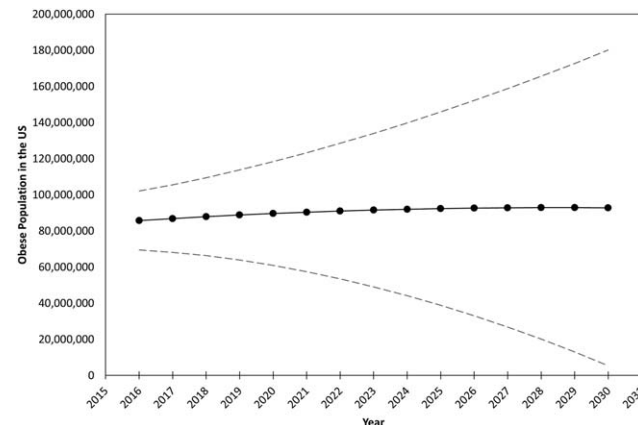


FIG. 2. Prediction of the obese population in the United States.

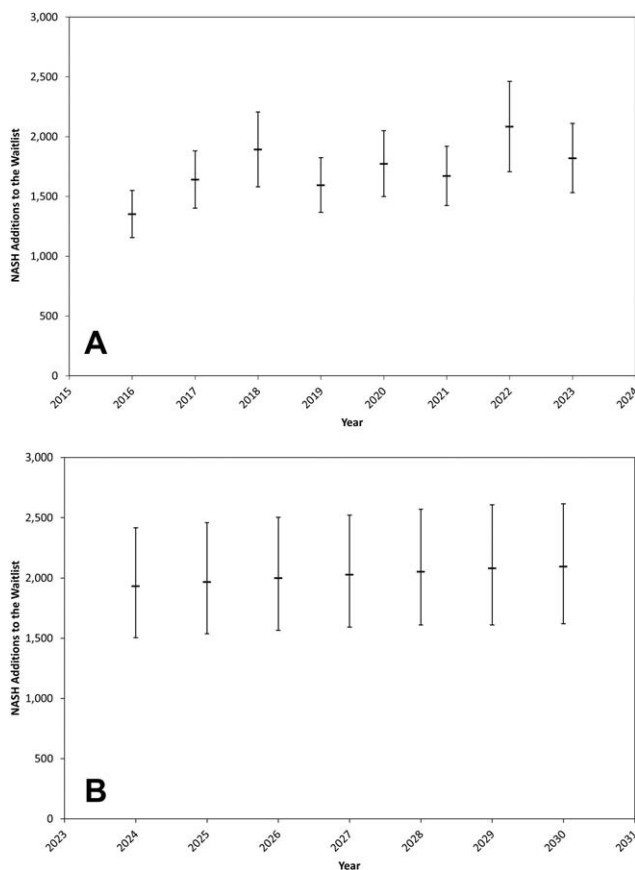


FIG. 3. (A) Point estimates and prediction intervals of NASH-related transplant waitlist additions from 2016 to 2023 using linear regression. (B) Point estimates and prediction intervals of NASH-related transplant waitlist additions from 2024 to 2030 using stochastic simulation.

lags of 0-10 years before waitlist addition (Supporting Table S2). Our results showed that projected waitlist additions by 2030 increased in all cases, but varied based on the degree of time lag. As expected, long-term projections had more variability in the range of NASH-related waitlist additions: 1,354-1,771 in 2016; from 1,574 to 1,880 in 2020; and from 1,694 to 2,413 in 2030.

Sensitivity Analysis on Obese Population

Supporting Fig. S2 shows the projected obese population in the United States with continued linear growth in obesity rates. By 2030, there will be over 100 million obese adults in the United States if current trends continue. Figure 4 shows the point estimates and 95% prediction intervals for the additions to the

waitlist attributed to NASH from 2024 to 2030, assuming linear growth of obesity in the United States. As in our base case, these estimates were obtained using stochastic simulation. If obesity prevalence in the United States grows linearly, we would expect 3.3% more NASH additions to the waitlist (from 1,932 to 1,995) in 2024 and 10.6% more NASH additions to the waitlist (from 2,104 to 2,327) in 2030, when compared to the linear growth case. With a linear model, we project a 71.9% increase in yearly NASH related waitlist addition from 2016 to 2030.

REGIONAL PROJECTIONS

Table 2 shows the regression coefficients (i.e., rate of change of NASH-related additions to the waitlist per year per 1,000,000 population) and *P* values for the obese population estimates and UNOS region as predictors for NASH-related waitlist additions with a lag time of 9 years. The general obese population and the regional categorical predictor were statistically significant for explaining additions to the LT waiting list attributed to NASH (*P* < 0.01). However, the interaction between the general obese population and the regional categorical predictor was not significant (*P* = 0.16), indicating that the rate of change or slope of the model is not significantly different across the regions. The differences in the intercept of the model between region 6 and region 1 and between region 9 and region 1 were statistically significant (both *P* < 0.01). Furthermore, the intercepts in regions 6 and 9 were not statistically significant from each other (*P* = 0.63). These results suggest that, given a fixed obese

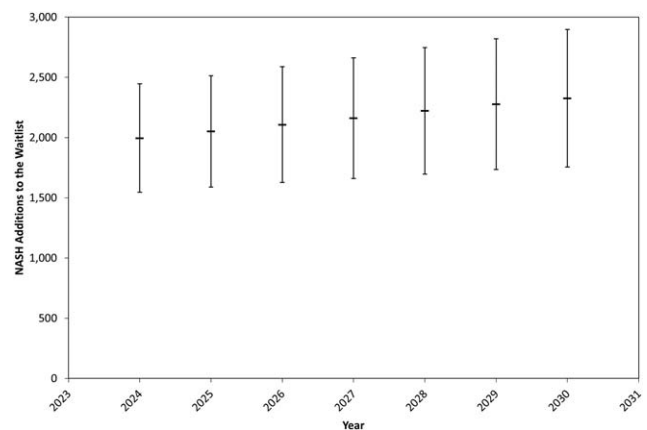


FIG. 4. Sensitivity analysis of NASH additions to the waitlist modeling the effects of linear growth of the national obesity rate.

TABLE 2. Regional Analysis for NASH-Related LT Waitlist Additions

Variables	Coefficient	95% CI		P Value
		Lower	Lower	
Intercept	-18.70	-38.99	1.59	0.070
BMI >30	36.23	27.96	44.51	<0.01
Region 1		Reference Level		
Region 2*	1.52	-28.33	31.37	0.919
Region 3*	-24.67	-71.41	22.07	0.295
Region 4*	-1.13	-29.12	26.87	0.936
Region 5*	-35.67	-81.16	9.82	0.122
Region 6*	-26.28	-44.72	-7.83	<0.01
Region 7*	-12.16	-36.95	12.63	0.330
Region 8*	-9.10	-28.86	10.67	0.360
Region 9*	-31.04	-51.54	-10.54	<0.01
Region 10*	-20.74	-50.61	9.13	0.170
Region 11*	-15.25	-48.71	18.21	0.365

*The value of the intercept (-18.70) should be added to the values of the coefficients of the regional predictors, with the exception of the reference level, to quantify the effect of the different region categories in a regression equation.

population, the number of additions to the waitlist attributed to NASH at regions 6 and 9 are expected to be smaller than the number of additions to the waitlist attributed to NASH at the rest of the regions. Based on our historical data, these results may be attributed to the fact that region 6 had similar obese population estimates to region 1, but less additions to the waitlist. On the other hand, region 9 had approximately the same number of additions to the waiting list attributed to NASH, but it had a greater obese population than region 1. This suggests regional differences in center practice with regard to adding patients with NASH to the waiting list or underlying differences in the obese population in regions 6 and 9 that either decrease the chances of those patients developing NASH or of NASH patients being added to the waitlist.

BMI CATEGORICAL ANALYSIS

In our multivariate model using obesity categories (BMI 30 to <35, BMI 35 to <40, and BMI 40+ kg/m²), no individual BMI category was a significant predictor of NASH-related waitlist additions with a 9-year lag. In our univariate analysis, the number of individuals with BMI 30 to <35 and BMI 35-40 were both significant predictors of additions to the waitlist attributed to NASH (both $P < 0.01$). The number of individuals in the BMI >40 category was not a statistically significant predictor of NASH additions to the waitlist ($P = 0.16$).

Discussion

NASH-related cirrhosis and HCC are the fastest growing indication for LT in the United States and many countries worldwide.^(1,3,24) Our analysis provides epidemiological insight into the relationship between obesity in the general population and the NASH-related additions to transplant waitlists. We demonstrated that an increase in NASH-related LT waitlist additions is expected to occur 9 years after population-level increases in obesity. This has potential future implications for the United States and other countries around the world where obesity prevalence is rising.⁽²⁵⁾ We have shown the impact on rising obesity with our projections of a 55.4% increase NASH-related LT waitlist additions in the United States over the next 15 years, likely making NASH the dominant indication for LT in the United States in coming years. Our sensitivity analysis shows that with future increases in obesity, additions to the waitlist for NASH would commensurately increase. Given limited donor supply in the United States, reductions in obesity on a population-level are particularly important to reduce the burden of NASH and NASH-related complications.

We found anticipated regional variation in growth of NASH-related waitlist additions. UNOS regions 6 and 9 lower rates of NASH additions to the waitlist when compared to region 1, likely reflecting either differential patient selection or underlying differences in the population in these regions. In our BMI categorical analysis, we found that obesity classes I and II (BMI 30 to <35 and BMI 35 to <40 kg/m²) are predictive of NASH-related waitlist additions, whereas class III obesity (BMI > 40 kg/m²) was not predictive. This likely reflects the fact that many transplant centers do not consider extremely obese individuals for LT, and patients very rarely lose significant amounts of weight.^(26,27) Patients who have a BMI >40 have a low likelihood of dropping in BMI category over a 9-year period, have a higher competing risk of non-liver-related mortality, and thus are typically selected out of being added to the transplant waitlist.⁽²⁸⁾

This study quantifies the burden of NASH on the future transplant list, which is only a proxy of the overall burden NASH will have on the U.S. health care system. Only a minority of patients with cirrhosis will be eligible for LT because of age, obesity, other comorbidities, or psychosocial barriers. This may be especially salient in patients with NASH given that cirrhosis tends to occur in obese, older patients with

cardiovascular comorbidities.^(29,30) Furthermore, our analysis underlies the need for better diagnostic and screening tools for identifying those with NASH in order to provide earlier interventions, such as weight loss strategies.^(31,32) Unfortunately, most patients who have NASH are unaware of their diagnosis and many only present when they have hepatic decompensation or develop advanced stage HCC, at which time there are few options that can modify the disease course. Thus, the overall impact of the increase in NASH is underestimated by this analysis; however, we have provided an important estimation of the impact will have on LT in the United States.

Our study has many notable strengths and weaknesses that warrant attention. We included 2000–2003 to increase the number of data points in the analysis; however, there was not formal coding for NASH in the UNOS database at that time, thus we may have underestimated the prevalence of NASH during these early years. The correlation between obesity and NASH additions to the waitlist, although biologically plausible, is an association and we have not proven for causation. Similarly, the estimated time lag of 9 years is limited by the data we have, and longer time lags may have superior prediction ability if more data were available. The data used for our historical analysis and development of projections are based on single-source data from the U.S. Census Bureau and the OPTN, thus we lack the ability to pool data sources for ranges in sensitivity analyses. Our model had high R^2 values and low rMSE, suggesting high performance, and results were consistent across sensitivity analyses and subanalyses; however, it is well known that model performance is lower in validation cohorts than derivation cohorts. We performed internal cross-validation, but could not externally validate our results. Given lack of adequate granular data, we were forced to use different methods (i.e., linear regression and stochastic simulation) for point estimates and prediction intervals for the NASH LT addition projections. Finally, our analyses assume the current state of NASH-related care. Public health efforts to reduce obesity prevalence could affect our projections, given that weight loss is associated with decreased steatosis and possible regression of fibrosis.^(33,34) However, such efforts have largely failed thus far, as observed in our historical analysis of obesity prevalence. Similarly, several new investigational treatments are being studied for the treatment of NASH, which, if effective, could significantly impact our projections.⁽³⁵⁾

In conclusion, we have shown that a lag of 9 years best explains the rise in obesity in the U.S. population

and the rise in NASH related additions to the waitlist. Using this lag and the anticipated increase of obesity in the U.S. population, we have projected a 55.4% increase in NASH-related transplant waitlist additions. This has several public health implications for the transplant community and for the overall burden of NASH-related liver disease in the United States.⁽³⁶⁾ It is especially worrisome in the setting of a plateauing donor supply, making receipt of an LT more difficult for those on the waitlist.^(37–39) Continued public health efforts to curb obesity prevalence and improvement in the diagnosis of, and treatment of, NASH will be important to mitigate the overall impact of our projections.

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Supporting Information

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