Original Article

Nonalcoholic fatty liver disease burden – Saudi Arabia and United Arab Emirates, 2017–2030

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Abstract

Background/Aim: Due to epidemic levels of obesity and type 2 diabetes mellitus (DM), nonalcoholic fatty liver disease (NAFLD) and resulting nonalcoholic steatohepatitis (NASH) will be driving factors in liver disease burden in the coming years in Saudi Arabia and United Arab Emirates (UAE).

Materials and Methods: Models were used to estimate NAFLD and NASH disease progression, primarily based on changes in adult prevalence rates of adult obesity and DM. The published estimates and expert interviews were used to build and validate the model projections.

Results: In both countries, the prevalence of NAFLD increased through 2030 parallel to projected increases in the prevalence of obesity and DM. By 2030, there were an estimated 12,534,000 NAFLD cases in Saudi Arabia and 372,000 cases in UAE. Increases in NASH cases were relatively greater than the NAFLD cases due to aging of the population and disease progression. Likewise, prevalent cases of compensated cirrhosis and advanced liver disease are projected to at least double by 2030, while annual incident liver deaths increase in both countries to 4800 deaths in Saudi Arabia and 140 deaths in UAE.

Conclusions: Continued high rates of adult obesity and DM, in combination with aging populations, suggest that advanced liver disease and mortality attributable to NAFLD/NASH will increase across both countries. Reducing the growth of the NAFLD population, along with potential therapeutic options, will be needed to reduce liver disease burden.

See accompanying editorial

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a leading cause of advanced liver disease in multiple regions,[1-3] and is characterized by excessive liver fat in the absence of other causes.[4,5] Overweight/obesity, type 2 diabetes mellitus (DM), and metabolic syndrome are the most important risk factors for NAFLD.[4,6] Morbidity related to NAFLD and resulting nonalcoholic steatohepatitis (NASH) is likely to increase dramatically in the coming decades, especially in the Gulf countries, where there is already an epidemic of obesity[7] and DM.[8]

For this analysis, NAFLD cases were classified into two groups: NAFL (steatosis only) and NASH, where inflammation can progress to liver fibrosis, which is the primary risk factor for development of decompensated cirrhosis and hepatocellular carcinoma (HCC),[9] as well as liver-related mortality.[10] Increasing age, obesity, and DM have been consistently identified as risk factors for fibrosis progression and cirrhosis.[6] Most liver-related outcomes occur with the development of significant fibrosis and cirrhosis. HCC usually develops in patients with cirrhosis secondary to NASH; however, HCC can occur in noncirrhotic NASH patients.[11] NASH with end-stage liver disease is increasingly listed as an indication for liver transplantation.[12,13]

There is a pressing need to understand the current and future burden of NAFLD-related liver disease. A model of disease burden allows for more efficient allocation of limited healthcare resources and assists in the development of national strategies. Several recent analyses assessed the disease and economic burden associated with NASH[14-16] based on the existing literature. In addition, a recently developed dynamic model of NAFLD progression for the United States overcomes several limitations in data availability.[17] In this analysis, we report the development of such a model for two countries, Saudi Arabia and UAE, based on the changing trends for obesity and DM in this region.

MATERIALS AND METHODS

A Markov model was constructed for Saudi Arabia and UAE. Fibrosis progression rates were back-calculated using surveillance data[17] and adjusted for the relative prevalence of obesity in each country.[6] Progression rates to HCC, decompensated cirrhosis, and liver-related death were based on published estimates.[17]

The populations in each country were tracked beginning in 1950. As described below, trends for adult prevalence of obesity and DM were used to estimate the annual number of new NAFLD cases over time and track cases by METAVIR fibrosis stage, with progression to advanced liver disease and liver-related death [Figure 1].

Inputs: For both countries, indexed articles and nonindexed sources, including national data reports, were utilized. A literature search was conducted to identify reported estimates of NAFLD or NASH prevalence,[18-21] including reports of advanced liver disease attributable to NAFLD or NASH. National estimates for adult prevalence of obesity (body mass index (BMI) ≥30 kg/m^2) and DM were also incorporated in the analysis. In addition to literature review, a Delphi process was used to incorporate expert input based on interviews to identify key model inputs and review outputs against available estimates of disease burden.

The proposed model calculated the NAFLD population by fibrosis stage and NASH status (NAFL or NASH). Progression of disease through fibrosis and liver disease stages [Figure 1] was calculated with adjustment for all-cause mortality (including background, excess cardiovascular disease (CVD), and liver-related mortality).

New NAFLD cases: Annual changes in the number of new cases were back-calculated based on the adult prevalence of obesity and DM for which more robust data exist than those for NAFLD. For obesity, the fastest growth in prevalence was estimated to occur prior to the

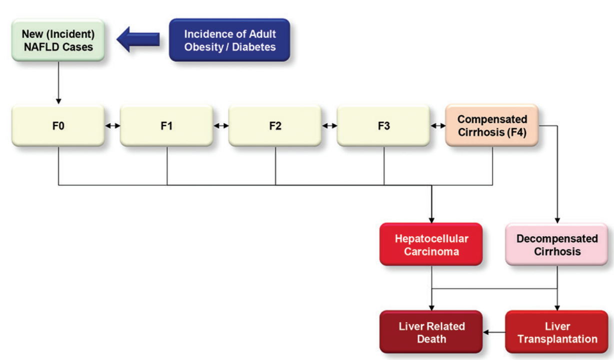

Figure 1: NAFLD progression model

greatest relative increases in NAFLD prevalence, while the fastest growth in DM prevalence was estimated to occur after the greatest increase in NAFLD at the general population level. National estimates of obesity for Saudi Arabia and UAE were available through published estimates.[7,22-25] For both countries, relative changes in obesity were estimated using global burden of disease estimates for adult obesity in Saudi Arabia in 1980, 1990, 2000, and 2013, due to the availability of estimates at different time points.[23] Similar estimates were available for UAE, but were partially based on studies in limited populations that may not be representative of the national population. Published[26-29] and unpublished data were used to estimate changes in adult prevalence of DM in Saudi Arabia. While longitudinal diabetes data for UAE were sparse, it was assumed that increases over time would follow the trends observed for Saudi Arabia.

NAFLD prevalence: It was assumed that 30% of individuals aged ≥15 years of age in 2015 experienced NAFLD. After adjustment for lower prevalence in the population aged <15 years, the all ages prevalence was estimated at 24.8% (Saudi Arabia) and 23.7% (UAE). For the age and gender distribution of the NAFLD population, data from general population studies in multiple countries were used where prevalence is 1.3 times higher in males as compared to females and there is increasing prevalence with age.[30-32] Prevalence studies often did not include younger age groups, and it was assumed that prevalence rates would decrease with decreasing age. One study of NAFLD prevalence in Saudi Arabia used computed tomography (CT) scan data from 100 adult hospital patients in 2012, and reported 18–54% NAFLD depending on the criteria applied.[33] A study of 230 DM patients at Jazan General Hospital in 2013 reported overall prevalence of 47.8%. Among these patients, there was slightly higher prevalence in males (49.1%) than females (46.3%), and prevalence was 52.9% among the middle-aged population (ages 40–59 years).[34]

NASH status: NASH prevalence was based on reported estimates and fibrosis progression that varied by sex and age group. Given that inflammatory and fibrotic changes can regress in NAFLD patients,[9] it was assumed that up to 5% of NAFLD cases without NASH could be NASH regressors, with increasing fibrosis score modeled to have a lower probability of being a regressed NASH case. Therefore, a relatively small number of fibrotic cases (F1–F4) were classified as non-NASH NAFLD.

The model assumed that approximately 15–20% of NAFLD cases would be classified as NASH in 2015.[35-37] Fibrosis progression and NASH status were calibrated to US surveillance data for NASH-related HCC[17] and then extrapolated to other countries, with adjustments between countries based on relative rates of overweight/obesity and published odds of disease progression to advanced fibrosis.[6] For disease progression adjustment, obesity and overweight prevalence data from the Saudi Health Information Survey were used.[22] Due to demographic factors,[38] the proportion of NASH cases varies between countries, with overall aging of the population and increased overweight/obesity rates associated with increased proportion of NASH cases among the total NAFLD population. During initial model calibration to surveillance data for NAFLD-related HCC, it was assumed that 15–20% of NASH cases would be classified as ≥F3 in 2015.[39] In settings with younger affected populations and/or where the obesity epidemic began later, the proportion of NASH cases was lower. Similar to NASH status, some countries had a higher proportion of advanced fibrosis cases due to the advanced age of the overall population, as well as the timing of the growth in obesity and DM prevalence that began at different time points.

Population: The United Nations population database was used to estimate population for Saudi Arabia. Because UAE has a very high population of expatriate individuals (approximately 90% of total population), the NAFLD model for UAE only considered Emirati citizens. Estimates of the citizen population were available for 1975–2005[40] through national databases. It was assumed that the age and gender distribution of the Emirate population would mirror the Saudi Arabia population in 1950 and 2050,[38] and the population data were linearly interpolated for 1951–1974 and 2006–2050, when national data by citizen status were unavailable.

Mortality: Background deaths were based on data from the United Nations population database for both Saudi Arabia and UAE[38] divided by population estimates by age group and gender from the same database.[38] Background rates were adjusted to account for incrementally increased mortality related to CVD.[41-43] A standard mortality ratio 1.15 [uncertainty range: 1.00–1.31] was applied to all background mortality rates in all years of the model.[41-43] While incremental CVD mortality may increase with severity of liver disease and vary by age group, data were largely unavailable, and a constant multiplier was applied. Liver-related mortality was calculated separately as part of liver disease progression modeling. Liver-related deaths were calculated as a progression rate among prevalent HCC, decompensated cirrhosis, and liver transplant cases.

Transplants: Annual transplant data by indication are sparse for Saudi Arabia and UAE. Using the total annual transplant data, along with expert input for total transplants,[44] it was assumed that up to 25% of current liver transplants could be attributable to NASH. These estimates were used to validate the model outputs and informed by studies showing that numerous transplants indicated for cryptogenic or idiopathic cirrhosis are NAFLD-related based on obesity rates in these populations.[13,45] Given the uncertainties around transplant demand and availability, it was assumed that the annual number of NAFLD-related transplants would remain constant through 2030. This was a conservative estimate, as data already suggest that the proportion of NAFLD-related transplants is increasing in areas of high obesity.[13]

Uncertainty and sensitivity analysis: Uncertainty analyses were conducted for the models. Beta-PERT distributions[46] were defined for key model inputs, including total NAFLD prevalence, excess background mortality multipliers, and fibrosis transition probabilities. Monte-Carlo simulation was conducted using Crystal Ball® (11.1.3708.0 by Oracle®), an Excel® add-in, to estimate 95% uncertainty intervals (UI). Sensitivity analyses were conducted to identify the inputs that accounted for the greatest variation in modeled outcomes. Prevalent NAFLD and NASH cases in 2017 and 2030 with 95% UI are shown in Figures 2 and 3.

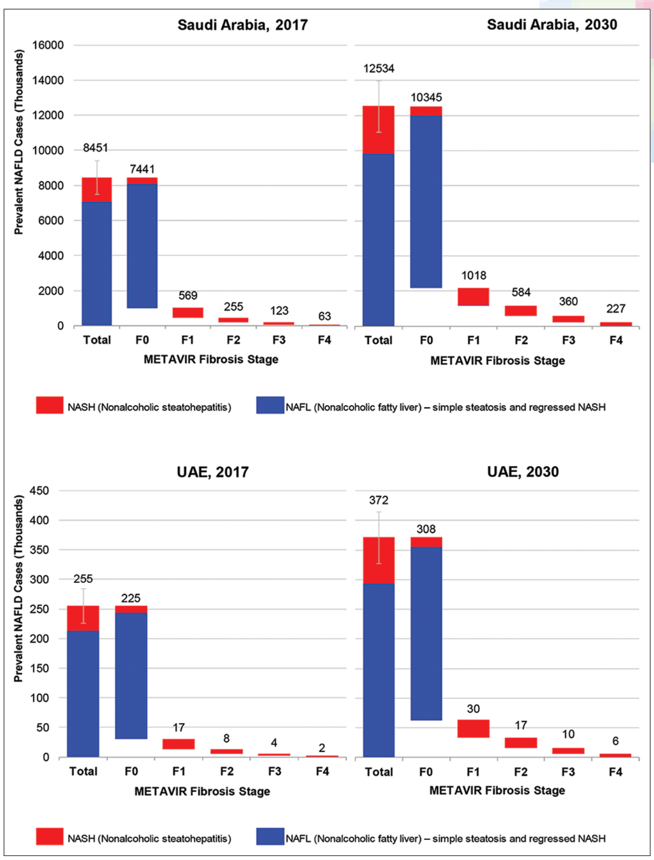

Figure 2: Distribution of NAFLD population by fibrosis stage – 2017 and 2030

Table 1: 2017 Model Forecasts – Saudi Arabia and United Arab Emirates, 2017 and 2030

	Saudi Arabia	UAE
2017 Country Population (000)	32,900	1,020
2030 Country Population (000)	39,500	1,230
NAFLD		
2017 Total Cases	8,451,000	255,000
2017 Prevalence (all ages)	25.7%	25.0%
2030 Total Cases	12,534,000	372,000
2030 Prevalence (all ages)	31.7%	30.2%
NAFL		
2017 Total Cases	7,078,000	213,000
2017 Prevalence (all ages)	21.5%	20.9%
2030 Total Cases	9,846,000	294,000
2030 Prevalence (all ages)	24.9%	23.9%
NASH		
2017 Total Cases	1,372,700	41,800
2017 Prevalence (all ages)	4.2%	4.1%
2030 Total Cases	2,688,000	78,300
2030 Prevalence (all ages)	6.8%	6.4%
Incident NAFLD		
2017 Total Cases	413,700	13,300
2017 Incidence Rate (per 1000)	12.6	13.0
2030 Total Cases	386,100	12,400
2030 Incidence Rate (per 1000)	9.8	10.1
NASH Mortality		
2017 Liver Related Mortality	1,220	40
2017 Excess CVD Mortality	1,810	80
2030 Liver Related Mortality	4,800	140
2030 Excess CVD Mortality	4,590	180

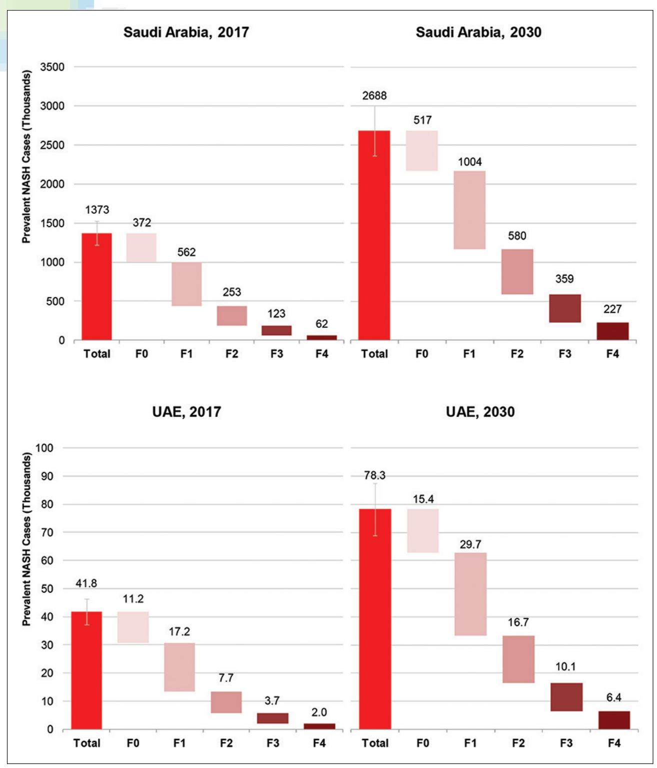

Figure 3: Distribution of NASH population by fibrosis stage – 2017 and 2030

RESULTS

NAFLD population: The total 2017 NAFLD prevalence was estimated at 8,451,000 (25.7%) in Saudi Arabia and 255,000 (25.0%) in UAE [Table 1]. By 2030, the total NAFLD population was projected to increase 48% in Saudi Arabia to 12,534,000 and 46% in UAE to 372,000 cases [Figure 2], with overall prevalence rates estimated at 31.7 and 30.2%, respectively. The number of prevalent cases with NAFLD-related compensated cirrhosis was projected to increase 262% during 2017–2030 in Saudi Arabia, from 55,900 to 202,100 cases, while such cases increased 232% in UAE from 1710 to 5700 cases in 2030 [Figure 4].

NAFL population: The NAFL population was assumed to be cases with steatosis only that never progressed to NASH, with a relatively small number of cases that were formerly NASH and would experience disease regression. In 2017, the NAFL population was estimated at 7,078,000 in Saudi Arabia (83.6% of all NAFLD cases) and increased to 9,846,000 cases in 2030 (78.6% of all NAFLD cases), a 39% increase. In UAE, the NAFL population was estimated to increase 37% from 213,600 cases in 2017 (83.6% of all NAFLD cases) to 293,400 cases in 2030 (78.9% of all NAFLD cases) [Figure 2].

NASH population: The number of NASH cases in 2017 was estimated at 1,373,000 in Saudi Arabia and 41,800 in UAE, equivalent to 16.2 and 16.4% of the total NAFLD populations, respectively.

General population: NASH prevalence in 2017 was estimated at 4.2% (Saudi Arabia) and 4.1% (UAE). In

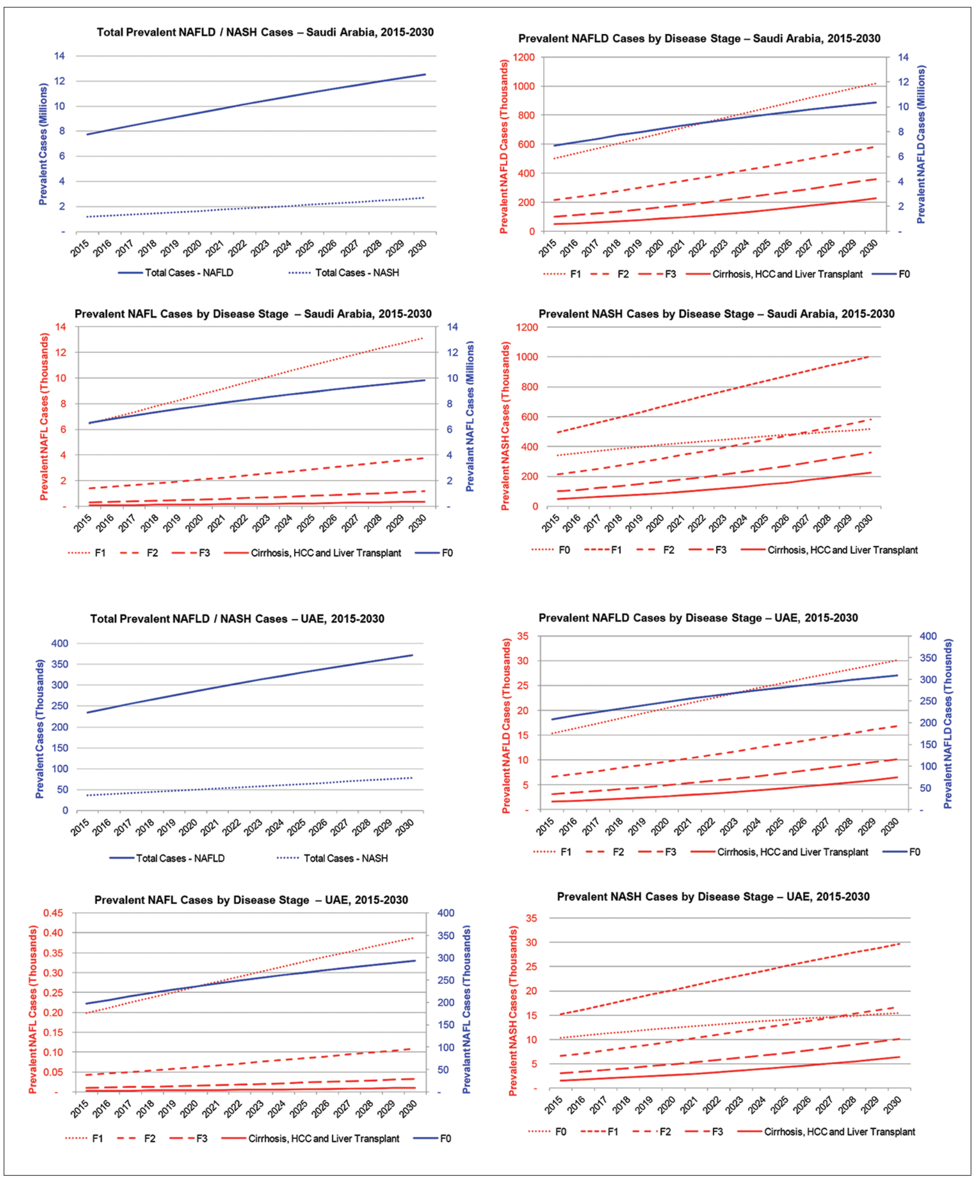

Figure 4: Prevalent NAFLD, NAFL (simple steatosis and regressed NASH), and NASH cases – 2015-2030

Saudi Arabia, NASH cases were projected to increase 96% to 2,688,000 cases in 2030, while NASH increased 87% in UAE to 78,300 cases [Figure 3]. Among NASH cases in Saudi Arabia, 185,500 were estimated to have F3/F4 fibrosis or advanced liver disease (decompensated cirrhosis or HCC), encompassing approximately 13.5% of all NASH cases [Figure 3] and 0.56% of the total population (all ages). By 2030, this number was expected to increase 216% to 586,000 cases, and account for 21.8% of all NASH cases. In UAE, there were 5670 such cases in 2017, equivalent to 13.6% of total NASH and 0.56% of the total population. By 2030, these cases increased 191% to 16,500 cases, or 21.1% of total NASH.

Decompensated cirrhosis and HCC: In Saudi Arabia, incident decompensated cirrhosis was projected to increase by 273%, from 1830 cases in 2017 to 6840 cases in 2030, while cumulative incidence during 2017–2030 was estimated at 55,500 cases [Figure 5]. In UAE, incident decompensation was estimated at 60 cases in 2017, increasing 241% to 190 cases in 2030, while cumulative incidence was estimated at 1620 cases.

Prevalent HCC cases related to NAFLD increased 209% in Saudi Arabia, from 580 cases in 2017 to 1790 cases in 2030, while such cases increased 181% in UAE from 18 to 51 prevalent cases during 2017–2030. In Saudi Arabia, incident HCC cases increased by 199% during 2017–2030 from 300 to 890 cases [Figure 5]. UAE was projected to have an increase of 178% from 9 incident cases in 2017 to 25 incident cases in 2030. Cumulative incidence of HCC during 2017–2030 was estimated at 7860 cases in Saudi Arabia and 230 cases in UAE.

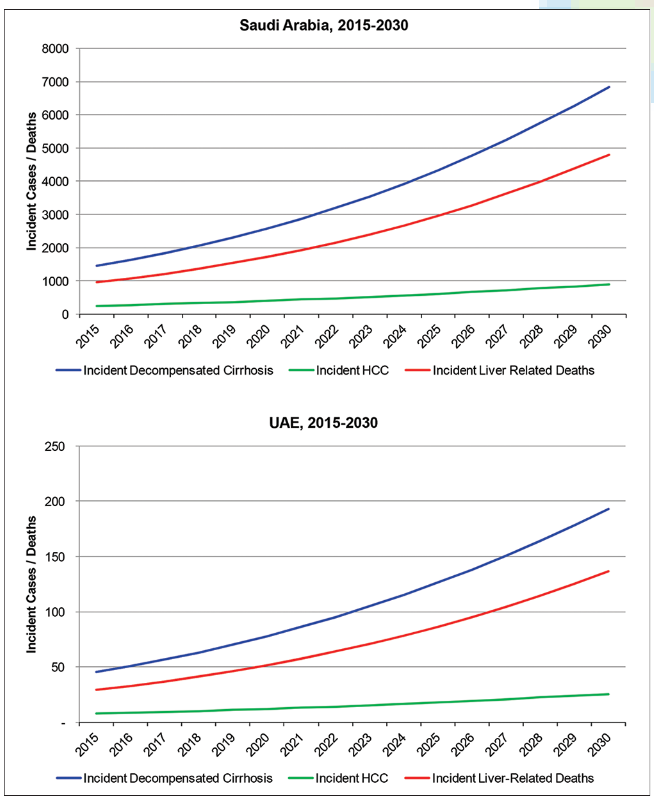

Figure 5: Incident decompensated cirrhosis, HCC and liver-related deaths among prevalent NAFLD population – 2015–2030

Mortality: In the total NASH population in Saudi Arabia in 2017, there were 1810 deaths classified as excess cardiovascular and 1220 liver-related deaths. In UAE, NASH deaths in 2017 included 80 excess cardiovascular deaths and 40 liver-related deaths (1.5%). By 2030, annual liver-related deaths were estimated at 4800 deaths in Saudi Arabia (295% increase from 2017) and 140 deaths in UAE (270% increase). By 2030, liver-related mortality was estimated to comprise 4.4% of all deaths in the total NAFLD population in Saudi Arabia and 2.9% of such deaths in UAE [Figure 5].

DISCUSSION

Levels of obesity and diabetes in Saudi Arabia and UAE are on par with the high levels observed in Western countries.[7] The burden of NAFLD-related liver disease may reach very high levels in the Gulf countries, which have relatively young populations, potentially implying relatively lower rates of advanced liver disease in the near term and potentially large increases in disease burden in the coming decades. Pediatric and adolescent obesity in Saudi Arabia,[47,48] UAE,[49] and other Arab countries[50] is already at epidemic levels and increasing rapidly. There may be an age impact of developing NAFLD in young populations with resulting NASH that may require a liver transplant at an earlier age.[51] In the coming decade, NASH will likely be the leading indication for liver transplantation in Gulf countries, due to a reduced burden of viral hepatitis, in combination with skyrocketing obesity rates. Increasing prevalence of obesity and diabetes will reduce the potential pool of donors as well. One study in the region reports that approximately 25% of potential donors were excluded due to diabetes or BMI > 28 kg/m^2.[52]

Both literature review and expert interviews were utilized to design the model and validate model outputs. For changes over time in obesity levels, estimates from the global burden of disease study were used, as data were available at four time points.[23] Data from the Saudi Health Information Survey[22] were used in adjustments of disease progression,[6] as these data were considered representative of the long-term populations of both countries. For both countries, if the national obesity prevalence levels off, it is estimated that the prevalence of NAFLD will also level off. The proportion of NASH subjects among the NAFLD population is likely to increase in the coming decades due to aging populations, even if adult obesity prevalence remains at the current high levels without further increase.

The results of modeling have potential to inform healthcare systems. Effective strategies are needed to prevent and treat NAFLD/NASH in order to avert a marked increase in the incidence of end-stage liver disease and related mortality. A future with increasing disease burden is supported by recent data demonstrating the growing contribution of NASH toward demand for liver transplantation.[1,13]

Another important result of the modeling is the rapid increase in the number of individuals with cirrhosis, especially decompensated cirrhosis due to NASH. Data from multiple countries demonstrate that the proportion of HCC attributed to NAFLD is growing rapidly.[1,53] Among 235 HCC patients presenting at a Saudi medical center during 2009–2011, the majority were overweight/obese (mean BMI = 27.6 ± 5.9 kg/m^2) and had NAFLD risk factors, including 57.9% with DM, 52.3% with hypertension, and 12.8% with dyslipidemia. Among the HCC cases, 21.7% were classified as cryptogenic cirrhosis,[54] which potentially includes cases attributable to NAFLD.[13] A further impact of the growing burden of NAFLD in Saudi Arabia and UAE is increasing incidence and prevalence of HCC.

This analysis calculated mortality among NAFLD cases with classification as background, excess CVD and liver-related mortality. Large increases in liver-related mortality will be associated with increasing numbers of cirrhotic cases within a growing NASH population. Aging of the population is a risk factor for more advanced disease[6] and the progression of disease to advanced stages of NASH.[4,9] Given the long course of the disease, the burden of liver-related morbidity and mortality will continue to increase for decades. This emphasizes the necessity of identifying NAFLD cases, especially persons with clinically significant fibrosis, who may be candidates for therapy.

Limitations of this study included those inherent to modeling a condition with a long course of disease in countries with large expatriate populations. Data from the UAE National Diabetes and Lifestyle Study show that expatriates in UAE experience Western levels of obesity and diabetes, similar to the Emirati population.[25] However, it is unknown how many expatriate individuals will develop NAFLD while in the UAE or for what duration of the disease they will be residents of UAE. Saudi Arabia also has a high proportion of expatriate individuals included in their population, but they do not constitute a majority of the population.

A limitation of modeling is a lack of data from general population studies measuring hepatic steatosis and fibrosis with consistent methods. Some estimates are based on data collected years ago, and likely do not reflect current disease burden, given increases in obesity and DM. Many studies conducted NAFLD screening using ultrasound, which only reliably detects steatosis of >20%, failing to identify a significant proportion of the NAFLD population.[5]

While the model adjusted for the greater current magnitude of obesity and DM, there has been a dramatic increase in childhood obesity in recent decades, and the onset of DM at younger ages is expected,[55] suggesting a longer course of disease with potentially greater risk to develop end-stage liver disease. The largest relative increase in diabetes prevalence over the past two decades has occurred among adults aged ≥ 65 years,[56] with increased age also a predictor of advanced fibrosis.[6]

A lack of consistent diagnostic measures means that reported NAFLD prevalence rates vary between studies,[14] and NASH can be histologically detected in some NAFLD cases with normal liver enzyme measures.[57] NAFLD is asymptomatic among most stages, and typically there is a long period between incident steatosis and a diagnosis of liver disease. However, staging of fibrosis alone can be a useful predictor of long-term outcomes.[58,59] Noninvasive tests such as transient elastography are relatively easy to perform, and have been shown to reliably predict the degree of liver fibrosis,[60,61] but still have not been approved for this purpose.

CONCLUSION

This analysis confirms a large and growing burden of disease associated with NAFLD and NASH, in tandem with a global pandemic of obesity.[62] The World Health Organization has called for a halt to the increase in diabetes and obesity at the global level,[63] with sustainable development goal 3.4 calling for a reduction by one-third in premature mortality from noncommunicable diseases by 2030. There is an urgent need to address the factors contributing to obesity in the Eastern Mediterranean Region, including dietary factors and inactivity,[64] and to meet World Health Organization goals to stop the increase in noncommunicable disease.[63]

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Conflicts of interest

There are no conflicts of interest.

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