JGH Journal of Gastroenterology and Hepatology

JGHF

doi:10.1111/jgh.14270

SUPPLEMENT ARTICLE

Burden of non-alcoholic fatty liver disease in Australia

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Key words
cirrhosis, fatty liver, general population, prevalence.

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Declaration of conflict of interest: S. M. and L. A. have no conflicts of interest to declare.
Financial support: Editorial support was provided for the development of the article by Elizabeth Hutchings RN MNSc from WriteSource Medical, Sydney, Australia, and funded through an Unrestricted Educational Grant from Gilead Sciences, Melbourne, Australia, in accordance with Good Publication Practice (GPP3) guidelines (http://ismpp.org/gpp3). S. M. and L. A. received no honorarium in association with this article.

Abstract

Non-alcoholic fatty liver disease (NAFLD) is the commonest cause of chronic liver disease in the Australian population, although precise estimates of prevalence are lacking. NAFLD may progress to liver fibrosis, cirrhosis, decompensated liver disease, and liver cancer and is becoming an increasingly common indication for liver transplantation in Australia and New Zealand. There is an extrahepatic burden of NAFLD extending beyond the liver, which is manifested by an increased risk of developing cardiovascular disease, diabetes, and chronic renal impairment, all of which are common causes of morbidity in the Australian population. Early recognition of those patients at high risk of developing advanced liver disease is essential in order to target those who will benefit from intensive lifestyle modification. In this review, we present data on the epidemiology of NAFLD within Australia, its associated health burden in terms of hepatic and extrahepatic complications, common clinical presentations, and indications for treatment. We also propose a research agenda that highlights knowledge needed to improve diagnosis and management specific to the Australian context.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is defined as > 5% liver fat in the absence of excess alcohol consumption (< 20 g daily for women and < 30 g daily for men). NAFLD encompasses a spectrum from hepatic steatosis to liver fibrosis, compensated cirrhosis, and decompensated liver disease. Increased insulin resistance underlies most cases of NAFLD; hence, other features of the metabolic syndrome frequently coexist, including increased waist circumference, impaired glucose tolerance/type 2 diabetes (T2DM), hypertension, and hypertriglyceridemia. NAFLD is the commonest cause of elevated liver enzymes in the Australian population[1,2] and is expected to become one of the most frequent indications for liver transplantation in developed countries in the next decade.[3]

In this review, we present available data on the prevalence of NAFLD in Australia, its associated health burden in terms of hepatic and extrahepatic complications, common presentations, and evidence-based therapeutic options. We also outline a research agenda highlighting gaps in knowledge that are needed to improve diagnosis and management of people with NAFLD specific to the Australian context.

Prevalence of non-alcoholic fatty liver disease in Australia

A diagnosis of NAFLD may be established by exclusion of excess alcohol consumption and confirmation of hepatic steatosis by noninvasive imaging methods including ultrasound, computed tomography, or magnetic resonance spectroscopy or by liver biopsy. An elevated alanine aminotransferase (ALT) level also suggests NAFLD in the appropriate clinical context and exclusion of alternative causes such as viral hepatitis; however, it is less reliable or specific for NAFLD than imaging. Prevalence estimates vary substantially depending on the diagnostic tool used. Although histology is considered the gold standard for diagnosis, it is not feasible in population-based settings because of its invasive nature, side effects, and cost. Scoring systems for NAFLD also exist, using a combination of noninvasive variables to estimate the likelihood of presence of NAFLD, but these have limited diagnostic accuracy and will not be covered here.[4]

Prevalence studies in Australian adults using imaging methods. Imaging remains the preferred diagnostic tool for NAFLD, particularly liver ultrasound where the liver will typically appear bright with an increased echotexture. Ultrasound has limited sensitivity for the disease when hepatic fat is below 30% or in the presence of obesity. There are no population-based studies of prevalence of NAFLD using ultrasound in Australian adults; however, a meta-analysis of the global prevalence found a range between 25% in Caucasians and over 40% in ethnic groups such as Mexicans and South Americans.[5] Prevalence studies using magnetic resonance spectroscopy or magnetic resonance imaging have greater diagnostic accuracy for NAFLD but have not been

undertaken in Australia because of cost and limited availability. Thus, the prevalence of NAFLD in Australian adults remains uncertain; however, it is likely to correlate with the prevalence of obesity, which was estimated at more than one quarter of the Australian population in the recent Australian Bureau of Statistics Health Survey. Between July 2014 and June 2015, the Australian Health Survey (2014–2015) collected data from a random sample of ~19 000 individuals in all Australian states and territories, including those from urban, rural, and remote areas. Data included both self-reported information (interviews and questionnaires) and biochemical analysis[6] (Fig. 1).

Prevalence studies in Australian adults using alanine aminotransferase. Elevated serum ALT is suggestive of NAFLD when it is sustained, more than one-third the upper limit of normal,[7] and seen in association with other features of the metabolic syndrome.[1] As a diagnostic tool, elevated ALT will underestimate NAFLD prevalence compared with ultrasound[5] but is frequently used because of its ease of use, low cost, and noninvasive nature.

A number of population-based studies have assessed the frequency of elevated enzymes in Australian adults (Table 1). These consistently show elevated ALT in approximately 10–14% of the general population and are higher in male individuals than female individuals.[1] There is a robust, reproducible association of elevated ALT with components of the metabolic syndrome, particularly hypertriglyceridemia and waist circumference. Data from the Australian Health Survey, which is the largest cross-sectional study conducted in the general population to date, showed that among 9447 adults, 14% of male individuals and 9% of female individuals had elevated ALT using standard cutoffs of 40 IU/L for men and 30 IU/L for women.[1] Other population-based studies include the Busselton Health Study, which assessed 2610 individuals and found that 9% had elevated ALT following exclusion of viral hepatitis, iron overload, and autoimmune liver disease.[2]

Prevalence studies using liver biopsy. Prevalence studies using the reference standard of liver biopsy are subject to selection bias; however, these provide the opportunity to assess the prevalence of non-alcoholic steatohepatitis (NASH) and fibrosis. An outpatient-based study from the USA recruited patients from a primary care clinic and were offered ultrasound followed by biopsy if ultrasound was suggestive of NAFLD.[8] The prevalence of NAFLD was estimated at 46%, with 30% of the NAFLD group displaying the more aggressive inflammatory form of NAFLD, NASH. While the studied cohort was overweight, with a mean body mass index (BMI) of 29 kg/m^2, which is higher than that found in Australia, these data support that NAFLD and NASH are highly prevalent in overweight/obese persons in primary care.[5]

Within Australia, studies using liver biopsy in morbidly obese patients undergoing bariatric surgery have found the prevalence

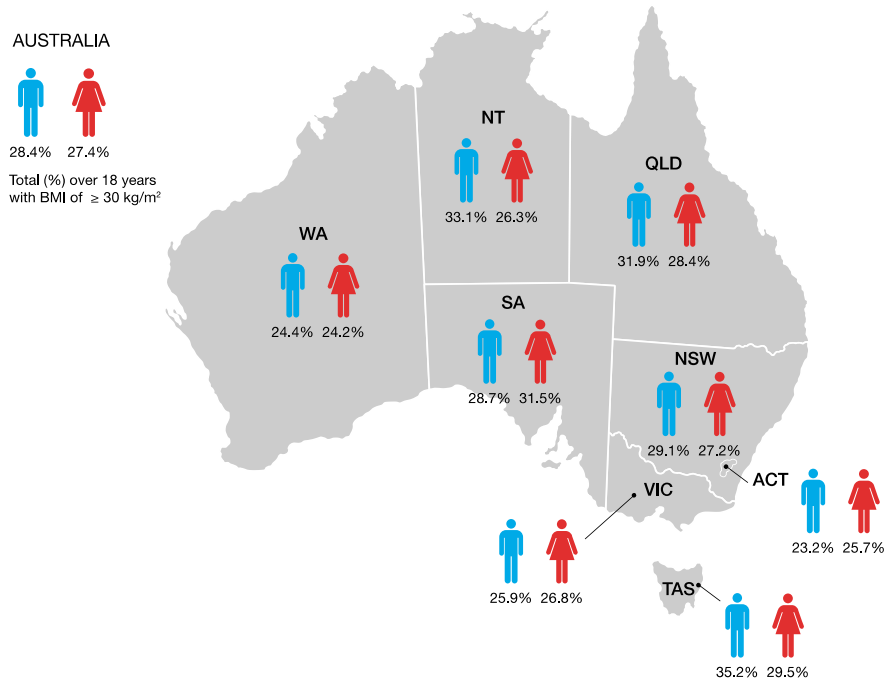

Figure 1 Proportion of Australian adults with a body mass index (BMI) of ≥ 30 kg/m^2 by state/territory and by sex. Limited epidemiological data for non-alcoholic fatty liver disease (NAFLD) exist in Australia; however, the prevalence of obesity is well documented. Obesity is the leading risk factor for NAFLD with 60% of obese individuals having NAFLD. The trends in NAFLD prevalence in Australia are likely to reflect the underlying prevalence of obesity. , male (%) over 18 years with BMI of ≥ 30 kg/m^2; , female (%) over 18 years with BMI of ≥ 30 kg/m^2. Data source: Australian Bureau of Statistics. National Health Survey, 2014–2015, Canberra, 2015. Available from http://www.abs.gov.au/.

Table 1 Summary of studies examining the prevalence of NAFLD in Australia

Reference	Patient population	Method of diagnosis	Prevalence	Summary of findings	Limitations
Prevalence of NAFLD using serum ALT					
Adams *et al.*[2]	1326 male and 1284 female	Elevated serum ALT levels (> 40 IU/L) and exclusion of other causes	9% overall had elevated ALT.	Elevated ALT was more common with obesity than with alcohol excess, indicating that obesity is a bigger driver of elevated enzymes.	ALT has limited sensitivity and specificity for NAFLD. Data are from 1994/1995.
Mahady *et al.*[1]	9447 people from general population	Elevated serum ALT (> 40 IU/L for men and > 30 IU/L for women)	11% overall had elevated ALT.	Elevated ALT was independently associated with metabolic cofactors.	ALT has limited sensitivity and specificity for NAFLD. Greater than 50% of the population attributable fraction of elevated ALT is due to truncal obesity. Chronic viral hepatitis not excluded.
Booth *et al.*[14]	500 adolescents (15 years)	Upper normal limit—ALT (32 U/L [boys] and 20 U/L [girls])	Elevated ALT levels found in 10% of adolescents using cutoffs.	Mean ALT levels correlated strongly with obesity in male but not in female.	
Prevalence using imaging techniques (pediatric studies only available from Australian data)					
Ayonrinde *et al.*[11]	1170 adolescents (17 years)	Ultrasound	15.2% NAFLD across the total cohort. By sex, 19.6% female and 10.8% male.	NAFLD in male was associated with a more significant metabolic abnormalities and greater disturbance in adipokines.	Ultrasound-based diagnosis may miss milder cases or result in misclassification.
Prevalence using liver biopsy (in highly selected populations)					
Dixon *et al.*[9]	105 bariatric surgery patients	Liver biopsy	96% NAFLD, 25% NASH, and 9.5% advanced fibrosis.	NASH predicted by insulin resistance, ALT, and hypertension.	Highly selected morbidly obese population.
Ooi *et al.*[10]	182 bariatric surgery patients	Liver biopsy	83% NAFLD, 12% NASH, and 2.2% advanced fibrosis.	—	Highly selected morbidly obese population.

ALT, alanine aminotransferase; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis.

of NAFLD to be 83–96%, and among those with NAFLD, the prevalence of NASH and advanced (stages F3 and F4) fibrosis was 15–26% and 3–10%, respectively.[9,10] NASH was associated with insulin resistance, hypertension, and an elevated ALT. These data provide information on the prevalence of NASH in morbidly obese Australians but are from a highly selected population and difficult to generalize.

Prevalence of non-alcoholic fatty liver disease in the Australian pediatric population. Assessment of the prevalence of NAFLD in children and adolescents is important because insulin resistance and metabolic dysfunction commence in childhood,[11,12] presenting a timely opportunity to intervene to reduce long-term morbidity. Notably, NAFLD has been shown in Australian adolescents to be additive to conventional cardiometabolic risk factors in increasing arterial stiffness, which is a predictor of cardiovascular morbidity and mortality.[13] Booth *et al*. assessed a population of healthy Australian adolescents derived from a random sample of 500 school students aged 15 years[14] and showed that 10% of Australian adolescents had an elevated ALT using a reference standard of 32 IU/L for boys and 20 IU/L for girls, and the degree of elevation was linearly associated with BMI. Of note, the correlation of elevated ALT and BMI was robust in boys but not in girls, and this sex-specific difference is also seen in adulthood.[14]

In a further study in incarcerated adolescents, 18% had an elevated ALT in the context of a low hepatitis C virus antibody positivity of 3%.[12] Those with elevated ALT had a significantly greater BMI (28 *vs* 22 kg/m^2) and increased rates of dyslipidemia and elevated γ-glutamyltransferase, and 90% of those with elevated ALT also had at least one feature of the metabolic syndrome. These data provide further insights that obese adolescents are an "at-risk" population for future morbidity.

The most reliable estimate in late adolescence stems from the Raine Health Study Cohort, which is representative of the general population. Among 1170 individuals who underwent ultrasound at age 17, NAFLD was found in 13% and was more common in girls than boys (16% *vs* 10%); however, this was related to more female individuals being centrally obese.[15] Children with excess weight at age 3 were more likely to have NAFLD in teenage years.[11,15]

Slowly increasing liver transplant rates for non-alcoholic steatohepatitis cirrhosis in Australia. The rates of liver transplant for end-stage liver disease from NASH provide an alternative way of estimating burden of disease; however, these are imperfect given the high prevalence of comorbid cardiometabolic disease, which may preclude potential patients from transplantation. Prior to the year 2000, there were no cases of liver transplantation recorded for NAFLD/NASH, although some may have been misclassified as cryptogenic cirrhosis. Since then, NASH has been increasing as an indication for transplantation in Australia and New Zealand, and in the period 2010–2014, NAFLD/NASH accounted for 6% of transplants in Australia.[16,17] By 2015, NAFLD/NASH had risen to be the third commonest indication for listing for liver transplantation in Australia and New Zealand, accounting for 9% of listings behind hepatitis C infection and alcohol-related liver disease.[18]

In the USA, there has been a much greater increase in NAFLD requiring transplantation, such that it is now the second leading indication for activation and is projected to become the commonest cause of liver transplantation in the USA by 2030.[19,20] Given the increase in obesity in the USA occurred approximately one decade prior to Australia's epidemic,[21] it is possible that the incidence of long-term consequences such as end-stage liver disease due to NASH will parallel the US experience in the future.

Recognizing the burden of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis within Australia

The majority of people with NAFLD/NASH in the Australian population are asymptomatic and undiagnosed. The commonest mode of presentation is generally through abnormal liver enzymes or imaging, often performed for reasons not related to NAFLD. Nevertheless, routine screening of the general population and higher risk patients such as diabetic or obese patients is not recommended because of uncertainty regarding cost-efficacy and treatment options.[22]

Among Australian specialists and general practitioners, there is an underappreciation of the prevalence of NAFLD and uncertainty of how to assess liver fibrosis.[23,24] Consequently, patients with advanced fibrosis are often not recognized, with one study of 100 NASH cirrhotic patients from an Australian tertiary center, demonstrating that two-thirds were diagnosed incidentally.[25] An incidental diagnosis of cirrhosis was associated with more advanced liver disease and a higher likelihood of concomitant hepatocellular carcinoma (HCC), highlighting the importance of staging fibrosis in patients with NAFLD.

Natural history of non-alcoholic fatty liver disease

There is limited Australian data regarding the course of NAFLD; however, progression rates have been remarkably similar between studies from different ethnic and geographical areas suggesting findings are likely to be generalizable to the Australian population.

Histological course. Overall, approximately 30% of patients with NAFLD or NASH will develop progressive fibrosis, whereas 20% will have regression over an average follow up between 2.2 and 13.8 years.[26] Progression is slow with a meta-analysis indicating it takes an average of 7.7 years to progress one fibrosis stage[27]; the rate of progression is twice as high in NASH subjects compared with those without NASH. A small proportion of patients also progress rapidly from no fibrosis to advanced fibrosis within 5–10 years.[27] Reliable predictors of fibrosis progression are lacking; however, it appears that worsening metabolic disease (weight gain, diabetes, and insulin resistance) parallels worsening histology.[28,29]

Genetic polymorphisms may play a role in determining disease progression with the heritability of liver fibrosis in NAFLD patients estimated at 50%.[30] The rs738409 and rs58542926 single nucleotide polymorphisms in the *PNPLA3* and *TM6SF2* genes are common in the Australian population with minor allele frequencies of 20–25% and 7–8%, respectively.[31] These single

nucleotide polymorphisms have been identified by genome-wide association studies to be associated with an increased risk of NAFLD, as well the presence of more severe liver histology (i.e. NASH and advanced fibrosis).[31–34] At the individual patient level, however, they are not sufficiently predictive in isolation to stage disease severity or determine prognosis.

Clinical course of non-alcoholic fatty liver disease

Liver cirrhosis, decompensation, and liver-related mortality. Only a minority of patients with NAFLD will develop cirrhosis and decompensation, with a population-based study from the USA demonstrating a 3.1% incidence for both end points over 7.6 years.[35] The risk of progression to end-stage liver disease is dependent on the underlying liver histology; simple steatosis is associated with low risk with 0–4% of patients progressing to cirrhosis over a 20-year period.[36–38] In contrast, 25% of NASH patients may develop cirrhosis, and up to 10% develop decompensated liver disease over 9–13 years[39] (Fig. 2). Fibrosis rather than NASH is the dominant histological predictor of liver-related morbidity and mortality outcomes.[40–42] A large (n = 619) international multicenter cohort study including Australian patients found mild fibrosis (stage 1) to be associated with a greater risk for overall mortality compared with no fibrosis (hazard ratio 1.9, 95% confidence interval 1.3–2.8), although only moderate fibrosis (stage F2 and above) was associated with increased risk of liver decompensation (ascites, encephalopathy, or varices).[41]

Progression to cirrhosis is not uniform, and metabolic factors such as diabetes are likely to portend a higher risk.[43,44] Once cirrhosis has developed, approximately one quarter will develop a major liver complication after 3 years, and 50% will develop a complication at 10 years.[45] Following an episode of decompensation, the survival of NASH patients falls markedly to a median of 2 years.[46]

Hepatocellular carcinoma. The incidence of HCC has been steadily increasing in Australia over the past two decades and is projected to have the greatest incidence increase of any cancer in Australia, increasing 38% in male individuals and 78% in female individuals from 2007 to 2020.[47] Chronic hepatitis B and C infections are driving part of the increasing burden. In addition, the prevalence of risk factors for NAFLD (and HCC) including the metabolic syndrome, T2DM, and obesity has increased in the Australian population over the past two decades, suggesting that NAFLD may be contributing.[48,49] Analysis of the population-based Surveillance, Epidemiology and End Results Program database from the USA demonstrated that NAFLD-related HCC increased 54% from 2004 to 2009, leading NAFLD to account for 14% of HCCs overall.[50] Data from Australia are similar with contemporary cohorts from the states of Western Australia and Victoria demonstrating NAFLD to be the underlying cause of liver disease in 14% of HCC cases.[51,52]

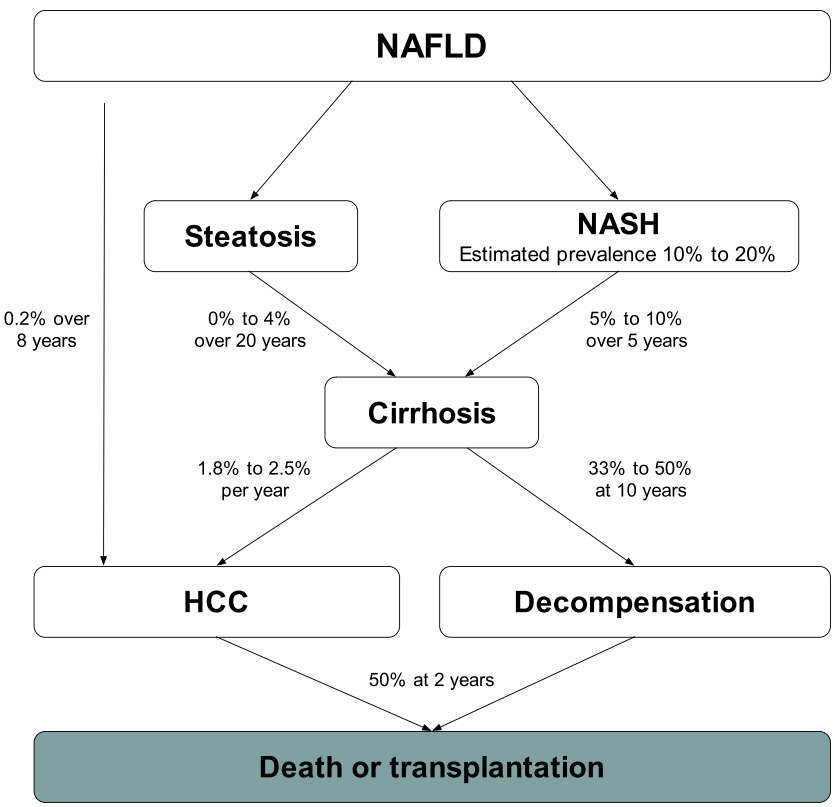

Figure 2 Natural history of disease progression in non-alcoholic fatty liver disease (NAFLD). HCC, hepatocellular carcinoma; NASH, non-alcoholic steatohepatitis.

Overall, HCC remains an uncommon complication of NAFLD, and its development is heavily influenced by the presence of underlying cirrhosis. For example, a Japanese cohort of 6508 NAFLD subjects found the HCC incidence to be only 0.2% after 8 years; however, subjects with advanced fibrosis had a 25-fold increase in risk.[53] Among NAFLD patients with cirrhosis, the cumulative incidence of HCC is 2–13% over a 3- to 7-year period.[54] Putative risk factors for HCC in NAFLD cirrhotic patients include diabetes, age, previous alcohol consumption, and intrahepatic iron.[55,56] Interestingly, a meta-analysis of observational studies of different types of liver disease including NAFLD demonstrated the use of metformin in patients with T2DM to be associated with a reduced risk of HCC, suggesting that HCC risk may be modifiable.[57]

Once HCC develops in NAFLD cirrhotic patients, survival appears to be shorter than in patients with HCC related to other causes such as hepatitis C.[50] Although this may in part be related to lead time bias due to lower rates of HCC surveillance in NAFLD patients, older age and larger tumor size at time of diagnosis may also contribute.[58] In patients who undergo curative HCC treatment, overall survival is comparable with patients with hepatitis C or alcohol-related HCC.[58,59]

Non-alcoholic fatty liver disease subjects without cirrhosis may also develop HCC; however, this is uncommon.[53] Australian data demonstrate one quarter of cases are diagnosed without cirrhosis.[51] Limited data suggest that male sex and the presence of the metabolic syndrome may be risk factors for the development of non-cirrhotic HCC; however, these factors are not sufficiently predictive to justify screening in this population.[60,61]

Extrahepatic manifestations of non-alcoholic fatty liver disease

The liver is a secretory organ that is responsible for the generation of lipoproteins, hormones, inflammatory cytokines, and mediators. In NASH, lipid metabolism is disturbed, and liver-derived inflammatory cytokines and hypercoagulable factors are upregulated.[62] NAFLD is also associated with hepatic insulin resistance, increased fasting glucose levels, and an atherogenic lipid profile.[63] Thus, it is proposed that the liver may play a central role in the genesis of extrahepatic complications, and consequently, the burden of NAFLD may extend beyond the liver to include an increased risk of developing cardiovascular disease (CVD), diabetes, and chronic renal impairment (Fig. 3).

Cardiovascular morbidity and mortality. Ischemic heart disease is the leading cause of death in Australia, responsible for 12% of all deaths in 2016.[64] Cross-sectional population-based studies have demonstrated NAFLD to be associated with

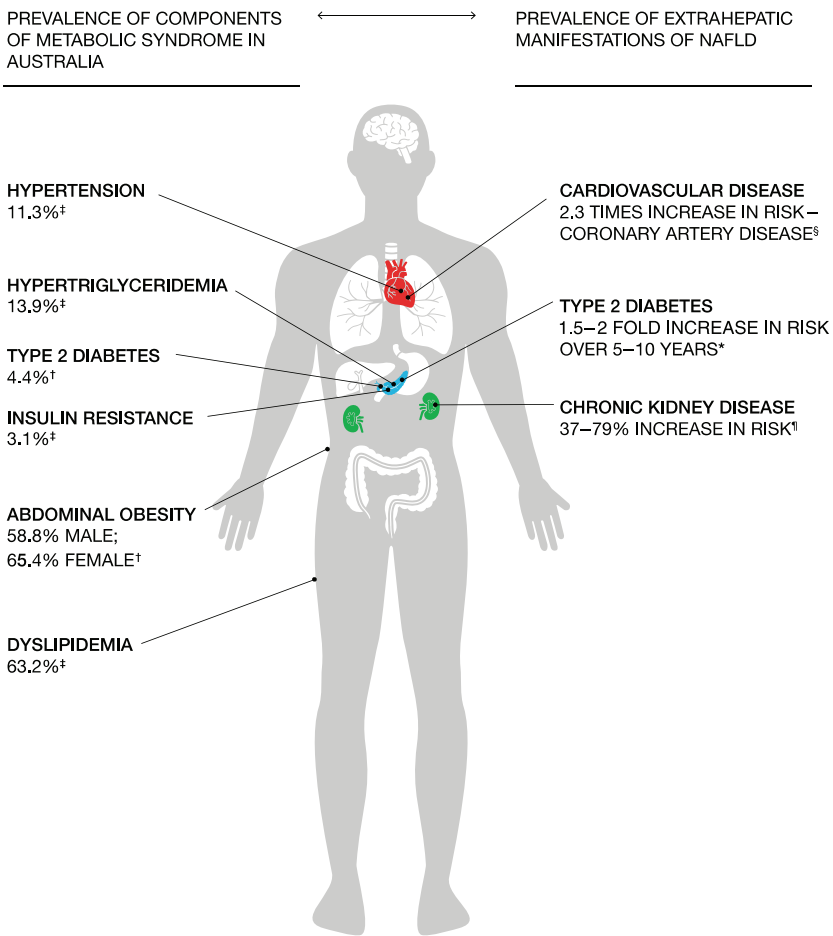

Figure 3 Prevalence of metabolic risk factors for non-alcoholic fatty liver disease (NAFLD) in Australia and the associated increased risk of extrahepatic manifestations. †Australian Bureau of Statistics. National Health Survey, 2014–2015, Canberra, 2015. Available from http://www.abs.gov.au/. ‡Australian Bureau of Statistics. Australian Health Survey: Biomedical Results for Chronic Diseases, 2011–2012, Canberra, 2013. Available from http://www.abs.gov.au/. §Wu *et al.*[67] ¶Musso *et al.*[79] and Mantovani *et al.*[80] *Adams LA, Anstee QM, Tilg H, Targher G. Non-alcoholic fatty liver disease and its relationship with cardiovascular disease and other extrahepatic diseases. Gut. 2017.

predictors of heart disease such as endothelial dysfunction, arterial stiffness, and myocardial dysfunction, independent of traditional cardiovascular risk factors.[13,65,66] A systematic review and meta-analysis of 34 studies found NAFLD to be associated with 2.3-fold increased risk of incident coronary artery disease although not CVD mortality.[67] The severity of NAFLD, which generally parallels severity of underlying metabolic diseases, may stratify cardiovascular mortality risk. One cohort study found subjects with baseline liver histology confirming simple steatosis were not at increased risk of cardiovascular death, but those with NASH were twice as likely to die from CVD compared with the general population.[42] Similarly, a US cohort of 11 000 participants demonstrated increased (69%) overall mortality in NAFLD patients with advanced fibrosis, which was largely driven by CVD (adjusted hazard ratio 2.7 to 3.5).[68] It remains unclear if reversal of NASH or NAFLD leads to a reduction in cardiovascular risk that is independent of improvement in other metabolic factors.

Diabetes. Multiple large cohort studies have consistently shown NAFLD to be independently associated with increased incidence of T2DM with a 1.5-fold to 2-fold increased risk over 5 to 10 years.[69–74] Similar to the risk of CVD, the severity of underlying NAFLD appears proportional to the risk of T2DM, with subgroups of NAFLD patients, particularly those with elevated ALT, underlying NASH or advanced fibrosis, to have an increased risk of incident T2DM.[39,69,75] New-onset diabetes incidence appears to fall following the improvement or resolution of NAFLD.[74,76,77]

The majority of observational data supporting a link between NAFLD and diabetes are derived from Asian populations, with confirmation required in other ethnic groups.

Chronic kidney disease. Chronic kidney disease (CKD) presents a substantial health burden in Australia, with 1.7 million hospitalizations and 17 000 deaths in 2015.[78] Two meta-analyses of observational studies have concluded that NAFLD is associated with a 37–79% increased risk of incident CKD (defined as estimated glomerular filtration rate of < 60 mL/min and/or proteinuria).[79,80] Adjustment for potential confounding risk factors did not significantly alter the risk. Similar to the association between NAFLD and CVD and T2DM, the risk of future CKD increased further in those with advanced fibrosis or those with NASH. These studies have largely originated in Asian populations limiting generalizability to the Australian setting and have been limited by the lack of histological assessment and are observational, preventing conclusions regarding causality. Nevertheless, resolution of NASH and improved fibrosis in patients undergoing successful lifestyle intervention is associated with improvement in estimated glomerular filtration rate independently of potential confounding factors including weight change, blood pressure, and insulin resistance.[81] No study has demonstrated NAFLD to increase the risk of dialysis or stage 5 CKD.

Reducing the burden by targeting those at highest risk

Recognition of those patients most likely to progress is essential in order to target individuals most likely to benefit from intensive lifestyle modification and reduce future burden of disease. Based on natural history studies, those at greatest risk are NASH patients with at least moderate fibrosis. There remains no approved pharmacological therapies for people with NAFLD/NASH, and lifestyle modification remains key, as recently reviewed.[82] There is good evidence that lifestyle recommendations leading to weight loss result in reduced fibrosis in a clinical trial setting,[83] but the challenge remains maintaining these changes for the long term, and research into the most effective behavioral strategies to facilitate this is required.

Dietary modifications in non-alcoholic fatty liver disease. In Australia, the typical diet is the "Western style" diet, which is high in carbohydrate and processed foods. Among Australian adolescents, a Western diet and high fructose consumption (in obese individuals) have been associated with an increased risk of future NAFLD.[84,85] Evidence suggests a Mediterranean style diet that is high in monounsaturated fats and low in dairy and red meat is preferable for those with NAFLD. A crossover trial from Australia where patients were randomized to a Mediterranean diet or usual diet and assessed with magnetic resonance spectroscopy showed a significant reduction in hepatic fat stores and improved insulin sensitivity with a Mediterranean style diet, even in the absence of weight loss.[86] Metabolic benefits for this diet have also been seen in T2DM and CVD.[87,88]

People with NAFLD should be advised to avoid excess carbohydrate, in particular fructose and foods sweetened with high fructose corn syrup. In Australia, because of the ready availability of sucrose, high fructose corn syrup is less common than in the USA, but observational data suggest overconsumption of either form is associated with increased liver fat and reduced insulin sensitivity.[89,90] Consumption of trans-fatty acids should also be minimized because of its association with dyslipidemia and severe hepatic necroinflammation in animal studies,[91] but in Australia, it is not mandatory to declare trans-fatty acid content as it is in other countries. It is reasonable to minimize saturated fats[92] and substitute with monounsaturated fats,[93] although robust data to support these recommendations are lacking. Coffee appears beneficial in observational data,[94] but there is insufficient evidence to recommend probiotics currently.

Exercise. Any form of exercise should be encouraged in patients with NAFLD, as both aerobic and anaerobic exercise reduce liver fat. Evidence suggests that people with NAFLD do less exercise than the general population.[95] Specific exercise advice from the European Association for the Study of the Liver suggests 150 min of moderate exercise per week (such as walking) and 75 min of vigorous exercise per week (such as running), and muscle strengthening work twice a week[96] is desirable. However, choice of exercise depends on patient preferences and what is feasible to maintain over the long term.[97] Recent Australian and international studies on the relationship of sedentary time and insulin resistance consistently show that prolonged inactivity is an independent risk factor for insulin resistance, even when short periods of vigorous exercise are interspersed, and patients should also be advised to reduce sedentary time as much as possible.[98,99] Importantly, the absolute reduction in hepatic steatosis with exercise is modest, and it is unclear whether exercise also improves liver

inflammation and fibrosis, so other lifestyle measures including dietary modification should be performed in parallel.

Weight loss. Weight loss should be promoted to all patients with NAFLD, as even small amounts are associated with reduced hepatic fat and inflammation[100] and larger amounts (> 10% body weight) may induce fibrosis regression.[83] A variety of dietary approaches may be used to induce weight loss, aiming for a daily calorific deficit of around 500 kcal/day for women and 750 kcal/day for men, approximating a 30% energy deficit.[101] Importantly, weight loss improves quality of life for people with NAFLD/NASH.[102] A caveat, however, is that rapid weight loss via ketogenic diets should be avoided as they may worsen liver histology.[103]

Pharmacotherapy. There is no consensus on pharmacotherapy in NAFLD. A meta-analysis of randomized trials showed improved fibrosis for the insulin sensitizer pioglitazone,[104] but it is unclear if this is maintained after drug cessation.[105] The safety of long-term use also remains unclear, with concern around increased risk of fractures and weight gain.[104] The antioxidant vitamin E has demonstrated histological benefit in nondiabetic patients in randomized trials,[106] but increased mortality at high-dose vitamin E was suggested in a meta-analysis of observational data,[107] and further studies are needed. Recent data from a phase II trial on incretin mimetics such as liraglutide indicated improvement in liver histology and metabolic risk factors without significant side effects, and phase 3 trials are awaited.[108] Ongoing phase 3 trials that are awaited include obeticholic acid, which works via the farnesoid X receptor, elafibranor, which is a peroxisome proliferator receptor α/δ agonist, and selonsertib, which is an apoptosis signal-regulating kinase 1 inhibitor.

Bariatric surgery. When successful at inducing significant weight loss, bariatric surgery has been shown to reduce inflammation in 85% of liver biopsies and improve fibrosis in one-third of patients at 1-year follow up.[109] Clearly, these benefits need to be weighed up against the potential complications of major surgery, and whether the weight loss is sustained,[110] and ongoing research into the benefits to harm profile in NASH patients will be informative.

Economic burden of non-alcoholic fatty liver disease/non-alcoholic steatohepatitis in Australia

The financial burden of NAFLD/NASH in the Australian context is difficult to measure accurately given the lack of accurate diagnostic tools. Within these limitations, a recent study modeling the projected economic burden of NAFLD in North American and European populations provides some data.[5] This study used global prevalence rates of NAFLD and modeled the potential costs as people progressed through to end-stage liver disease or HCC and captured the associated costs. The authors proposed an annual cost of $100m to the US healthcare economy, although it was recognized that key assumptions such as progression to fibrosis remain uncertain, and thus, cost estimates are imprecise. Modeling studies are limited by the quality of the imputed data and assumptions made, and high-quality longitudinal studies on key estimates used are needed to improve accuracy of projections.[111]

Research agenda within Australia

To accurately estimate current prevalence and future healthcare burden from NAFLD, studies in the general Australian population using accurate diagnostic tools are needed. Long-term, high-quality cohort studies would inform natural history including identifying those who are highest risk of disease progression and HCC. Data on hospital admissions for decompensated liver disease due to NAFLD specifically are also needed. In addition, the rates of NAFLD and NASH in the Australian Indigenous population are unknown but important given the high rates of metabolic syndrome, T2DM, and premature death from metabolic and liver disease in this population. Finally, longitudinal studies of children or adolescents with NAFLD would help to inform the long-term outcomes of this group from liver disease and metabolic diseases.

Conclusion. The prevalence of NAFLD in Australia has not been accurately estimated but is likely to parallel that of similar countries, and high-quality, locally based studies are needed to better inform this evidence gap. Current data indicate that NAFLD is present in a significant proportion of the Australian population, particularly those who are overweight or obese. Quantification of the prevalence of NAFLD through general population-based studies and burden represented by NAFLD-related hospitalizations, NAFLD-related HCC, and transplantation is needed for current and future healthcare planning.

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