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Co-leads for the National Institute of Health Research- funded research partnership for early detection and management of Metabolic Dysfunction Associated Steatotic Liver Disease in the Tees Valley.

We note that from previous evidence submitted to the committee on the 14th of March 2024, reference was made to metabolic dysfunction associated steatotic liver disease (MASLD) and research in this area. MASLD is new nomenclature that has recently replaced nonalcoholic fatty liver disease (NAFLD) as a term to describe the pathological accumulation of fat within the liver and at least one cardio metabolic risk factor such as obesity or type 2 diabetes. Research conducted up until the nomenclature change has used the term NAFLD to define its target

population, however there is good concordance between the two definitions (MASLD and NAFLD).

Metabolic dysfunction associated steatotic liver disease (MASLD) is an umbrella term for the pathological accumulation of fat within the liver. This represents the most common liver disease worldwide and its incidence is increasing in line with increasing rates of obesity and type 2 diabetes (i.e., MASLD is caused by a build-up of fat in the liver and is usually seen in people who have overweight or obesity). Current estimates suggest MASLD may affect up to 38% of the global adult population (1). A subset of patients (5.3%) develop advanced forms of the disease that comprises persistent inflammation within the liver known as metabolic dysfunction associated steatohepatitis (MASH) leading to scar formation (fibrosis) (1). For some patients, the scars form nodules within the liver defining the presence of liver cirrhosis. Patients with liver cirrhosis are at risk of losing organ function (decompensated cirrhosis), liver cancer and mortality. MASLD is largely asymptomatic during the early stages and detection during these early stages is problematic – i.e., the gold standard test used to diagnose inflammation and scarring remains an invasive liver biopsy imbued with significant risk. Importantly, 90% of liver disease is preventable (2). MASLD in most cases can be prevented by tackling obesity.

At present there is no approved pharmacotherapy in the UK for MASLD, MASH and its advanced complications. Targeting changes in diet and

physical activity to promote weight loss of around 10% total body weight is the current cornerstone of management. Diet composition is also important. The recommended dietary approach for people with MASLD a Mediterranean style diet and to reduce/avoid highly processed foods and foods high in sugar and saturated fats. Notably, the US Food and Drug Administration (FDA) have recently given early approval to resmitirom for the treatment of advanced MASLD based on promising results of a phase 3 trial at 52 weeks follow-up. (3) Unfortunately, some patients require liver transplantation. A recent study analysed the United States Scientific Register of Transplant Recipients from 2013 to 2022. The primary reason for transplant in 31% of patients (transplanted for liver cancer) was advanced MASLD (3). The number of individuals transplanted for advanced MASLD (without liver cancer) increased from 19% to 27% over the 9-year period of the study (4).

Likewise, MASLD presents a significant health challenge to UK health policy. A recent study analysed data from a UK multicentre retrospective observational cohort study including patients acutely admitted to hospital with decompensated cirrhosis in November 2019 across the UK (5). The study suggests that 15% of liver disease admissions to National Health Service (NHS) hospitals across the UK are due to MASLD. Hospitals in NHS Scotland included in the study had a higher proportion of admissions related to NAFLD (30 [23.4%] of 128 admissions (5).

We note that the committee had questions regarding the effect of liver disease in children. Paediatric liver disease is not within the remit of or research partnership in liver disease. However, evidence suggests that individuals are being diagnosed with MASLD at a much earlier age. A recent study using a non-invasive scan to detect fat within the liver and scarring has shown that 1 in 5 young adults had fat accumulation within the liver, and 1 in 40 had non-invasive evidence of scar formation around the age of 24 years (6). This suggests that MASLD was present from a younger age.

Emerging evidence suggests that the risks of liver fat accumulation and liver disease is increased in people who consume sugar sweetened beverages (SSBs). A systematic review published in 2019 reported that high intake of SSBs was significantly associated with NAFLD/MASLD (40% increased odds of NAFLD) (7). Our NIHR funded Tees valley partnership team is currently updating this systematic review, incorporating the new MASLD nomenclature.

Ultra-processed food (UPF) consumption is also gaining significant attention in the context of MASLD due to its association with the development of obesity and association with type 2 diabetes. A recent systematic review published in 2023 has shown an association between UPF and NAFLD/MASLD (8). Although findings should be treated with some caution, i.e., the included studies were mainly observational, and not designed to detect incidence of NAFLD/MASLD.

Finally, most patients with MASLD are diagnosed and managed within primary care settings. Currently there is no national strategy for early diagnosis, detection and management of MASLD in primary care. Our NIHR funded research partnership in the Tees Valley is specifically interested in developing research aimed at improving early detection, management and healthcare service delivery in the context of MASLD within the primary care.

In summary. 90% of liver disease is preventable and in the context of MASLD can be prevented by tackling obesity. MASLD represents a highly prevalent, worldwide healthcare problem that is increasing with obesity and type 2 diabetes, and advanced forms of the disease are already causing significant burden in hospitals and transplant programmes worldwide. Up to 1 in 5 healthy young adults may have liver fat accumulation. Specific dietary factors such as UPF and SSB consumption have shown strong associations with liver fat accumulation. Currently, national and international guideline recommended approaches for MASLD management are diet and physical activity behaviour change/modification and this remains the cornerstone of management, although medication for advanced forms of the disease may be available in the UK soon.

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