

# Non-alcoholic fatty liver disease and cardiovascular risk: gender differences

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**Summary.** Non-alcoholic fatty liver disease is characterized by fat accumulation in the liver in people who do not drink alcohol. Non-alcoholic fatty liver disease prevalence is constantly increasing. Prevalence is greater in males than in premenopausal females. It is associated with various cardiovascular risk factors and metabolic syndrome and this review aims to shed light on the association between sex and risk of cardiovascular diseases.

**Key words.** Non-alcoholic fatty liver disease, cardiovascular risk, gender differences.

## *Steatosi epatica non alcolica e rischio cardiovascolare: differenze di genere*

**Riassunto.** La steatosi epatica non alcolica è caratterizzata da accumulo di grasso nel fegato in persone che non bevono alcolici. La prevalenza della steatosi epatica non alcol correlata è in costante aumento. La prevalenza è maggiore negli uomini rispetto alle donne in premenopausa. Essa è associata a vari fattori di rischio cardiovascolare e alla sindrome metabolica e questa revisione della letteratura scientifica vuole far luce sull'associazione tra sesso e rischio di malattie cardiovascolari in pazienti con diagnosi di NAFLD.

**Parole chiave.** Steatosi epatica non alcol correlata, rischio cardiovascolare, differenze di genere.

## Introduction

Non-alcoholic fatty liver disease (NAFLD) is characterized by fat accumulation in the liver above 5-10% by weight, or a percentage of hepatocytes that contain lipid droplets greater than 5%, when analyzed with an optical microscope<sup>1</sup>. It develops in people who are not heavy drinkers and in the absence of other known liver pathologies. The pathobiology of NAFLD is complex and multi-phasic and includes dysfunctional adipose tissue, systemic inflammation, insulin resistance (IR), hepatic lipid accumulation and intestinal dysbiosis<sup>2</sup>. NAFLD includes a spectrum of hepatic pathologies that ranges from simple steatosis (namely non-alcoholic fatty liver or NAFL) and non-alcoholic steatohepatitis (NASH), the intermediate form of liver damage, to the most advanced stages of liver disease, namely cirrhosis and hepatocellular carcinoma (HCC)<sup>3,4</sup>. The identifica-

tion of individuals who have NASH with fibrosis has significant prognostic implications. Follow-up studies of patients with NASH and fibrosis demonstrates that almost 30% of these individuals become cirrhotic within 5-10 years. In contrast, only about 3% of individuals with milder forms of NAFLD develop cirrhosis after more than a decade of follow-up. Therefore, NASH with fibrosis progresses to cirrhosis both more consistently and more rapidly than simple NAFL<sup>5</sup>. The prevalence of NAFLD in adults and children in the general population is not certain and is difficult to assess accurately because there is a lack of simple, non-invasive diagnostic tests. The 'gold standard' for diagnosing NAFLD and its severity is represented by liver biopsy, but this invasive technique is neither feasible nor ethical to use in healthy populations. Even in clinical practice, liver biopsies are used to clarify the diagnosis in chronic hepatitis (for example, in patients with indeterminate or discordant results unable to exclude advanced fibrosis)<sup>6,7</sup>. Consequently, its prevalence is usually estimated by serum biomarkers of NAFLD and/or evidence of fatty liver on ultrasonography (US) or magnetic resonance imaging (MRI). Nevertheless, NAFLD is considered the most common chronic liver disease worldwide and its prevalence has been estimated to be approximately around 20-30% in the general population (NAFLD 16-24%, NASH 2.1-6.3%), to be higher in obese people (mean prevalence 34.2%)<sup>8,9</sup>, and to range from 29.6% to 87.1% in type 2 diabetes mellitus (T2DM) subjects<sup>10</sup>. Fatty liver can be present since childhood, with an estimated prevalence of about 7-10%, which reaches 34.2% in obese children<sup>11</sup>. NAFLD has been widely associated with the cardio-metabolic syndrome and its components: hepatic and systemic insulin resistance (IR), dyslipidemia, visceral obesity, hypertension, impaired fasting glucose and increased stroke risk<sup>12-14</sup>. The Dionysos nutrition and liver study reported the risk factors for NAFLD in a representative sample of the general population. They were: body mass index  $\geq 30$ , glucose  $> 110$ , insulin, HOMA and HDL-cholesterol alteration, triglycerides  $> 150$ , blood pressure  $> 130/80$ <sup>15</sup>. Interestingly, these are the same risk factors that are associated with cardiovascular diseases (CVD)<sup>16</sup>. Moreover, in NAFLD patients, liver enzymes have been demonstrated to predict the incidence of

CVDs, independently of the traditional risk factors, including C-reactive protein and metabolic syndrome (MS). As a matter of fact, the extent of liver damage has been correlated with early carotid atherosclerosis, suggesting that the injury to both vessels and liver share similar inflammatory mediators<sup>16</sup>. For these reasons, NAFLD has been recently proposed as an early marker of atherosclerosis and endothelial dysfunction and, consequently, as an independent cardiovascular risk factor<sup>17</sup>. Musso et al. in 2008 reported that the causes of death in patients with NAFLD are represented by ischemic heart diseases in 25% of cases, thus demonstrating that CVDs have an important weight in NAFLD<sup>17</sup>.

There are many differences based on sex in NAFLD<sup>18</sup>. The study of sex differences is a rapidly growing area of medicine and there is an increase in the number of publications on this specific topic. With the aim of better clarifying the sex differences in NAFLD, we carried out a review of the literature highlighting the gender specific findings published in the literature. The biological sex differences in normal physiology and diseases originate mainly from sex chromosomes and sex hormones<sup>11,19</sup>.

### Prevalence of NAFLD and gender differences

A meta-analysis of 74 studies demonstrated that NAFLD prevalence in children/adolescents was higher on average in males than females, both in the general population and in clinical studies<sup>11</sup>. However, when stratified by diagnostic method and gender, in general population studies NAFLD prevalence estimates were similar in males and females using USS as the diagnostic method, whereas they were higher in males in those studies that used alanine aminotransferase (ALT) to assess NAFLD<sup>11</sup>. On the contrary, in clinical studies, pooled estimates were consistently higher in males, regardless of the diagnostic method used<sup>11</sup>. When considering only obese children/adolescents, both in the general population and clinical studies, the prevalence was consistently higher in males than in females, with the exception of general population studies using USS, in which prevalence estimates were similar in both sexes<sup>11</sup>. Menopause or age-specific sex difference was infrequently considered in published studies, but when examined, NAFLD prevalence and incidence were higher in men than in premenopausal women (or aged  $\leq 50$ -60 years) while they tended to become more common in women after menopause (or aged  $\geq 50$ -60 years)<sup>20</sup>. However, after menopause, NAFLD occurs at a higher rate in women, suggesting a protective effect of estrogen<sup>2</sup>. In fact, postmenopausal women on hormone replacement therapy (HRT) had a lower prevalence of NAFLD compared to postmenopausal women not on HRT<sup>22,20</sup>.

### Cardiovascular risk and NAFLD

NAFLD can be considered as a hepatic manifestation of the metabolic syndrome. A significant number of patients with either clinical or histological diagnosis of NAFLD develop metabolic problems<sup>21</sup>. NAFLD appears to be a feature of the metabolic syndrome, and its detection on abdominal ultrasound should alert to the existence of an increased cardiovascular risk<sup>21</sup>. Indeed, it has been widely associated with cardio-metabolic syndrome and its components: hepatic and systemic insulin resistance (IR), dyslipidemia, visceral obesity, hypertension, impaired fasting glucose and increased stroke risk<sup>22,23</sup>. These conditions are well-known cardiovascular risk factors, and patients affected by this syndrome have an elevated probability of developing a cardiovascular pathology that, in turn, represents one of the main causes of death in this population<sup>24</sup>. In recent years, the role of NAFLD in inducing CVDs has been highlighted to the point that it has been considered as an independent risk factor for cardiovascular pathologies<sup>25,26</sup>. Among the several processes involved in the mechanism linking NAFLD and CVDs, oxidative stress and endothelial dysfunction (in turn, strongly inter-correlated) appear to play an important pathogenic role<sup>27</sup>. Recent studies have shown that NAFLD is associated to endothelial dysfunction, which is characterized by oxidative stress accumulation and considered as a surrogate marker of CVD<sup>28</sup>. Even though a large number of insights on the link between IR and liver damage are not known yet, what we do know is that IR is responsible for endothelial dysfunction, for example via the imbalance of the enzymatic system of nitric oxide (NO) production<sup>29</sup>. Insulin, in fact, induces endothelial Nitric Oxide Synthase (eNOS) activation, resulting in vasodilation and vascular protection<sup>30</sup>. When IR appears, it can also lead to endothelial dysfunction, through the impairment of NO production and the inhibition of insulin-induced vasorelaxation<sup>31</sup>, and eNOS function impairment has been widely associated with it<sup>32</sup>. IR, widely demonstrated in NAFLD, might be the main trigger of eNOS dysfunction, which, therefore, might play a crucial role in the onset of NAFLD<sup>33,34</sup>. Moreover, endothelial dysfunction with impaired NO production is involved in the progression of advanced liver diseases<sup>33,34</sup> and is associated with increased vascular resistance (resulting in portal hypertension) and hepatic stellate cell activation in the liver and collagen deposition in the space of Disse (resulting in fibrosis)<sup>35</sup>. IR-associated eNOS dysfunction may represent a peculiar and essential mechanism of liver damage in NAFLD, which might also represent a pathological link between NAFLD and CVDs<sup>14,35</sup>. In insulin-resistant subjects, the presence of fatty liver has been correlated with an impairment of the systemic oxidant/antioxidant balance

(indicated as oxidative stress) and endothelial dysfunction, independently of the presence of MS, adiposity and high levels of adipokines<sup>35,36</sup>. It is well known that oxidative stress is associated with endothelial dysfunction and CVDs<sup>37,38</sup> and, in NAFLD patients, it triggers an inflammatory cascade and extracellular matrix deposition in the liver, promoting the development of non-alcoholic steatohepatitis (NASH). Even though the mechanisms linking NAFLD to increased oxidative stress and endothelial dysfunction have not yet been fully clarified, impaired mitochondrial  $\beta$ -oxidation, high levels of oxidized low-density lipoprotein (LDL), dietary saturated fat and reduced antioxidant intake have been proposed as potential pathogenetic factors<sup>39-42</sup>.

### Gender difference and CVDs in NAFLD

In the general population, the male sex has a greater risk of developing CVDs under the age of 50 years compared to women but, after menopause, the incidence in women drastically increases until it reaches that of males<sup>43,44</sup>. Sex modulates the association of NAFLD with incident CVDs/mortality in studies in which the diagnosis of NAFLD was based on surrogate indices, such as raised liver enzymes. Most of the population-based cohort studies and meta-analyses reported an independent association between raised gamma-glutamyl-transpeptidase (GGT) and incident CVDs in both sexes<sup>44,45</sup>. Conversely, a German population-based cohort study found that increased GGT was associated with higher risk of CVDs only in men but not in women, and this association was stronger in men who had a diagnosis of steatosis by USS<sup>46</sup>. Increased ALT has been variably associated with incident CVDs either in both sexes<sup>44,47,48</sup> or in men only<sup>49</sup>. In 2016, a South Korean study, in which the diagnosis of NAFLD was based on USS, reported that men had a higher prevalence of NAFLD and carotid plaques, and higher values of carotid intima-media thickness (IMT) than women, but NAFLD independently predicted subclinical carotid atherosclerosis (IMT and plaques)

only in women<sup>50</sup>. No gender differences were reported regarding the association between NAFLD assessed with USS and incident CVDs<sup>51</sup>. Another study, based on a Danish registry, showed that patients with a hospital discharge diagnosis of NAFLD had CVDs similar between two sexes<sup>44,51</sup>. A Japanese study, conducted on apparently healthy subjects, found that the USS diagnosis of NAFLD was a predictor of CVDs in both sexes equally<sup>52</sup>. A significant correlation between NAFLD (based on CT scanning findings) and prevalence of coronary artery calcification (CAC) was found in the only study carried out in postmenopausal women. However, NAFLD was not independently associated with CAC<sup>53</sup>.

### Conclusions

NAFLD is a disease that is constantly increasing its prevalence among the global population. The data currently available in the literature shows a higher prevalence in men than in pre-menopausal women. In post-menopausal age, its prevalence seems to equalize between male and female sex<sup>2,11,20</sup>. Male patients carry an increased risk of CVDs. However, NAFLD seems to be associated with CVDs independently of metabolic factors in both sexes<sup>42</sup>. Few data are available in postmenopausal women and studies should specifically be conducted to ascertain whether NAFLD is a specific/independent cardiovascular risk factor in this population of patients<sup>43</sup>.

### References

1. Neuschwander-Tetri BA, Caldwell SH. Non alcoholic steatohepatitis: summary of an AASLD single topic conference. *Hepatology*. 2003;7:1202-19.
2. Lonardo A, Nascimbeni F, Ballestri S, Fairweather D, Win S, Than TA, et al. Sex differences in NAFLD: state of the art and identification of research gaps. *Hepatology*. 2019 Mar 29. [Epub ahead of print].
3. Buzzetti E, Pinzani M, Tsochatzis EA. The multiple-hit pathogenesis of non-alcoholic fatty liver disease (NAFLD). *Metabolism*. 2016;65:1038-48.
4. Brunt EM. Non-alcoholic steatohepatitis. *Semin Liver Dis*. 2004;24:3-20.
5. McCullough AJ. The clinical features, diagnosis and natural history of nonalcoholic fatty liver disease. *Clin Liver Dis*. 2004;8:521-33.
6. Kim D, Kim WR, Kim HJ, Therneau TM. Association between noninvasive fibrosis markers and mortality among adults with nonalcoholic fatty liver disease in the United States. *Hepatology*. 2013;57:1357-65.
7. Ratziu V, Bellentani S, Cortez-Pinto H, Day C, Marchesini G. A position statement on NAFLD/NASH based on the EASL 2009 special conference. *J Hepatol*. 2010;53:372-84.
8. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of non-alcoholic fatty liv-

#### Key messages

- NAFLD is a constantly increasing disease in the population.
- There is a higher prevalence of NAFLD in males compared to pre-menopausal females.
- In postmenopausal age, the prevalence of NAFLD is very similar between male and female sex.
- NAFLD seems to be associated with CVD independently of metabolic factors in both sexes.

- er disease-meta-analytic assessment of prevalence, incidence and outcomes. *Hepatology*. 2016;64:73-84.
9. Masarone M, Federico A, Abenavoli L, Loguercio C, Persico M. Non alcoholic fatty liver: epidemiology and natural history. *Rev Recent Clin Trials*. 2014;9:126-33.
10. Dai W, Ye L, Liu A, Wen SW, Deng J, Wu X, et al. Prevalence of nonalcoholic fatty liver disease in patients with type 2 diabetes mellitus: a meta-analysis. *Medicine*. 2017;96:e8179.
11. Anderson EL, Howe LD, Jones HE, Higgins JP, Lawlor DA, Fraser A. The prevalence of non-alcoholic fatty liver disease in children and adolescents: a systematic review and meta-analysis. *PLoS One*. 2015;10:e0140908.
12. Perlemuter G, Bigorgne A, Cassard-Doulcier AM, Naveau S. Non-alcoholic fatty liver disease: from pathogenesis to patient care. *Nat Clin Pract Endocrinol Metabol*. 2007;3:458-69.
13. Santoliquido A, Di Campli C, Miele L, Gabrieli ML, Forgiione A, Zocco MA, et al. Hepatic steatosis and vascular disease. *Eur Rev Med Pharmacol Sci*. 2005;9:269-71.
14. Persico M, Masarone M, Damato A, Ambrosio M, Federico A, Rosato V, et al. Non alcoholic fatty liver disease and eNOS dysfunction in humans. *BMC Gastroenterol*. 2017;17(1):116.
15. Bedogni G, Miglioli L, Masutti F, Tiribelli C, Marchesini G, Bellentani S. Prevalence of and risk factors for nonalcoholic fatty liver disease: the Dionysos nutrition and liver study. *Hepatology*. 2005;42:44-52.
16. Targher G, Bertolini L, Padovani R, Rodella S, Zoppini G, Zenari L, et al. Relations between carotid artery wall thickness and liver histology in subjects with non-alcoholic fatty liver disease. *Diabetes Care*. 2006;29:1325-30.
17. Musso G, Gambino R, Bo S, Uberti B, Biroli G, Pagano G, et al. Should nonalcoholic fatty liver disease be included in the definition of metabolic syndrome? A cross-sectional comparison with adult treatment panel III criteria in non obese non diabetic subjects. *Diabetes Care*. 2008;31:562-68.
18. Adams LA, Lymp JF, St Sauver J, Sanderson SO, Lindor KD, Feldstein A, et al. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. *Gastroenterology*. 2005;129:113-21.
19. Clayton JA, Collins FS. Policy: NIH to balance sex in cell and animal studies. *Nature*. 2014;509:282-3.
20. Clark JM, Brancati FL, Diehl AM. Nonalcoholic fatty liver disease. *Gastroenterology*. 2002;122:1649-57.
21. Brea A, Mosquera D, Martín E, Arizti A, Cordero JL, Ros E. Nonalcoholic fatty liver disease is associated with carotid atherosclerosis: a case-control study. *Arterioscler Thromb Vasc Biol*. 2005;25:1045-50.
22. Perlemuter G, Bigorgne A, Cassard-Doulcier AM, Naveau S. Nonalcoholic fatty liver disease: from pathogenesis to patient care. *Nat Clin Pract Endocrinol Metab*. 2007;3:458-69.
23. Santoliquido A, Di Campli C, Miele L et al. Hepatic steatosis and vascular disease. *Eur Rev Med and Pharmacol Sci*. 2005;9:269-71.
24. Sundström J, Risérus U, Byberg L, Zethelius B, Lithell H, Lind L. Clinical value of the metabolic syndrome for long term prediction of total and cardiovascular mortality: prospective, population based cohort study. *Br Med J*. 2006;332:878-82.
25. Buzzetti E, Pinzani M and Tsochatzis EA. The multiple-hit pathogenesis of non-alcoholic fatty liver disease (NAFLD). *Metabolism*. 2016;65:1038-48.
26. Söderberg C, Stål P, Askling J, Glaumann H, Lindberg G, Marmur J, et al. Decreased survival of subjects with elevated liver function tests during a 28-year follow-up. *Hepatology*. 2010;51:595-602.
27. Luo J, Xu L, Li J, Zhao S. Nonalcoholic fatty liver disease as a potential risk factor of cardiovascular disease. *Eur J Gastroenterol Hepatol*. 2015;27:193-9.
28. Long MT, Wang N, Larson MG, Mitchell GF, Palmisano J, Vasan RS, et al. Non-alcoholic fatty liver disease and vascular function: cross-sectional analysis in the Framingham heart study. *Arterioscler Thrombo Vasc Biol*. 2015;35:1284-91.
29. Kim JA, Montagnani M, Koh KK, Quon MJ. Reciprocal relationships between insulin resistance and endothelial dysfunction: molecular and pathophysiological mechanisms. *Circulation*. 2006;113: 1888-904.
30. Steinberg HO, Brechtel G, Johnson A, Fineberg N, Baron AD. Insulin-mediated skeletal muscle vasodilation is nitric oxide dependent. A novel action of insulin to increase nitric oxide release. *J Clin Invest*. 1994;94:1172-9.
31. Zeng G, Quon MJ. Insulin-stimulated production of nitric oxide is inhibited by wortmannin. Direct measurement in vascular endothelial cells. *J Clin Invest*. 1996;98:894-8.
32. Duncan ER, Crossey PA, Walker S, Anilkumar N, Poston L, Douglas G, et al. Effect of endothelium-specific insulin resistance on endothelial function in vivo. *Diabetes*. 2008;57:3307-14.
33. Gupta TK, Toruner M, Chung MK, Groszmann RJ. Endothelial dysfunction and decreased production of nitric oxide in the intrahepatic microcirculation of cirrhotic rats. *Hepatology*. 1998;28:926-31.
34. Rockey DC, Chung JJ. Reduced nitric oxide production by endothelial cells in cirrhotic rat liver: endothelial dysfunction in portal hypertension. *Gastroenterol*. 1998;114:344-51.
35. Deleve LD, Wang X, Guo Y. Sinusoidal endothelial cells prevent rat stellate cell activation and promote reversion to quiescence. *Hepatology*. 2008;48:920-30.
36. Masarone M, Rosato V, Dallio M, Gravina AG, Aglitti A, Loguercio C, et al. Role of oxidative stress in pathophysiology of nonalcoholic fatty liver disease. *Oxid Med Cell Longev*. 2018;11:9547613.
37. Conti V, Corbi G, Russomanno G, Simeon V, Ferrara N, Filippelli W, et al. Oxidative stress effects on endothelial cells treated with different athletes' sera. *Med Sci Sports Exerc*. 2012;44:39-49.
38. Reriani MK, Lerman LO, Lerman A. Endothelial function as a functional expression of cardiovascular risk factors. *Biomark Med*. 2010;4:351-60.
39. Musso G, Gambino R, Durazzo M, Biroli G, Carello M, Fagà E, et al. Adipokines in NASH: postprandial lipid metabolism as a link between adiponectin and liver disease. *Hepatology*. 2005;42:1175-83.
40. Musso G, Cassader M, Gambino R, Durazzo M, Pagano G. Association between postprandial LDL conjugated dienes and the severity of liver fibrosis in NASH. *Hepatology*. 2006;43:1169-70.
41. Musso G, Gambino R, De Michieli F, Cassader M, Rizzetto M, Durazzo M, et al. Dietary habits and their relations to



- insulin resistance and postprandial lipemia in non-alcoholic steatohepatitis. *Hepatology*. 2003;37:909-16.
42. Musso G, Gambino R, De Michieli F, Biroli G, Premoli A, Pagano G, et al. Nitrosative stress predicts the presence and severity of nonalcoholic fatty liver at different stages of the development of insulin resistance and metabolic syndrome: possible role of vitamin A intake. *Am J Clin Nutr*. 2007;86:661-71.
  43. Wells GL. Cardiovascular risk factors: does sex matter? *Curr Vasc Pharmacol*. 2016;14:452-7.
  44. Ballestri S, Nascimbeni F, Baldelli E, Marrazzo A, Romagnoli D, Lonardo A. NAFLD as a sexual dimorphic disease: role of gender and reproductive status in the development and progression of nonalcoholic fatty liver disease and inherent cardiovascular risk. *Adv Ther*. 2017;34:1291-326.
  45. Fraser A, Harris R, Sattar N, Ebrahim S, Smith GD, Lawlor DA. Gamma-glutamyltransferase is associated with incident vascular events independently of alcohol intake: analysis of the British women's heart and health study and meta-analysis. *Arterioscler Thromb Vasc Biol*. 2007;27:2729-35.
  46. Haring R, Wallaschofski H, Nauck M, Dörr M, Baumeister SE, Völzke H. Ultrasonographic hepatic steatosis increases prediction of mortality risk from elevated serum gamma-glutamyl transpeptidase levels. *Hepatology*. 2009;50:1403-11.
  47. Ioannou GN, Weiss NS, Boyko EJ, Mozaffarian D, Lee SP. Elevated serum alanine aminotransferase activity and calculated risk of coronary heart disease in the United States. *Hepatology*. 2006;43(5):1145-51.
  48. Schindhelm RK, Dekker JM, Nijpels G, Bouter LM, Stehouwer CD, Heine RJ, et al. Alanine aminotransferase predicts coronary heart disease events: a 10-year follow-up of the Hoorn Study. *Atherosclerosis*. 2007;191(2):391-6.
  49. Feitosa ME, Reiner AP, Wojczynski MK, Graff M, North KE, Carr J, et al. Sex-influenced association of nonalcoholic fatty liver disease with coronary heart disease. *Atherosclerosis*. 2013;227(2):420-4.
  50. Kim HJ, Lim CW, Lee JH, Park HB, Suh Y, Cho YH, et al. Gender-based differences in the relationship between fatty liver disease and atherosclerosis. *Cardiovasc J Afr*. 2016;27(5):281-6.
  51. Jepsen P, Vilstrup H, Mellemejaer L, Thulstrup AM, Olsen JH, Baron JA, et al. Prognosis of patients with a diagnosis of fatty liver - a registry based cohort study. *Hepatogastroenterology*. 2003;50(54):2101-4.
  52. Hamaguchi M, Kojima T, Takeda N, Nagata C, Takeda J, Sarui H, et al. Nonalcoholic fatty liver disease is a novel predictor of cardiovascular disease. *World J Gastroenterol*. 2007;13(10):1579-84.
  53. Kim MK, Ahn CW, Nam JS, Kang S, Park JS, Kim KR. Association between nonalcoholic fatty liver disease and coronary artery calcification in postmenopausal women. *Menopause*. 2015;22(12):1323-7.

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