Prevalence of non-alcoholic fatty liver disease and its relation to hypoadiponectinaemia in the middle-aged and elderly Chinese population

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Abstract

Introduction: Hypoadiponectinaemia is an important risk factor for non-alcoholic fatty liver disease (NAFLD). However, little is known about its role in the Chinese population. This study sought to assess the prevalence of NAFLD and its association with hypoadiponectinaemia in middle-aged and elderly Chinese.

Material and methods: We conducted a population-based cross-sectional study in an urban Shanghai sample of 2201 participants age 50 years to 83 years (973 men, 1228 women). Hepatic ultrasonographic examination was performed for all participants. Serum adiponectin concentrations were measured by ELISA methods.

Results: The prevalence of NAFLD was 19.8% (16.0% in men, 22.8% in women). Serum adiponectin levels were significantly higher in female than in male subjects ($p < 0.001$). Serum adiponectin levels were significantly lower in NAFLD subjects than those in control subjects ($p < 0.001$). The prevalence of NAFLD progressively increased with declining adiponectin levels ($p_{for\ trend} < 0.001$). The participants in the lowest adiponectin quartile had a significantly increased risk for acquiring NAFLD (OR = 2.31, 95% CI 1.72-3.15) after adjustment for potential confounders.

Conclusions: Population-based screening suggests that NAFLD is highly prevalent in middle-aged and elderly people in Shanghai, particularly among women. Serum adiponectin level is negatively associated with NAFLD independently of potential cofounders, indicating that hypoadiponectinaemia may contribute to the development of NAFLD.

Key words: non-alcoholic fatty liver disease, prevalence, risk factor, hypoadiponectinaemia.

Introduction

During the past two decades, China has experienced rapid economic growth and aging of its population. Resulting changes in lifestyle and

Zhen Yang, Xuanchun Wang, Jie Wen, Zi Ye, Qin Li, Min He, Bin Lu, Charlotte Ling, Songhua Wu, Renming Hu

longer life expectancy have led to an increased burden of cardiovascular and other chronic diseases [1, 2]. Non-alcoholic fatty liver disease (NAFLD) is a clinicopathological entity which is characterized by the presence of fat droplets in the hepatocytes in the absence of alcohol consumption, representing a spectrum of hepatic injuries, ranging from pure fatty infiltration (steatosis) to inflammation (non-alcoholic steatohepatitis [NASH]), fibrosis, and cirrhosis [3, 4]. Non-alcoholic fatty liver disease is the most common chronic liver condition worldwide, affecting approximately 20% of the general population, with increasing prevalence [5], and paralleling the increasing prevalence of obesity [6], type 2 diabetes [7], metabolic syndrome [8] and cardiovascular disease (CVD) [9]. Non-alcoholic fatty liver disease is now receiving greater attention and is regarded as a public health issue. Therefore, managing NAFLD is crucial to the prevention of CVD and metabolism-related diseases.

Adiponectin is an adipocyte-derived cytokine known to mediate insulin action [10]. Hypo-adiponectinaemia has been demonstrated to be linked with insulin resistance, while increased adiponectin levels by supplementation of adiponectin attenuated the insulin resistance [11]. A specific role for adiponectin in the liver has also been suggested. Adiponectin levels correlate inversely with hepatic fat and hepatic insulin resistance in diabetic patients [12], whereas in healthy subjects, low adiponectin levels are significantly associated with increased serum concentration of alanine transaminase (ALT) and γ-glutamyl transpeptidase, suggesting a possible contribution of adiponectin in maintaining liver integrity [13, 14]. Moreover, adiponectin also manifests anti-inflammatory action by neutralizing tumour necrosis factor-α (TNF-α) [15] and anti-fibrotic action by inhibiting hepatic stellate cell proliferation and migration [16].

The mechanisms behind the hepato-protective properties of adiponectin have been extensively studied. In the NAFLD mouse model, adiponectin has anti-inflammatory and insulin-reducing effects, and improves the pathological condition of NAFLD [17]. Recently a study indicated that adiponectin/AdipoR2 signalling in hepatocytes regulated steatohepatitis progression by changing PPAR-α activity and ROS accumulation, a process in which TGF-β signalling is implicated [18]. AdipoR2 is expressed predominantly in the liver; decreased expression of AdipoR2 in the livers of patients with NASH has been reported [19], suggesting that adiponectin signalling might play an important role in the pathogenesis of NAFLD.

Few studies have published information on the prevalence of NAFLD in Chinese populations [20, 21]. There is increasing evidence indicating the close association between circulating adiponectin levels and NAFLD in different ethnic groups such as Caucasian [22, 23], Japanese [24] and Korean [25]. However, data about the role of adiponectin with regards to NAFLD in the Chinese population are limited.

Therefore, this study intended to determine the prevalence of NAFLD and to examine the relation between NAFLD and serum adiponectin levels in a population-based survey of middle-aged and elderly Chinese people in Shanghai, China.

Material and methods

Subjects

In 2007, China launched a Study on Metabolic Syndrome of Aging Population in China, a population-based cross-sectional study, designed to evaluate the prevalence of metabolic syndrome, and other age-related chronic diseases. All studied individuals come from Simenerlu Community of Jingan District and Jiangninglu Community of Putuo District in Shanghai, China. A multistage stratified cluster sampling method was used to select subjects from these two communities. Only one participant (≥ 50 years) was randomly selected from each household without any of the following conditions: severe psychological disorders, physical disabilities, cancers, senile dementia or currently diagnosed with tuberculosis, acquired immune deficiency syndrome, clinical signs or symptoms of inborn errors of metabolism, a history of use of toxins or drugs associated with liver steatosis or any other communicable disease. Elevated liver enzymes (serum alanine transaminase [ALT], aspartate aminotransferase [AST] and γ-glutamyl transferase [GGT]) were not an exclusion criterion. Fatty liver patients consuming more than 20 g of alcohol per day were excluded. This study is a population-based study. In our study subjects, the controls just non-NAFLD subjects.

A total of 2,219 subjects (986 men, 1,233 women) completed the survey. Altogether 454 subjects (NAFLD group) were diagnosed with fatty liver by ultrasound examination in this study. A total of 18 individuals were excluded from analysis due to alcohol consumption ≥ 20 g/day. Written informed consent was obtained from all the participants. The study was approved by the Institutional Review Broad of Huashan Hospital.

Data collection

A standardized questionnaire was used by trained physicians to collect information such as age, sex, smoking (yes/no), alcohol drinking, and medication use. Physical activity level was classified as low, moderate, or high according to the International Physical Activity Questionnaire scoring

protocol. All subjects were assessed after overnight fasting for at least 10 h. Detailed anthropometric measurements including height, weight, waist circumference, hip circumference and blood pressure were carried out by trained physicians. Height was measured in metres (without shoes), and weight in kilograms (with heavy clothing removed and 1 kg deducted for remaining garments). Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in metres. We measured waist circumference in standing subjects with a soft tape midway between the lowest rib and the iliac crest. Hip circumference was measured over the widest part of the gluteal region, and the waist-to-hip ratio was calculated as a measure of central obesity. Two blood pressure recordings were obtained from the right arm of patients in a sitting position after 30 min of rest; measurements were taken in 5-min intervals, and mean values were calculated.

Laboratory measurements

Peripheral venous blood samples were collected in tubes containing liquid EDTA, centrifuged at 4°C, 10 min, 3000 rpm and stored at –80°C until analysis. The fasting glucose, glucose 2 h after oral glucose tolerance test (OGTT), total cholesterol, triglycerides, LDL cholesterol and HDL cholesterol were measured enzymatically on an automatic analyser (Hitachi 7080). Levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were measured by the UV method. γ-Glutamyltransferase (GGT) was measured by the Szasz-Persijn method. Fasting insulin was determined by radioimmunoassay (Linco Research, St. Charles, USA). Insulin resistance was estimated using homeostasis model assessment index-insulin resistance (HOMA-IR).

The serum CRP and adiponectin were determined in duplicate by ELISA with a Duoset kit (R&D Systems, Minneapolis, USA) as recommended by the manufacturer. The ELISA system had an intra-assay coefficient of variation of 3-7% and an inter-assay coefficient of variation of 4-9%.

Diagnosis of non-alcoholic fatty liver disease

Ultrasound examinations were performed by a single examiner using a Siemens Versa Plus (Siemens, Munich, Germany) equipped with a 3.5-MHz convex-array probe and a 9-MHz linear-array probe. Scans were performed after a fasting period of at least 5 h. All subjects received hepatic ultrasound scanning. According to established diagnostic criteria [26-28], the degree of fatty infiltration of the liver was classified as "mild" (hepatic steatosis grade I), "moderate" (hepatic steatosis grade II), or "severe" (hepatic steatosis

grade III). Biopsy studies in adults demonstrate that ultrasonography has a high sensitivity (89%) and specificity (93%) for the detection and classification of hepatic steatosis [27], and the correlation with microscopic fat content in macrovesicular steatosis is good compared to the correlation achieved by hepatic fat quantification with magnetic resonance imaging (MRI) ($r = 0.90$, $p < 0.001$) [29].

Statistical analysis

Normally distributed data were expressed as means ± SD, whereas variables with a skewed distribution were reported as median (interquartile range) and log transformed to approximate normality before analysis. Categorical variables were represented by frequency and percentage. Analysis of covariance for continuous variables and χ^2 test for categorical variables were applied for the comparison. Correlation coefficients between adiponectin and metabolic features were calculated by simple and partial correlation analysis on ranks (Spearman correlation). Factors' scores were used in multivariate logistic regression analysis to determine the factors that were significantly related to hepatic steatosis, using the presence of hepatic steatosis as a dependent variable, and adiponectin, age, BMI, C-reactive protein (CRP), waist circumference, and homeostatic model assessment of insulin resistance (HOMA-IR) as independent variables. Multivariate logistic regression models were used to estimate the odds ratios (ORs) for hepatic steatosis. Potential confounding variables including age, gender, smoking, physical activity, CRP, adiponectin, HOMA-IR, BMI, waist circumference, and waist to hip ratio were controlled in the regression models. When appropriate, natural log-transformed values were used for the analyses. All statistical analysis were performed with the SPSS Statistical Package (version 13.0; SPSS Inc., Chicago, IL). Value of $p < 0.05$ was considered statistically significant.

Results

Anthropometric, clinical, and laboratory data

Clinical and biochemical variables of the patients included in the study are summarized in Table I. The NAFLD subjects have higher age, BMI, waist circumference, waist to hip ratio, smoking, systolic bood pressure (SBP), diastolic blood pressure (DBP), fasting plasma glucose, fasting plasma insulin, HOMA-IR, CRP, ALT, AST, GGT, triglyceride and total cholesterol than those of control subjects (all $p < 0.05$). In contrast, the control subjects have higher physical activity and HDL cholesterol (all $p < 0.001$).

Adiponectin levels ranged from 0.230 μg/ml to 51.740 μg/ml in the study population. The median

Zhen Yang, Xuanchun Wang, Jie Wen, Zi Ye, Qin Li, Min He, Bin Lu, Charlotte Ling, Songhua Wu, Renming Hu

Table I. Baseline characteristics of NAFLD and control subjects

Characteristics	NAFLD	Control	Value of p
N	436	1765	–
Age [year]	61.1 ±8.3	59.6 ±8.2	< 0.001
BMI [kg/m^2]	26.6 ±3.0	24.5 ±3.2	< 0.001
Waist circumference [cm]	88.6 ±8.2	82.3 ±9.0	< 0.001
Waist to hip ratio	0.89 ±0.07	0.86 ±0.07	< 0.001
Smoking (yes)	82 (18.8)	196 (11.1)	< 0.001
Physical activity:			< 0.001
Low	170 (39.0)	120 (6.8)	
Moderate	228 (52.3)	1234 (69.9)	
High	38 (8.7)	411 (23.3)	
SBP [mmHg]	133.4 ±17.1	127.7 ±17.5	< 0.001
DBP [mmHg]	84.0 ±10.3	80.8 ±17.6	0.003
Fasting plasma glucose [mmol/l]	5.9 ±1.3	5.6 ±1.3	0.002
Fasting plasma insulin [µU/ml][e]	9.08 (6.05-13.70)	6.59 (4.45-9.68)	< 0.001
HOMA-IR[e]	2.30 (1.46-3.70)	1.59 (1.01-2.39)	< 0.001
CRP [µg/ml]	6.3 ±4.9	4.4 ±4.1	< 0.001
Adiponectin [µg/ml][e]	7.73 (5.43-10.63)	9.65 (6.77-13.36)	< 0.001
ALT [U/l]	35.3 ±16.8	24.4 ±14.6	< 0.001
AST [U/l]	29.7 ±5.1	21.5 ±4.8	< 0.001
GGT [U/l]	33.7 ±10.4	13.1 ±7.7	< 0.001
Triglycerides [mmol/l][e]	2.3 ±1.7	1.6 ±1.3	< 0.001
Total cholesterol [mmol/l]	5.5 ±1.1	5.4 ±1.0	0.108
LDL-c [mmol/l]	3.2 ±0.8	3.2 ±0.8	0.968
HDL-c [mmol/l]	1.2 ±0.3	1.4 ±0.5	< 0.001

BMI – body mass index, SBP – systolic blood pressure, DBP – diastolic blood pressure, CRP – C-reactive protein, ALT – alanine aminotransferase, AST – aspartate aminotransferase, GGT – γ-glutamyltransferase, LDL-c – low-density lipoprotein cholesterol, HDL-c – high-density lipoprotein cholesterol, HOMA-IR – homeostasis model of assessment-insulin resistance, [e]these variables were log transformed before analysis

Table II. Distribution of adiponectin and nonalcoholic fatty liver disease prevalence by gender and age

Subgroup	Number	Adiponectin [µg/ml]*	NAFLD prevalence [%]
Gender			
Male	973	7.79 (5.38-11.13)	16.03
Female	1228	9.95 (7.23-13.93)	22.80
Value of p		< 0.001	< 0.001
Age group [years]			
50-59	1159	8.81 (5.99-12.31)	17.00
60-69	691	10.26 (7.74-13.99)	24.31
≥ 70	351	12.27 (8.41-15.78)	20.22
Value of p		< 0.001	0.001

data expressed as median (interquartile range)

adiponectin concentration in women was significantly higher than that in men (p < 0.001) (Table II). In addition, adiponectin levels in subjects older than 70 years were significantly higher than those in subjects in their fifties and sixties (p < 0.001) (Table II). Adiponectin levels were significantly lower in NAFLD patients (Figure 1). In relation to gender, adiponectin concentrations were systematically lower in men, both in NAFLD and in controls.

Adiponectin levels in relation to clinical, anthropometric, and biochemical parameters

Adiponectin was significantly correlated with several clinical, anthropometric and biochemical variables in the total studied population (Table III). In particular, adiponectin was strongly negatively associated with central adiposity, insulin resistance, and hyperlipidaemia. Adiponectin levels also
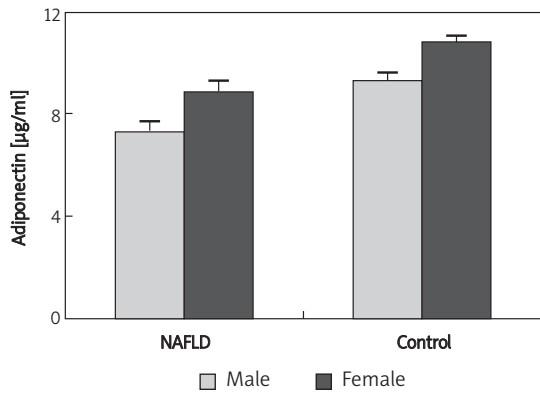
Figure 1. Serum adiponectin in patients with nonalcoholic fatty liver disease and control subjects
*Data are expressed as mean ± SEM, *p < 0.001 vs. control for both genders*

Table III. Crude and partial correlation between serum adiponectin and clinical parameters in the study subjects

| Variable	Crude r	Partial r[†]
Age [year]	0.18**	
BMI [kg/m²]	−0.20**	−0.21**
Waist circumference [cm]	−0.20**	−0.19**
SBP [mmHg]	−0.08*	−0.12**
DBP [mmHg]	−0.09*	−0.07*
ALT [U/l]	−0.14**	−0.10**
AST [U/l]	−0.12**	−0.09*
GGT [U/l]	0.11**	−0.07*
Total cholesterol [mmol/l]	0.11**	0.04
Triglycerides [mmol/l]	−0.12**	−0.11**
HDL-c [mmol/l]	0.24**	0.20**
CRP [µg/ml]	−0.03	−0.02
Fasting plasma glucose [mmol/l])	−0.11**	−0.11**
Fasting insulin [µU/ml]	−0.23**	−0.24**
HOMA-IR	−0.20**	−0.21**

*abbrevaitions – see Table I, *p < 0.05, **p < 0.001, †adjusted for age, sex*

decreased with increasing prevalence of NAFLD (*p* for trend < 0.001) (Figure 2).

Prevalence of non-alcoholic fatty liver disease

Hepatic steatosis was diagnosed by ultrasound in 19.8% of the subjects. Most subjects were affected by mild to moderate fatty infiltration of the liver (hepatic steatosis grade I to II) (the proportions of hepatic steatosis in total subjects were 14.4%, 4.0% and 1.3%, respectively). We observed a clear gender difference in prevalence rates, with significantly more females affected by NAFLD (Table II). Interestingly, prevalence of NAFLD in subjects aged 60-69 years (24.31%) was significantly higher than in subjects in their fifties (17.0%) and in subjects older than 70 years (20.22%) (*p* < 0.001).

Association between adiponectin levels and non-alcoholic fatty liver disease

In multivariate logistic regression analysis the presence of NAFLD was used as the dependent variable, while all other variables were designated the independent variables. Age, BMI, serum CRP level, waist circumference, HOMA-IR and serum adiponectin level were independent factors significantly associated with NAFLD. The odds ratios (OR) were calculated for NAFLD with female sex (OR = 1.43, 95% confidence interval [CI]: 1.11-1.94), age (OR = 1.29, 95% CI: 1.05-1.68), BMI (OR = 1.18, 95% CI: 1.09-1.31), CRP (OR = 1.20, 95% CI: 1.02-1.43), waist circumference (OR = 1.12, 95% CI: 1.02-1.30), HOMA-IR (OR = 2.56, 95% CI: 1.19-5.62), adiponectin (OR = 0.45, 95% CI: 0.17-0.81).

Table IV displays the ORs for NAFLD by adiponectin quartiles. As expected, decreased ORs for NAFLD were observed from the 1st to the 4th adiponectin quartiles in all subgroups: male and

female (*p* for trend < 0.001 for all) after adjustment for smoking, physical activity, SBP, DBP, CRP, triglycerides, HOMA-IR, BMI.

Discussion

The findings of our study reinforce the observation that NAFLD is highly prevalent in middle-aged and elderly subjects, with a clear female predominance in the study population. Furthermore, we further investigated the relationship of NAFLD and serum adiponectin. To our best knowledge, this is the first large-scale population-based study investigating the association of adiponectin with NAFLD in middle-aged
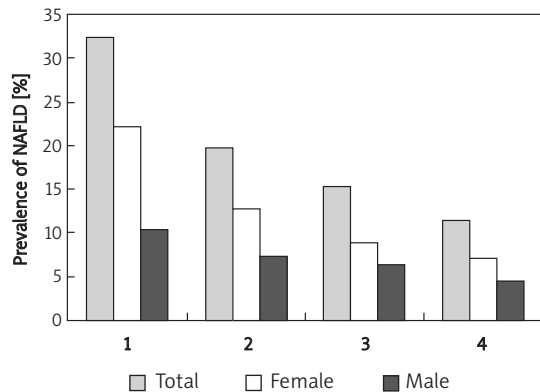
Figure 2. Prevalence of non-alcoholic fatty liver disease in each quartile of adiponectin concentration
p for trend < 0.001 for each group

Zhen Yang, Xuanchun Wang, Jie Wen, Zi Ye, Qin Li, Min He, Bin Lu, Charlotte Ling, Songhua Wu, Renming Hu

Table IV. Adjusted ORs and 95% CIs for non-alcoholic fatty liver disease according to adiponectin quartiles (with Q4 as reference)

NAFLD	ORs (95% CI)			
	Q1	Q2	Q3	Q4
Total				
Model 1*	2.72 (1.84-4.12)	1.45 (1.11-1.82)	1.17 (0.89-1.48)	1
Model 2†	2.64 (1.90-3.63)	1.42 (1.07-1.95)	1.15 (0.86-1.47)	1
Model 3‡	2.45 (1.80-3.37)	1.40 (1.05-1.92)	1.12 (0.85-1.43)	1
Model 4ᶜ	2.34 (1.74-3.16)	1.37 (1.02-1.88)	1.09 (0.81-1.45)	1
Women				
Model 1*	3.03 (2.03-4.62)	1.83 (1.51-2.35)	1.29 (0.74-2.12)	1
Model 2†	2.89 (1.99-4.23)	1.72 (1.29-2.38)	1.25 (0.83-1.88)	1
Model 3‡	2.73 (1.84-4.13)	1.65 (1.31-2.44)	1.23 (0.79-1.82)	1
Model 4ᶜ	2.61 (1.91-3.73)	1.59 (1.24-2.35)	1.18 (0.83-1.71)	1
Men				
Model 1*	2.59 (1.70-3.97)	1.39 (1.03-1.97)	1.11 (0.84-1.49)	1
Model 2†	2.54 (1.73-3.77)	1.27 (0.83-1.88)	1.09 (0.81-1.47)	1
Model 3‡	2.32 (1.50-3.93)	1.22 (0.84-1.79)	1.08 (0.82-1.43)	1
Model 4ᶜ	2.24 (1.51-3.42)	1.18 (0.79-1.81)	1.04 (0.77-1.41)	1

Model 1 adjusted for age, in total group, model 1 adjusted for age and gender, †model 2 further adjusted for smoking, physical activity, SBP and DBP, ‡model 3 further adjusted for CRP, triglycerides and HOMA-IR, ᶜmodel 4 further adjusted for BMI

and elderly Chinese. A strong inverse association was found between adiponectin levels and NAFLD, independent of well-known NAFLD risk factors. Hypoadiponectinaemia, as indicated in other population studies, is also an important risk factor associated with NAFLD risk in the Chinese population.

The overall prevalence of fatty liver of 19.8% in our study cohort is notably lower than reported prevalence rates for the middle-aged and elderly population from other studies of China (24.8% in Shanghai and 25.7% in Guangzhou) [20, 21]. The discrepancy among the studies is probably due to the methods of sample selection, modalities used for diagnosis and diversity of life styles and dietary habits in different areas. The clear female predominance in NAFLD found in our study has been demonstrated before in most published case series and in a population-based study [20, 21]. Our data suggest a distinctive prevalence pattern of NAFLD dependent on gender similar to the prevalence rates reported previously in studies [20, 21]. Given that our study is a random cluster-selected sample with a relatively low bias by a sampling error, and taking into account the previously published results, it could also reflect the prevalence of distinct histological patterns of liver injury and possibly gender-specific role of sex steroids in the pathogenesis of NAFLD.

To investigate predictors of NAFLD, we chose factor analysis to reduce the number of available variables to a more manageable number of factors, each of which represents a linear combination of related variables. Therefore, factor analysis provides insight into the complex interrelationships of commonly investigated anthropometric and metabolic parameters and furthermore allows weighing the association of each complex factors with the phenotype of NAFLD when used in further analysis. Our analysis identified six factors in the set of investigated parameters – age, BMI, CRP, waist circumference, HOMA-IR and adiponectin – suggesting that age, low-grade systemic inflammation, visceral fat, insulin resistance and adipokine could play a causal role in the development of NAFLD.

Adiponectin has anti-inflammatory properties in the liver, and its deficiency might account for high aminotransferase and liver disease progression. In KK Ay-obese mice treated by lipopolysaccharide, pre-treatment with adiponectin reduces mortality, aminotransferase elevation, and the amount of apoptosis [30]. A direct anti-fibrotic effect of adiponectin has been suggested on the basis of adiponectin receptor gene expression in hepatic stellate cells and the inhibition of stellate cell proliferation and migration after adiponectin treatment [16]. Some studies have demonstrated that adiponectin deficiency correlated with increased liver fat [31-24], suggesting that adiponectin could be the critical factor regulating liver fat content. Furthermore, adiponectin has recently been shown to alleviate NAFLD in mice by increasing

carnitine palmitoyltransferase-1 activity and hepatic fat oxidation, and by suppressing TNF-α production in the liver and in plasma [16].

As in our present study, previous studies in different populations uniformly reported strong associations between hypoadiponectinaemia and the development of NAFLD by different imaging methods or histopathological correlates [35, 36]. However, there are very few population-based studies. Here we also demonstrate that increases in the degree of fatty infiltration of the liver, assessed according to established (and in the clinical setting readily available) ultrasound criteria, are associated with gradually decreasing serum adiponectin levels independent of potential confounders in a large-scale population.

In conclusion, our study indicates that NAFLD is highly prevalent in the middle-aged and elderly Chinese people living in urban Shanghai, especially among women. Developing effective public health strategies for the prevention, detection, and treatment of NAFLD should be an urgent priority to reduce the social and medical burden of NAFLD and its related metabolic abnormalities in China. We also found a close relation between serum adiponectin concentrations and NAFLD among the middle-aged and elderly Chinese, suggesting a potential role of adiponectin in the pathogenesis of NAFLD in middle-aged and elderly subjects.

Acknowledgments

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