

Impact of thyroid disorders on the incidence of non-alcoholic fatty liver disease in Germany

Christian Labenz^{1,2,3} | Karel Kostev⁴ | Angelo Armandi^{1,3,5} | Peter R. Galle^{1,2} |
Jörn M. Schattenberg^{1,2,3} 

¹Department of Internal Medicine I, University Medical Center of the Johannes Gutenberg-University, Mainz, Germany

²Cirrhosis Center Mainz (CCM), University Medical Center of the Johannes Gutenberg-University, Mainz, Germany

³Metabolic Liver Research Program, University Medical Center of the Johannes Gutenberg-University, Mainz, Germany

⁴Epidemiology, IQVIA, Frankfurt am Main, Germany

⁵Department of Medical Sciences, Division of Gastroenterology, University of Torino, Torino, Italy

Correspondence

Jörn M. Schattenberg, Department of Internal Medicine I, University Medical Centre of the Johannes Gutenberg-University, Langenbeckstrasse 1, 55131 Mainz, Germany. Email: joern.schattenberg@unimedizin-mainz.de

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Abstract

Background: Studies investigating a potential association between hypothyroidism and non-alcoholic fatty liver disease (NAFLD) showed conflicting results and large-scale population-based data from Germany on this topic are currently missing.

Objective: It was the aim of this analysis to investigate the impact of thyroid gland disorders on the prevalence of NAFLD in Germany.

Methods: In this case-control study, using the German disease Analyzer database (IQVIA), NAFLD patients were matched to patients without NAFLD by age, sex, index year, treating physician, diabetes mellitus type II, and obesity. The main outcome of the study was an association between thyroid gland disorders (hypothyroidism, hyperthyroidism and autoimmune thyroiditis) and incident NAFLD and was evaluated using logistic regression analyses.

Results: 57,483 patients with NAFLD were matched to 57,483 patients without liver disease. Mean age of the cohort was 60.3 years (± 14.1) and 52.3% were men. In regression analyses, hypothyroidism (OR 1.17, 95% CI 1.10 - 1.24, $p < 0.001$) as well as autoimmune thyroiditis (OR 1.53, 95% CI 1.35-1.73, $p < 0.001$) were associated with a higher risk of NAFLD. In contrast, hyperthyroidism was associated with a lower risk of NAFLD (OR 0.85, 95% CI 0.77-0.94, $p < 0.001$). The effect of hypothyroidism on the prevalence of NAFLD remained significant across men (OR 1.31, 95% CI 1.15-1.48) as well as women (OR 1.12, 95% CI 1.05-1.21).

Conclusion: Hypothyroidism seems to be a risk factor for incident NAFLD.

KEYWORDS

disease burden, liver disease, metabolic comorbidities, non-alcoholic steatohepatitis, thyroid gland disorders

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INTRODUCTION

The prevalence and the disease burden of non-alcoholic fatty liver disease (NAFLD) is increasing globally.¹ The asymptomatic nature of the disease and the lack of approved pharmacotherapy has led to an under-recognition of NAFLD, even in high-risk patient populations.² NAFLD constitutes a progressive disease spectrum encompassing non-inflammatory steatosis (non-alcoholic fatty liver, NAFL), hepatitis (non-alcoholic steatohepatitis, NASH) and end-stage liver disease with associated complications.³ At current epidemiological studies in NAFLD are hampered by the histological definition of the disease spectrum, however non-invasive biomarkers are emerging rapidly and these will help to better understand the group of patients affected by NAFLD.^{4,5} At current the identification of risk factors defining patients at highest risk for the development of NAFLD as well as risk factors of disease progression is of pivotal importance. Some of the well-established risk factors of NAFLD are compromised by the term – metabolic syndrome—including obesity, arterial hypertension and diabetes mellitus type II.⁶ Resulting insulin resistance and lipotoxicity promote liver injury and drive extrahepatic manifestations in patients with NAFLD. Recent evidence indicated that these metabolic substrates may share some pathogenic factors with hypothyroidism.⁷ In line, low concentrations of thyroid hormones have been linked to new onsets of metabolic syndrome and obesity.⁸

Although there is a growing body of evidence indicating a potential association between hypothyroidism and NAFLD,⁹ recent population-based evidence showed conflicting results.¹⁰ Currently, there are no large-scale population-based data from Germany on the effect of thyroid gland disorders on incident NAFLD available. A robust source to identify influencing factors at a population-based level is the German disease Analyzer database.^{11–14} While all limitations of database research have to be acknowledged,¹⁵ this data base captures the reality of patients currently diagnosed with NAFLD in primary care in Germany. Based on emerging results, the risk-profiling will allow to provide risk-based counselling aiming at secondary disease prevention. Therefore, we performed an analysis to dissect the impact of hypothyroidism, hyperthyroidism as well as autoimmune thyroiditis on the prevalence of NAFLD in over 100,000 German patients in primary care.

METHODS

Database

This study was based on data from the disease Analyzer database (IQVIA), which compiles drug prescriptions, diagnoses, and basic medical and demographic data obtained directly and in anonymous format from computer systems used in the practices of general practitioners and specialists in Germany.¹⁶ The database covers

Key summary

Summarise the established knowledge on this subject

- NAFLD and hypothyroidism share some pathogenic factors.
- Recent population-based evidence showed conflicting results on the potential association between hypothyroidism and NAFLD.

What are the significant and/or new findings of this study?

- Hypothyroidism as well as autoimmune thyroiditis were associated with a higher risk of NAFLD.
- Hyperthyroidism lowered the NAFLD-risk.
- The association between hypothyroidism and NAFLD remained significant in women as well as in men.
- The association between hypothyroidism and NAFLD was strongest in younger patients (age 18–50).

approximately 3% of all outpatient practices in Germany. Diagnoses (according to International Classification of Diseases, 10th revision [ICD-10]), prescriptions (according to Anatomical Therapeutic Chemical [ATC] Classification system), and the quality of reported data are being monitored by IQVIA. In Germany, the sampling methods used to select physicians' practices are appropriate for obtaining a representative database of general and specialized practices.¹⁶

Study population

This retrospective case-control study included adult patients (≥ 18 years) with an initial diagnosis of NAFLD (ICD-10: K75.8, K76.0) in 1262 general practices in Germany between January 2000 and December 2015 (index date; Figure 1). Further Inclusion criterion was an observation time of at least 12 months prior to the index date. NAFLD cases were matched to non-NAFLD cases by age, sex, index year, physician, diabetes, and obesity diagnosis. Diabetes (ICD-10: E10–E14) and obesity (ICD-10: E66) are known to be strongly associated with NAFLD.¹⁷ For this reason, these diagnoses were used as additional matching variables. Additionally, we compared the prevalence of hypertension (ICD-10: I10) and lipid metabolism disorders (ICD-10: E78.9) between both groups. For non-NAFLD patients, the index date was that of a randomly selected visit between January 2000 and December 2015 (Figure 1).

Study outcomes and covariates

The main outcome of the study was the association between hypothyroidism (ICD-10: E03), hyperthyroidism (ICD-10: E04), and

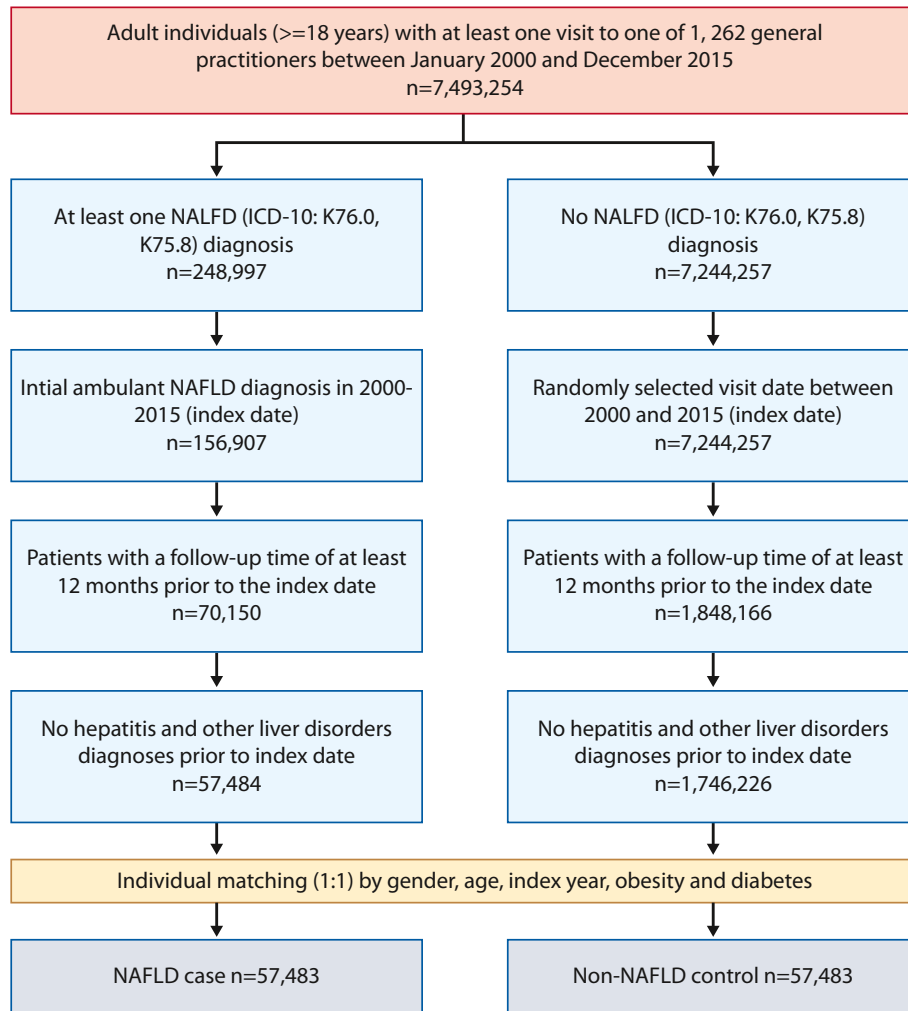


FIGURE 1 Selection of study patients

autoimmune thyroiditis (ICD-10: E06.3) and incident NAFLD. The three thyroid gland disorder diagnoses had to be documented at least once within 12 months prior to the index date.

Ethics

This study was conducted according to the ethical guidelines of the 1964 Declaration of Helsinki (amended, 2013). We used anonymous electronic medical records for research purposes with no directly identifiable data. Accordingly, this study did not collect informed consent from individual patients. Anonymized data were analyzed as aggregates with no protected health information available.

Statistical analyses

Differences in the sample characteristics between those with and those without NAFLD were tested using McNemar tests for categorical variables and Wilcoxon signed-rank tests for continuous

variables. Univariate logistic regression models were conducted to study the association between thyroid gland disorders and NAFLD. These models were performed separately for four age groups, women and men. To counteract the problem of multiple comparisons, p -values <0.01 were considered statistically significant. Analyses were carried out using SAS version 9.4 (SAS institute, Cary, USA).

RESULTS

Characteristics of the study sample

The present study included 57,483 NAFLD patients and 57,483 matched pairs without coded NAFLD. The basic characteristics of study patients are displayed in Table 1. Mean age [SD] was 60.3 [14.1] years; 47.7% were women. The prevalence of diabetes mellitus type II and obesity at the index time point were 48.6% and 32.6% in both cohorts, respectively. Prescriptions of levothyroxine within 365 days prior to the index date: was 11.9% in the NAFLD versus 9.8% in non-NAFLD patients ($p < 0.001$).

TABLE 1 Basic characteristics of the study sample (after 1:1 matching by age, sex, index year, obesity, and diabetes mellitus)

Variable	Proportion affected among patients with NAFLD (%) N = 57,483	Proportion affected among patients without NAFLD (%) N = 57,483	p-value
Age (Mean, SD)	60.3 (14.1)	60.3 (14.1)	1.000
Age 18–50	24.3	24.3	1.000
Age 51–60	24.2	24.2	
Age 61–70	25.4	25.4	
Age >70	26.1	26.1	
Women	47.7	47.7	1.000
Men	52.3	52.3	
Obesity	32.6	32.6	1.000
Diabetes mellitus	48.6	48.6	1.000
Hypertension	43.2	44.0	0.006
Lipid metabolism disorder	26.7	24.3	<0.001

Note: Proportions of patients in % given, unless otherwise indicated.

Abbreviation: SD, standard deviation.

Association between thyroid gland disorders and incident NAFLD

In logistic regression analyses, hypothyroidism as well as autoimmune thyroiditis were independently associated with a higher risk of incident NAFLD (hypothyroidism: OR 1.17, 95% CI 1.10 – 1.24, $p < 0.001$; autoimmune thyroiditis: OR 1.53, 95% CI 1.35 – 1.73, $p < 0.001$). In contrast, hyperthyroidism was associated with a lower risk of incident NAFLD (OR 0.85, 95% CI 0.77 – 0.94, $p < 0.001$). The respective proportion of patients with and without NAFLD affected with the thyroid gland disorders are displayed in Table 2.

In sensitivity analyses, the association between hypothyroidism and NAFLD remained significant in women as well as men (Figure 2). The association between autoimmune thyroiditis was strongest in women (OR 1.57, 95% CI 1.37 – 1.80, $p < 0.001$), while it did not reach significance in men (OR 1.34, 95% CI 0.99 – 1.82, $p = 0.058$). In total, thyroid gland disorders were more frequent in women than in men (Table 2).

When separating the total cohort into different age groups, the effect of hypothyroidism on NAFLD was numerically strongest in patients aged 18 – 50 (OR 1.30, 95% CI 1.13 – 1.48, $p < 0.001$). In contrast, the negative association between hyperthyroidism and NAFLD was strongest in the oldest patient group aged >70 (OR 0.75, 95% CI 0.46 – 0.88, $p < 0.001$) (Table 2).

DISCUSSION

The identification of potential risk factors in the development of NAFLD is critical to inform clinicians and in particular primary care physicians and to allow for preventive measures. At current, the lack of perception with health care provider is linked to the histological

definition of the disease and the absence of pharmacological interventions.² In this large study, we found that hypothyroidism as well as autoimmune thyroiditis were associated with a moderately higher risk of incident NAFLD. In line with these findings, hyperthyroidism was associated with a protective effect on the risk of incident NAFLD.

Thyroid gland disorders are among the most common chronic diseases in the western world. The same holds true for NAFLD being the most common liver disease globally with an estimated prevalence of 24% in Europe.^{18,19} According to our current study, hypothyroidism was an independent risk factor of incident NAFLD after careful matching for other important risk-factors like age, gender, diabetes or obesity. This finding is supported by the fact that we observed a protective effect of hyperthyroidism on risk of incident NAFLD. These findings may be helpful in the establishment of patient pathways and screening strategies of NAFLD which are urgently required to identify at risk populations. The definition of NAFLD as an indicator disease of unfavourable outcome with increased incidence in cancer²⁰ or cardiovascular diseases,¹² highlights the need to identify these patients to allow for established preventive measures.

Our current findings are well in line with a recent meta-analysis including 13 studies in which NAFLD was diagnosed by ultrasound. Here, a total of 42,143 participants were analysed and the authors found an association between hypothyroidism and NAFLD with a pooled OR of 1.52.⁹ In contrast, a recent cross-sectional, population-based study from Catalonia (Spain) including a sample of 10,116 individuals found no association between hypothyroidism and NAFLD. The current study adds to the existing literature and especially to the aforementioned meta-analysis by solidifying the association between hypothyroidism and a higher risk of incident NAFLD. One of the biggest strengths of our analysis is the inclusion of more than

TABLE 2 Association between thyroid gland diseases and incident NAFLD in patients in general practices in Germany (logistic regression models)

Thyroid Gland Disease	Proportion affected among patients with NAFLD (%)	Proportion affected among patients without NAFLD (%)	Or (95% CI)	p-value
Total patients				
Hypothyroidism	3.9	3.4	1.17 (1.10–1.24)	<0.001
Hyperthyroidism	1.3	1.5	0.85 (0.77–0.94)	<0.001
Autoimmune thyroiditis	1.1	0.7	1.53 (1.35–1.73)	<0.001
Women				
Hypothyroidism	6.1	5.5	1.12 (1.05–1.21)	0.001
Hyperthyroidism	1.9	2.2	0.86 (0.77–0.97)	0.014
Autoimmune thyroiditis	2.0	1.3	1.57 (1.37–1.80)	<0.001
Men				
Hypothyroidism	1.9	1.5	1.31 (1.15–1.48)	<0.001
Hyperthyroidism	0.7	0.9	0.81 (0.68–0.98)	0.026
Autoimmune thyroiditis	0.3	0.2	1.34 (0.99–1.82)	0.058
Age 18–50				
Hypothyroidism	3.5	2.7	1.30 (1.13–1.48)	<0.001
Hyperthyroidism	0.7	0.8	0.93 (0.71–1.21)	0.575
Autoimmune thyroiditis	1.1	0.7	1.63 (1.26–2.10)	<0.001
Age 51–60				
Hypothyroidism	3.9	3.5	1.13 (0.99–1.28)	0.062
Hyperthyroidism	1.1	1.3	0.82 (0.69–1.06)	0.183
Autoimmune thyroiditis	1.3	0.8	1.74 (1.37–2.21)	<0.001
Age 61–70				
Hypothyroidism	4.0	3.7	1.10 (0.98–1.24)	0.117
Hyperthyroidism	1.4	1.5	0.96 (0.79–1.16)	0.678
Autoimmune thyroiditis	1.1	0.8	1.36 (1.08–1.73)	0.009
Age >70				
Hypothyroidism	4.2	3.6	1.17 (1.04–1.31)	0.009
Hyperthyroidism	1.8	2.4	0.75 (0.64–0.88)	<0.001
Autoimmune thyroiditis	0.9	0.7	1.40 (1.08–1.81)	0.011

Note: p-values <0.01 were considered statistically significant.

Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval.

100,000 patients in German primary care setting, which also allows additional subgroup analyses. However, the effect of hypothyroidism on incident NAFLD was by far more moderate in our analysis when compared to the effect described in the meta-analysis by He et al. (OR: 1.17 vs. 1.52).⁴

The mechanisms linking hypothyroidism to NAFLD are related to direct effects on the hepatic lipid metabolism. Thyroid hormones (TH) act through specific nuclear receptor and influence the biosynthesis of cholesterol, by inducing the liver-specific expression of step-limiting enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase.²¹ Additionally, TH induce the expression

of the hepatic Low-Density Lipoprotein (LDL) receptor, which allows LDL internalization through endocytosis. Thus, administration of TH has been shown to improve cholesterol levels, potentially by the enhancement of receptor-mediated lipid catabolism.^{22,23} Moreover, TH are involved in the conversion of cholesterol into biliary acids fostering the biliary excretion through the rate-limiting enzyme cholesterol seven α -hydroxylase.^{24,25} The association specifically with ICD-10 coded autoimmune thyroiditis in this study is interesting and novel. As we cannot determine the different mechanistic effects of the different cause of hypothyroidism in this type of database research study,

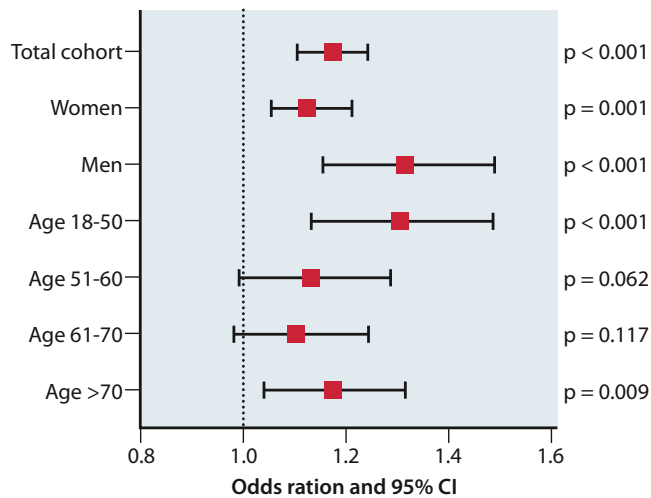


FIGURE 2 Hypothyroidism and risk of incident non-alcoholic fatty liver disease. Odds ratios and 95% confidence intervals of hypothyroidism on the risk of incident NAFLD in the total cohort, women, men and different age groups

further prospective evaluation seems warranted. However, it is likely that the effect on hepatic lipid metabolism as seen in non-autoimmune mediated hypothyroidism are partly redundant in different causes if hypothyroidism.

In humans, exploration of the potential role of thyroid metabolism in improving NAFLD has provided promising results, confirming the pre-clinical evidence of a causal link between thyroid dysfunction and liver damage through lipid metabolism alterations.^{26,27} In particular, hepatic-restricted isoform (β) of thyroid receptor (TR) has been investigated as a drug target for synthetic analogues, mimicking TH action upon the liver. Sobetirome²⁸ (explored in mice) and Eprotirome²⁹ (tested in humans with dyslipidemia) are TR- β agonists that have shown to reduce serum total cholesterol, LDL and triglycerides. A further improvement in liver steatosis was observed with sobetirome.³⁰

However, the best evidence derives from Resmitemom, a β -TR analogue that has been studied in a phase 2, randomized, double blind, placebo-controlled trial of patients with NASH. Resmitemom led to a reduction in hepatic fat determined by proton magnetic resonance spectroscopy exceeding 30%, and a consequential improvement in liver histology with regard to inflammatory features.³¹ Accordingly, a reduction in LDL and triglyceride levels was observed, together with an improvement in markers of liver inflammation (transaminases) and fibrogenesis (PRO-C3), highlighting the thyroid direct involvement in intrahepatic lipid metabolism, which alterations lead to a lipid-derived chronic inflammation and liver disease.

One of the biggest strengths of this study is the exploration of a large sample size representative for the German population. Furthermore, due to our large sample size we were able to establish a comparable control cohort with identical frequencies of known risk factors for the incidence of NAFLD like diabetes mellitus and obesity. Nevertheless, the study has some limitations

that have to be acknowledged and are mostly inherent to database analysis research. First, our analysis relies on ICD-10 codes for establishing diagnoses. This may cause a misclassification bias due to miscoding or undercoding. This current study, in particular, may be prone to undercoding of obesity, which was only present in 32.6% of both cohorts. However, this may be true for patients with and without NAFLD as well. Importantly, we were not able to describe the strategy that was used to diagnose NAFLD in this real-world database setting across different primary care centers. While guidelines recommend a combination of ultrasound and blood-based testing, this is likely heterogenous between different practices. Furthermore, the German disease Analyzer database does not capture detailed laboratory values nor details on liver histology or transient elastography. Therefore, the current study lacks information on disease severity of NAFLD, in particular fibrosis or NASH.

In conclusion, our study demonstrates that hypothyroidism as well as autoimmune thyroiditis were associated with a moderately higher risk of incident NAFLD. In line with these findings, hyperthyroidism had a protective effect on the risk of incident NAFLD. Considering the health burden caused by NAFLD, it is of importance to increase the awareness of physicians regarding a higher risk of NAFLD in patients with hypothyroidism.

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CONFLICT OF INTEREST

Jörn M. Schattenberg has received personal fees for consultancy to BMS, Echosens, Genfit, Gilead Sciences, Intercept Pharmaceuticals, Madrigal, Novartis, Pfizer, Roche. Research Funding from: Gilead Sciences and serves on the speakers bureau for the Falk Foundation. Karel Kostev is an employee of IQVIA. The other authors disclose no potential financial or non-financial conflict of interests.

ETHICS STATEMENT

This study was conducted according to the ethical guidelines of the 1964 Declaration of Helsinki (amended, 2013). We used anonymous electronic medical records for research purposes with no directly identifiable data. Accordingly, this study did not collect informed consent from individual patients. Anonymized data were analyzed as aggregates with no protected health information available.

AUTHOR CONTRIBUTION

Performed research: Christian Labenz, Karel Kostev, Jörn M. Schattenberg Designed the experiments and analyzed the data: Christian Labenz, Karel Kostev, Angelo Armandi, Peter R. Galle, Jörn M. Schattenberg Contributed reagents/materials/analysis tools: Karel Kostev Wrote the paper: Christian Labenz, Angelo Armandi, Jörn M. Schattenberg Statistical analysis: Karel Kostev All authors approved the final version of the manuscript and the authorship list. Guarantor of the article: Jörn M. Schattenberg.

DATA AVAILABILITY STATEMENT

Data are available from Karel Kostev upon reasonable request and approval of IQVIA.

ORCID

Jörn M. Schattenberg  <https://orcid.org/0000-0002-4224-4703>

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