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Research Article

Sex and Age Difference in the Impact of *Helicobacter Pylori* Infection on Glycolipid Metabolic Disorders among Health Checkup Population in Southwest China

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Abstract

Background: The association of *Helicobacter Pylori (H. pylori)* infection with glycolipid metabolic disorders in asymptomatic population is still controversial and few studies are concerning its discrepancy in age and gender. To bridge this gap, this study was aimed to investigate the zero-prevalence of *H. pylori* infection and its potential association with glycolipid metabolic disorders in a large Chinese health checkup population stratified by age and gender.

Methods: A case-control study was launched in a tertiary teaching hospital in Southwest China from April 2019 to December 2020. Subjects were enrolled at time of application for health checkup and blood tests. Demographic data and results of fasting plasma glucose and lipid pro-files were retrieved in laboratory information system and compared according to their serosta-tus of *H. pylori* antibodies, age and gender. Correlation was evaluated by binary logistic regres-sion analysis.

Results: The seroprevalence of *H. pylori* infection was 23.8% (8,869/37,304) and increased by age, with the highest rate of 28.0% among participants aged over 60 years. *H. pylori* seropositive par-ticipants were older than those seronegative ones and more vulnerable to suffer dysglucemia (10.0% *vs* 9.0%, p=0.002) and dyslipidemia (24.2% *vs* 22.8%, p=0.006). Approximately 12% and 24% of male participants have dysglucemia and dyslipidemia, respectively, in spite of their *H. pylori* serostatus, while *H. pylori* seropositive females were more vulnerable to have dysglucemia and dyslipidemia than seronegative ones (6.8% *vs* 5.1%, p=0.000 and 14.2% *vs* 12.1%, p=0.001, respec-tively). Binary logistic regression of subgroup analysis illustrated that *H. pylori* infection in-creased the risk of dysglucemia and dyslipidemia of female participants aged 25-60 years (OR=1.32, 95% CI: 1.12-1.56, p=0.001 and OR=1.273, 95% CI: 1.137-1.426, p=0.000, respectively), while among female participants aged over 60 years, *H. pylori* infection only increased the risk of dysglucemia (OR=1.75, 95% CI: 1.18-2.58, p=0.005).

Conclusion: The seroprevalence of *H. pylori* infection was relatively low in spite of age and gender, but *H. pylori* infection increased the risk of glucolipid metabolic disorders exclusively among female health checkup population at adult or elder age.

Keywords: *Helicobacter Pylori*; Dysglucemia; Dyslipidemia; Age; Gender association

Abbreviations

Hp: *Helicobacter Pylori*; Anti-Hp: *Helicobacter Pylori* Antibody; FPG: Fasting Plasma Glucose; TC: Total Cholesterol; TG: Triglycerides; HDL-C: High Density Lipoprotein Cholesterol; LDL-C: Low Density Lipoprotein Cholesterol; Non-HDL-C: TC minus HDL-C. OR: Odds Ratio, CI: Confidence Interval

Introduction

Past decades witnessed *Helicobacter Pylori* (*H. pylori*) prevalent in approximately 50% of populations in developed countries and over 80% in developing countries [1,2]. However, increasing epidemiological data have demonstrated the continuous decreasing prevalence of *H. pylori* worldwide [3,4], but few data concerning China. Added that a majority of *H. pylori* infected individuals are asymptomatic carriers, it is necessary to investigate the prevalence of *H. pylori* infection in this subpopulation.

Moreover, various studies have investigated the association of *H. pylori* infection with dysglucemia and dyslipidemia, but the conclusion is far from reached. Recent meta-analysis enrolled 41 case-control studies from 2009 to 2019 found a positive association between *H. pylori* infection and diabetes, alarming that Asian population suffered slightly higher risk of the effect of *H. pylori* infection on diabetes than other population [5], while a large Korean cohort study indicated that *H. pylori* infection was not associated with

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the development of diabetes [6]. As to dyslipidemia, a latest health examination survey in China also found *H. pylori* infection as a risk factor for less favorable lipid profiles [7]. However, a population-based KORA Study in Germany showed no association of *H. pylori* infection with dyslipidemia [8]. It seems that the association of *H. pylori* infection with dysglucemia and dyslipidemia varied across regions and populations, but these aforementioned studies failed to investigates the subpopulations stratified by gender or age, which may underestimate or overestimate this association and thus result in this discrepancy.

To clarify the association of *H. pylori* infection with dysglucemia and dyslipidemia in Chinese asymptomatic population, this study was launched to investigate the seroprevalence of *H. pylori* infection and evaluate the impact of *H. pylori* infection on lipid profiles and fasting plasma glucose among health checkup population between genders and age groups to present a baseline evidence for the efficient prevention and treatment of *H. pylori* infection and glucolipid metabolic disorders in Southwest China.

Materials and Methods

Study design and enrollment criteria

A cross-sectional, case-control study was carried out in the first affiliated hospital of Chongqing Medical University from April 2019 to December 2020. Individuals for health checkup were included at time of application for serum *H. pylori* antibody. Results of lipid profiles and fasting plasma glucose were retrieved from the Laboratory Information System (LIS). Subjects were excluded if younger than 15 years old, with missing of age, gender, results of lipid profiles and fasting plasma glucose, or with critical value of plasma fasting glucose no more than 2.22 mmol/L (Figure 1).

The lipid profiles and fasting plasma glucose of participants were firstly compared by the serostatus of *H. pylori* antibody and further stratified by age and gender. Then, the seropositivity rate of *H. pylori* antibody was compared by the glucolipid metabolic status of participants and further stratified by age and gender. Finally, the association of *H. pylori* infection with glucolipid metabolic disorders was evaluated by binary logistic regression.

Analytical methods

Serum samples were tested only when the internal quality control were satisfied. Li-pid profiles and fasting plasma glucose were tested by the automatic biochemistry ana-lyzer Roche Cobas c701 (Basel, Switzerland). *H. pylori* antibody was determined by the double-antigen (cagA and vacA) sandwich-gold immune-chromatography assay.

Definition

Dysglucemia was defined if Fasting Plasma Glucose (FPG) was higher than 6.1mmol/L. Dyslipidemia was defined if either TC≥6.2 mmol/L, LDL-C≥4.1mmol/L,TG≥2.3 mmol/L, non-HDL-C≥4.9 mmol/L or HDL-C < 1.0 mmol/L, ac-cording to the guideline for prevention and treatment of dyslipidemia in Chinese adults (2016) [9]. Teenage was defined if age between 15 to 24 years. Adult was defined if age be-tween 25 to 60 years. Elder was defined if age was over 60 years.

Statistical analysis

Categorical parameters and continuous parameters were shown by percentage and mean ± standard deviation, respectively. Chi-square and unpaired t test were adopted to compare the differences of distribution or mean values. Correlation was evaluated by bi-nary logistic regression analysis. Statistical significance was considered if p value was no more than 0.05.

Results

H. pylori Seroprevalance and glucolipid profiles in health checkup population

During this study period, 37,304 participants were enrolled and 44.3% (16,533/37,304) were females. The mean age of these participants was 43.08±13.08 years old. *H. pylori* antibody was prevalent in 23.8% (8,869/37,304) of all participants, with 24.2% in females and 23.5% in males. Despite females were found a slightly higher *H. pylori* seropositive rate than males, this difference is not statistically significant (p=0.11). When stratified by age, the seroprevalence of *H. pylori* infection was increased with age growing and peaked among participants aged over 60 years old in spite of gender (Figure 2).

Generally, the mean values of FPG, TC, TG, LDL-C, HDL-C and non-HDL-C in health checkup population were 5.39 mmol/L, 4.73 mmol/L, 1.64 mmol/L, 2.94 mmol/L, 1.39 mmol/L and 3.34 mmol/L, respectively. Dysglucemia was prevalent in 9.2% of all participants, while dyslipidemia was more common and prevalent in 22.8% of them. When stratified by gender, both of them were more prevalent in males than females (12.2% *vs* 5.5% for dysglucemia and 31.4% *vs* 12.6% for dyslipidemia, both p=0.000).

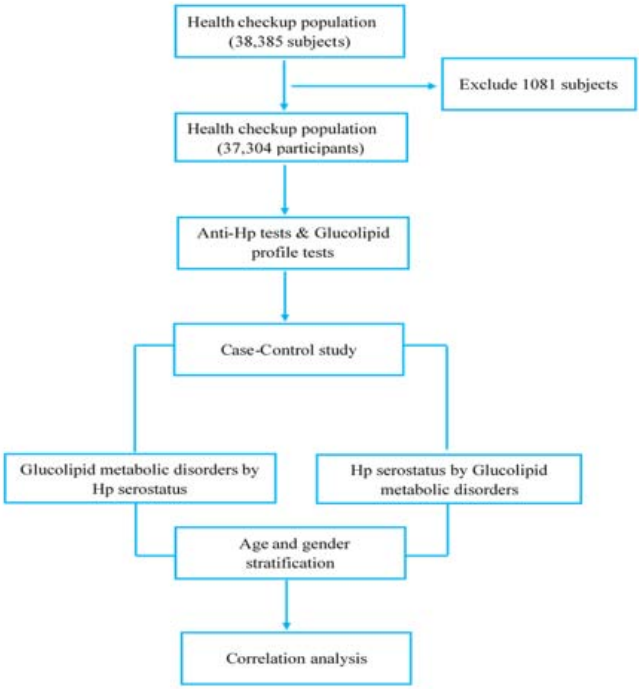

Figure 1: Flowchart of this study design. Hp: *Helicobacter Pylori*.

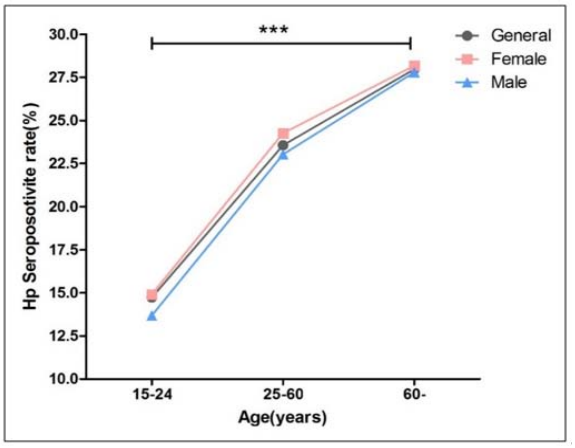

Figure 2: The seroprevalence of *Helicobacter Pylori* infection in health checkup population. Hp: *Helicobacter Pylori*, ***: p<0.001.

Table 1: Comparison of demographic and metabolic profiles of participants according to their serostatus of *Helicobacter Pylori* infection.

Variables*	Anti-Hp(+)	Anti-Hp(-)	p vaule
Age(years)	44.7±12.9	42.6±13.1	***0.000***
Female(%)	3996(45.1)	12537(44.1)	0.111
FPG (mmol/L)	5.41±1.13	5.38±1.13	0.059
Dysglucemia(%)	890(10.0)	2548(9.0)	***0.002***
TC(mmol/L)	4.78±0.90	4.72±0.90	***0.000***
TG(mmol/L)	1.67±1.39	1.63±1.54	0.071
HDL-C(mmol/L)	1.38±0.36	1.40±0.36	*0.000*
LDL-C(mmol/L)	2.99±0.82	2.93±0.81	***0.000***
Non-HDL-C(mmol/L)	3.40±0.92	3.32±0.94	*0.000*
Dyslipidemia(%)	2146(24.2)	6474(22.8)	***0.006***

*Categorical parameters and continuous parameters were shown by percentage and mean ± standard deviation, respectively. Chi-square and unpaired t test were adopted to compare the differences of distribution or mean value between these two groups.

Glucolipid disorders in participants by *H. pylori* serostatus

As shown in Table 1, seropositive participants were older than seronegative ones and suffered significantly higher TC, LDL but lower HDL. Chi-square test illustrated that dyslipidemia were more prevalent in *H. pylori* seropositive participants than seronegative ones (24.2% *vs* 22.8%, p=0.006). The average value of FPG among seropositive participants was marginally higher than that among seronegative participants and Chi-square test confirmed that dysglucemia was more frequent among seropositive participants(10.0% *vs* 9.0%, p=0.002).

When stratified by gender, dysglucemia and dyslipidemia were distributed among approximately 12% and 24% of male participants, respectively, in spite of the serostatus of *H. pylori* antibody, while they were more common in *H. pylori* seropositive females than seronegative ones (6.8% *vs* 5.1%, p=0.000 and 14.2% *vs* 12.1%, p=0.001, respectively), suggesting the potential association of *H. pylori* infection with dysglucemia and dyslipidemia in female participants (Table 2).

Table 2: Comparison of metabolic profiles of participants according to their serostatus of *Helicobacter Pylori* infection and gender.

Gender	Female			Male		
Variables*	Anti-Hp(+)	Anti-Hp(-)	*p value*	Anti-Hp(+)	Anti-Hp(-)	*p value*
Age (years)	44.03±12.76	41.59±13.14	**0.**000	45.30±12.89	43.33±13.10	**0.000**
FPG (mmol/L)	5.25±0.86	5.21±0.84	**0.**012	5.53±1.30	5.51±1.30	0.328
Dysglucemia (%)	272(6.81)	636(5.10)	**0.**000	618(12.7)	1912(12.0)	0.220
TC (mmol/L)	4.76±0.90	4.65±0.91	**0.**000	4.80±0.90	4.78±0.90	0.116
TG (mmol/L)	1.27±0.84	1.20±1.05	**0.**000	1.99±1.64	1.97±1.77	0.508
HDL-C (mmol/L)	1.56±0.35	1.59±0.35	**0.**000	1.23±0.29	1.25±0.30	**0.000**
LDL-C (mmol/L)	2.91±0.82	2.80±0.80	**0.**000	3.06±0.81	3.03±0.81	**0.033**
Non-HDL-C (mmol/L)	3.20±0.90	3.06±0.90	**0.**000	3.57±0.91	3.53±0.92	**0.007**
Dyslipidemia (%)	568(14.2)	1522(12.1)	**0.**001	1578(32.4)	4952(31.1)	0.105

*Categorical parameters and continuous parameters were shown by percentage and mean ± standard deviation, respectively. Chi-square and unpaired t test were adopted to compare the differences of distribution or mean value between these two groups.

Association of *H. pylori* seropositivity and glucolipid metabolic disorders in female participants

To investigate this potential association, we regrouped 16,533 female participants by their glucolipid profiles. Female participants with dysglucemia found higher seroprevalence of *H. pylori* infection than those without dysglucemia (30.0% *vs* 23.8%, p=0.000). Similar results also reached among those with dyslipidemia (27.2% *vs* 23.7%, p=0.001). Since we have found the seroprevalence of *H. pylori* infection is increased by age, we stratified this female subpopulation by age to further clarify this potential association in different age groups.

Generally, among participants with dysglucemia, the seropositive rate of *H. pylori* antibody was increasing with age growing and peaked among those aged over 60 years, with a rate of 39.0%, while this climbing tendency was disturbed among participants with dyslipidemia and the seropositive rate peaked among those aged between 25 to 60 years, with a rate of 28.4% (Figure 3). All these results suggested that seropositive rate of *H. pylori* infection among females with glucolipid metabolic disorders differed by age, so we further compare the distributions of *H. pylori* antibodies between females with glucolipid metabolic disorders and those without glucolipid metabolic disorders in different age groups.

Association of *H. pylori* seropositivity and glucolipid metabolic disorders in female participants by age

Among females aged 15-24 years, similar *H. pylori* seropositive rate was observed between participants with or without glucolipid metabolic disorders (Table 3). However, among participants aged 25-60 years, *H. pylori* antibody was positive in 29.7% of participants with dysglucemia, but 24.0 % of those without dysglucemia (p=0.001). Similar significant different but higher seroprevalence was also observed in the age group over 60 years (39.0% *vs* 27.4%, p=0.011). Likewisely, participants with dyslipidemia in the age group 25-60 years reported more seropositivity of *H. pylori* antibody than those without dyslipidemia (28.4% *vs* 23.7%, p=0.000). However, this significant difference disappeared in the age group over 60 years. Binary logistic regression illustrated that *H. pylori* infection increased

Table 3: Comparison of *Helicobacter Pylori* serostatus of female participants according to their glucolipid metabolic disorders and age.

Age (Years)	Hp serostatus	Dysglucemia (+)	(-)	p* value	Dyslipidemia (+)	(-)	p value
15-24	Anti-Hp(+)	10	125	0.715	19	116	0.700
	Anti-Hp(-)	52	718		120	650	
25-60	Anti-Hp(+)	216	3147	*0.001*	489	2874	*0.000*
	Anti-Hp(-)	512	9986		1231	9267	
60-	Anti-Hp(+)	46	452	*0.011*	60	438	0.236
	Anti-Hp(-)	72	1197		171	1098	

*Chi-square was adopted to compare the differences of distribution between these two groups.

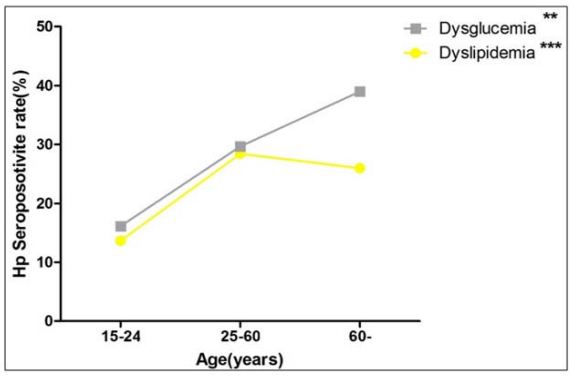

Figure 3: The seroprevalence of *Helicobacter Pylori* infection among female health checkup population with glycolipid metabolic disorders. Hp: *Helicobacter Pylori*, **: p<0.01, ***: p<0.001.

the risk of dysglucemia and dyslipidemia of female participants aged 25-60 years (OR=1.32, 95% CI: 1.12-1.56, p=0.001 and OR=1.273, 95% CI: 1.137-1.426, p=0.000, respectively), while *H. pylori* infection increased the risk of dysglucemia in female participants exclusively aged over 60 years, (OR=1.75, 95% CI: 1.18-2.58, p=0.005).

Discussion

This study presents the current available evidence of the seroprevalence of *H. pylori* infection and its association with dysglucemia and dyslipidemia among health checkup population in Southwest China. In contrast to recent hospital-based or community-based studies in other regions of China illustrating 28.2% to 53% of asymptomatic participants [10-12] infected with *H. pylori*, this present study reported a rate of 23.9% in Southwest China. The relatively inferior sensitivity of serological antibody test may be blamed for this relatively low seropositivity to a certain extent, since these previous studies adopted ^{13}C or ^{14}C-urea breath test to diagnose *H. pylori* infection and Cochrane analysis has concluded the sensitivity of urea breath test is higher than that of serological antibody test by approximately 10% [13]. Nevertheless, we suppose that serological testing is more appropriate for this epidemiological study, as its result suggests both current infection and past infection of *H. pylori* in large population. As to the seroprevalence of *H. pylori* infection in healthy population or health checkup population, Korea reported a seropositive rate of 41.5 % [14], Japan reported 27.5% [15] and Southeast Hungary reported 32% [16]. Our relatively low seroprevalence (23.9%) may be ascribed to the urbanization of regions and the improvement of sanitation facilities during the 13th Five-Year Plan in Southwest China, as the weighted mean prevalence of *H. pylori* infection in urban Chinese population reported 47% in 2015 [17].

Inconsistent with the results of stomach cancer pooling project [18], this study confirmed that it was elder age rather than gender that was related to seropositivity of *H. pylori* infection. This discrepancy is partially due to the distinct aim and enrollment criteria of studies, but our finding was supported by several population-based studies in Japan [15] and Indonesia [19], which also reported increasing tendency of *H. pylori* seropositivity by age. It is not difficult to understand this relationship, as the elderly are more vulnerable to be exposed to *H. pylori*.

Our finding illustrated *H. pylori* infected participants suffered high proportion of dysglucemia, but the impact of *H. pylori* infection on glucose metabolic disorders was exclusively found in female participants with age discrepancy. Latest cross-sectional study in China showed that *H. pylori* infection increased the risk of diabetes mellitus in elder females over 60 years old [20]. Consistent with this result to some extent, our study found that *H. pylori* infection increased the risk of dysglucemia in females over 60 years old and even younger than 60 years (25 to 60 years old), suggesting the early appearance of glucose metabolic disorders among *H. pylori* seropositive female adults in our setting. Several studies reported the correlation of *H. pylori* infection and dysglucemia but failed to discuss gender discrepancy. A recent Japanese study reported that *H. pylori* increased the risk of diabetes mellitus among health checkup population and this increased risk was not observed after eradicating *H. pylori*. Moreover, eradication of *H. pylori* in patients with type 2 diabetes mellitus had been found beneficial to glycemic control, hinting the correlation of *H. pylori* and glucose metabolic disorders.

Since previous clinical and animal studies have illustrated the protection effect of endogenous estradiol from type 2 diabetes mellitus by estrogen signaling pathway, the possible explanation of this correlation in our female participants is that *H. pylori* infection induces chronic inflammation and insulin resistance [21], sex hormones loss of postmenopausal women aggravate this pathogenesis and finally accelerate this glucose metabolic disorders in elderly females. Nevertheless, a population-based prospective study in China recently identified that *H. pylori* seropositivity was associated with lower risk of diabetes. Therefore, the association of *H. pylori* seropositivity and dysglucemia or diabetes mellitus requires more researches and well-designed subgroup analysis is necessary to verify this association between genders.

More importantly, age-specific association of *H. pylori* infection and dyslipidemia was firstly illustrated in this female adult population. *H. pylori* infection increased the risk of dyslipidemia in female participants aged 25 to 60 years. Recent meta-analysis results suggested positive association of *H. pylori* infection with LDL, TC and TG, but negative association with HDL [22]. This is concordant with our findings in females but not in males. Latest cross-sectional study in China also found that *H. pylori* infection is associated with nonalcoholic fatty liver disease (characterized with high TC but low HDL) in females [23]. Furthermore, emerging studies showed that successful eradication of *H. pylori* had favorable effects on lipid metabolism [24], suggesting the correlation of *H. pylori* infection and

lipid metabolism. Since emerging evidence support that eradication of *H. pylori* restores the secretion of ghrelin and reduces the Bacteroidetes-to-Firmicutes ratio, this relationship may be explained by the cross-talk between *H. pylori* and gut microbiota, but the underlying mechanisms of gender discrepancy in this relationship are not yet clear. We supposed that the different gut microbiota between genders [25,26] and their distinct manner in the interplay with *H. pylori* infection may contribute to our discrepancy in this correlation and further studies are advocated to illuminate the underlying mechanisms.

Several limitations should not be neglected in this present study. Firstly, since *H. pylori* infection was diagnosed by the seropositivity of anti- *H. pylori* antibodies, it is difficult for us to discriminate the current and past infection by *H. pylori*. However, as previous study has found that past *H. pylori* infection is not associated with glucolipid metabolic disorders. In consideration that the awareness and eradication rates of *H. pylori* infection in China were relatively low, it was supposed that a majority of health checkup population in this setting were current *H. pylori* infection and thus resulted in its positive association with glucolipid metabolic disorders. Secondly, due to inability to acquire the socioeconomic information of the participants, we failed to adjust these risk factors for glucolipid metabolic disorders. However, this tertiary teaching hospital is designated to fulfil the health examination of employees in government, public enterprises and institutions, so we speculated the discrepancy of socioeconomic status was subtle and this speculation could be verified by our relatively low seroprevalence of *H. pylori* infection due to the good socioeconomic status and public hygiene of this health checkup population. Thirdly, since this study is cross-sectional, case-control designed, it failed to follow the participants with high fasting plasma glucose and unfavorable lipid profiles and thus the clinical consequence of these participants were unknown.

Conclusion

This study illustrates the relatively low seroprevalence of *H. pylori* infection in spite of sex and age. The correlation between *H. pylori* seropositivity and glucolipid metabolic disorders were exclusively found in female health checkup population at adult or elder age. Careful interpretation and adoption of this correlation in the prevention and eradication of *H. pylori* infection among adult female health checkup population in this setting are advocated.

Author Contributions

Shuangshuang Yang designed this study, collected the data, fulfilled the data statistics and wrote the original draft. Hailan Shen participated in the data curation, reviewed and edited the draft. Ziqi Zhang and Yongjun Shi participated in the data collection, data statistics and calculation. Zheng Jiang supervised this study and presented the resources. All the author read this contribution and agreed this submission.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University (No.2020-705).

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