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Ankle-Brachial Index, Cognitive Impairment and Cerebrovascular Disease in a Chinese Population

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Key Words
Ankle-brachial index · Peripheral arterial disease · Neuroimaging · Cognitive impairment

Abstract
Background: Previous studies have assessed the association between ankle-brachial index (ABI) and cognition, mainly using brief cognitive tests. We investigated whether ABI was associated with cognition independent of neuroimaging markers of cerebrovascular disease. ***Methods:*** Chinese subjects (n = 278, aged ≥60 years) were recruited from the ongoing Epidemiology of Dementia in Singapore (EDIS) Study. Ankle and brachial blood pressures were measured, and low ABI was defined as ≤0.9. A neuropsychological battery was utilized to determine cognition. Cognitive impairment no dementia (CIND) and dementia were diagnosed according to standard diagnostic criteria. Magnetic resonance imaging (MRI) was used to obtain semiquantitative and quantitative markers of cerebrovascular disease and atrophy. ***Results:*** A low ABI was related to the presence of intracranial stenosis (odds ratio, OR = 1.71; 95% confidence interval, CI: 1.13–2.59), but not with the presence of infarcts, microbleeds or grey matter, white matter and white matter lesion volumes. Furthermore, a low ABI was associated with poorer overall cognitive function and CIND-moderate/dementia (OR = 2.26; 95% CI: 1.11–4.59), independent of cardiovascular risk factors, and the MRI markers related to cerebrovascular disease and atrophy. ***Conclusion:*** We found an association between a low ABI and cognitive impairment, independent of any MRI marker of cerebral small vessel disease or large artery atherosclerotic disease.

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Introduction

Ankle-brachial index (ABI), defined as the ratio of the ankle to brachial systolic blood pressure, is considered a surrogate marker of atherosclerosis. ABI is a simple non-invasive test that can be performed in clinical settings for detecting peripheral arterial disease [1–4]. Whilst persons with a low ABI may not have clinically evident symptoms of peripheral arterial disease, they are, nevertheless, at an increased risk of fatal cardiovascular and cerebrovascular events [5–8].

As vascular pathology has been implicated in the pathophysiology of cognitive impairment and dementia, several studies have also examined the relationship between ABI and cognition [9–15]. However, most previous studies have largely utilized a limited set of brief cognitive tests, most frequently the Mini Mental State Examination (MMSE) and the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) [11–15]. Furthermore, there is a paucity of data on the association of ABI and cognition in non-Caucasian populations. Considering the ethnic variations in the prevalence and risk factors of cardiovascular diseases, this gap needs to be addressed [16, 17]. Data in Chinese are limited to a single study that reported an association between low ABI and cognitive impairment, defined solely by the MMSE [18]. Moreover, with respect to subclinical vascular pathology on neuroimaging, a recent study showed that a low ABI was associated with silent cerebral infarcts on magnetic resonance imaging (MRI), independent of traditional vascular risk factors [19]. However, there are no data regarding the association of ABI with either markers of cerebrovascular disease, such as white matter lesions (WML), intracranial stenosis and cerebral microbleeds, or markers of atrophy.

Our aim, therefore, was to investigate the association between a low ABI and cognitive function, using an extensive neuropsychological battery in a Chinese population. In addition, we examined whether these associations were independent of MRI markers of cerebrovascular disease and atrophy.

Subjects and Methods

The ongoing Epidemiology of Dementia in Singapore (EDIS) study drew subjects from participants of the population-based study among Chinese aged 40–85 years who took part in the Singapore Chinese Eye Study. In order to use the limited resources in an efficient way, it was decided to focus on those subjects who were most likely to have cognitive problems. Hence, in the first phase of the EDIS Study, Chinese participants from the Singapore Chinese Eye Study aged ≥60 years (n = 1,538) were screened using the Abbreviated Mental Test (AMT) and a self-report of progressive forgetfulness. Screen-positives were defined as AMT score ≤6 among those with ≤6 years of formal education, AMT score ≤8 among those with >6 years of formal education, or if the subject or caregiver reported progressive forgetfulness. Screen-positive subjects (n = 612) were invited to take part in the second phase of this study, which included an extensive neuropsychological test battery and brain MRI. Of these 612 participants, 300 agreed to participate in phase II and hence were included in the present study. Ethics approval for the EDIS study was obtained from the Singapore Eye Research Institute and National Healthcare Group Institutional Review Boards. Informed consent was obtained for all participants prior to recruitment. The detailed methodology has been described elsewhere [20].

Ankle-Brachial Index

Ankle and brachial blood pressures were measured using a digital device (Omron HEM-7203, Japan) and Doppler ultrasound probe (Nicolet Vascular Elite 100). Blood pressure was measured over the brachial, dorsalis pedis and posterior tibial arteries bilaterally, after 5 min of rest in the supine position. ABI was calculated, separately for each leg, as the ratio of the higher of the two (posterior tibial or dorsalis pedis) at the ankle to the higher of the right and left systolic blood pressure [21]. For the purpose of analysis, the lower ABI value was utilized. ABI was categorized as normal (>0.9) and low (≤0.9).

Cognitive Assessment

A formal neuropsychological battery previously locally validated for the Singaporean elderly was administered for assessment of cognitive functions [22]. The following domains were tested using the specified neuropsychological tests:

(1) Executive Function (frontal assessment battery, maze task);
(2) Attention (digit span, visual memory span, auditory detection);
(3) Language (Boston naming test, verbal fluency);
(4) Visuomotor speed (symbol digit modality test, digit cancellation);
(5) Visuoconstruction (Wechsler Memory Scale – revised, visual reproduction copy task, clock drawing, WAIS-R subtest of block design);
(6) Verbal Memory (word list recall, story recall);
(7) Visual Memory (picture recall, Wechsler Memory Scale – revised, visual reproduction).

Education-adjusted cutoffs of 1.5 standard deviation (SD) below established norms were used on individual tests. Z-scores were derived for individual subtests; Z-scores for individual domains were computed by summing up the Z-scores of each subtest under that domain and dividing by the number of subtests. Domain-specific Z-scores were utilized to compute the final global cognitive composite score.

Diagnoses of cognitive impairment and dementia were made at weekly consensus meetings attended by study clinicians, neuropsychologists and clinical research fellows. In order to have an objective means of defining preclinical stages of dementia, we decided to use cognitive impairment no dementia (CIND). CIND was classified into mild (≤2 domains impaired) and moderate (>2 domains impaired) [20, 23]. The diagnosis of dementia was made according to the DSM-IV criteria.

Magnetic Resonance Imaging

MRI scans were performed on a 3-tesla Siemens Magnetom Trio Tim scanner, using a 32-channel head coil, at the Clinical Imaging Research Centre. T2-weighted (repetition time, TR = 3,000 ms, time to echo, TE = 10.1 ms, matrix = 256 × 247 mm^3) and fluid-attenuated inversion recovery (FLAIR) images (TR = 9.3 ms, TE = 140 ms, matrix = 256 × 192 mm^3) were utilized for assessing the presence of ischemic strokes and WML; susceptibility-weighted imaging (TR = 27 ms, TE = 20 ms, matrix = 240 × 240 mm^3) was utilized for detecting cerebral microbleeds, 3D time of flight magnetic resonance angiography (TR = 24 ms, TE = 4.1 ms, spatial resolution = 0.6 × 0.6 × 0.6 mm^3) was utilized for detection of intracranial stenosis and T1-weighted imaging (TR = 7.2 ms, TE = 3.3 ms, matrix = 256 × 256 × 180 mm^3) was used for grading atrophy. All MRIs were graded by one radiologist and two clinicians blinded to the neuropsychological and ABI data. Any disagreement was brought to consensus for a final decision. Data on the following MRI parameters were collated for each subject:

(1) Presence of ischemic stroke (including lacunar infarcts) [24];
(2) Cerebral microbleeds using the Brain Observer Micro Bleed Scale [25];
(3) Intracranial stenosis defined as narrowing exceeding 50% of the luminal diameter on 3D time-of-flight magnetic resonance angiography. The arteries that were assessed were the vertebral, basilar, internal carotid and middle cerebral and anterior cerebral arteries.
(4) Total brain volume and WML volume were quantified by automatic segmentation at the Erasmus Medical Center, Rotterdam, The Netherlands. Brain tissue segmentation was quantified using the proton density-weighted T1 sequence and T2-weighted images, whereas the WML volume was segmented using FLAIR, as described previously [26]. Briefly, as a marker of global atrophy, total brain volume was calculated as the sum of gray matter and white matter volumes of the five regions (frontal, parietal, occipital, temporal and central regions). WML volume was the summation of the WML in the above-mentioned five regions [27].

Other Subject Data

A detailed questionnaire was administered to collect data on relevant demographic and clinical characteristics, including age, gender, education, marital status, smoking, history of stroke, hypertension, hyperlipidemia, diabetes and ischemic heart disease [20]. Furthermore, blood samples were used to determine high-sensitivity C-reactive protein (hs-CRP), glycated hemoglobin and cholesterol levels. Hypertension was defined as previous diagnoses of hypertension, use of antihypertensive medication, systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg. Diabetes was defined as previously diagnosed diabetes, use of hypoglycemic agents or glycated hemoglobin ≥6.5%. Hyperlipidemia was defined as previously diagnosed high lipid levels, use of antihyperlipidemic medication or total cholesterol levels ≥4.14 mmol/l. Smoking was categorized into nonsmokers and smokers (past and current smokers). The modified 15-item Geriatric Depression Scale (GDS) was administered to all subjects [28]. Depression was defined as a GDS score >5.

Statistical Analysis

To assess differences between subjects included and those excluded from this analysis, the χ^2 test was utilized for categorical variables and the two-sample t test for continuous variables. For additional adjustments in the regression models, besides the variables that were statistically significant, we also decided to take the nonsignificant variables as they still might be considered as potential confounders. For further analyses, mean ABI of the study population was subtracted from individual ABI values; the results were then divided by the SD (of population ABI) to obtain standardized ABI.

With respect to MRI markers, logistic regression models were constructed to investigate the association between ABI and semi-quantitative MRI markers (presence of infarcts, intracranial stenosis and microbleeds), utilizing standardized ABI as a determinant and individual MRI marker as outcome. For quantitative MRI parameters a linear regression model was utilized to investigate the association with ABI. As WML volume was not normally distributed, this was logarithmically transformed. All these models were adjusted for confounders, including age, gender, smoking, hypertension, diabetes, hypercholesterolemia, GDS score and hs-CRP. Logistic regression models were used to investigate the association between ABI and cognition, comparing subjects with CIND-mild and CIND-moderate/dementia to those with no cognitive impairment. To examine the relationship between ABI and Z-scores for cognition (global cognitive composite score), linear regression models were used. These models were adjusted for confounders, including age, gender, smoking, hypertension, diabetes, hypercholesterolemia, GDS score, hs-CRP and MRI markers.

The parameter estimates and 95% confidence intervals (CI) were reported. p values <0.05 were considered statistically significant. These analyses were performed using standard statistical software (Statistical Package for Social Science, SPSS V19; SPSS Inc., USA).

Results

A total of 1,538 Chinese subjects participated in phase I of the EDIS Study, of whom 612 were screen-positive and thus were invited for the second phase. Of the 300 who agreed to participate in phase II, 27 subjects declined ABI assessment, leaving a total of 273 for the current analysis. Compared to the included subjects, those who were excluded were older, more likely to have hypertension and lower education and less likely to have hyperlipidemia. Demographic and clinical characteristics of the 273 subjects (stratified according to their cognitive status) are shown in table 1. Those who were cognitively impaired were more likely to be older women with no formal education and had higher prevalence of hypertension, hyperlipidemia, depression, history of stroke and lower ABI. A total of 126 persons had CIND, of whom 77 had CIND-mild and 66 CIND-moderate. An additional 4 persons had dementia. Due to the small numbers, subjects with dementia were combined with the CIND-moderate group for analysis. A low ABI was observed in a total of 28 subjects (10.3%), of whom 5

Table 1. Baseline demographic and clinical characteristics

Characteristics	NCI (n = 126)	CIND-mild (n = 77)	CIND-moderate/dementia (n = 70)	p value*
Age, years	67.3±4.8	70.8±6.5	74.7±5.4	<0.001
Gender (female)	55 (43.7)	39 (50.6)	47 (67.1)	0.007
Education (≤6 years)	59 (46.8)	59 (76.6)	53 (75.7)	<0.001
Smoking (yes)	38 (30.2)	25 (32.5)	18 (25.7)	0.66
Hypertension	88 (69.8)	55 (71.4)	60 (85.7)	0.04
Diabetes mellitus	26 (20.6)	19 (24.7)	23 (32.9)	0.17
Hyperlipidemia	70 (55.6)	47 (61.0)	50 (71.4)	0.09
History of stroke	4 (3.2)	7 (9.1)	8 (11.4)	0.06
Ischemic heart disease	4 (3.2)	4 (5.2)	1 (1.4)	0.44
hs-CRP (>3 mg/l)	17 (13.7)	6 (8.0)	12 (17.6)	0.23
WML volume, ml	1.3 (3.2)	1.7 (4.7)	3.3 (10.1)	<0.001
Grey matter volume, ml	536.8±51.5	536.4±72.6	526.0±69.4	0.49
White matter volume, ml	374.1±42.5	359.8±57.3	348.2±58.5	0.004
Presence of infarcts	5 (4.1)	15 (21.4)	22 (33.8)	<0.001
Presence of microbleeds	32 (26.4)	25 (35.7)	28 (43.1)	0.06
Intracranial stenosis	5 (4.1)	7 (10.1)	9 (13.8)	0.06
Depression (GDS >5)	5 (4.0)	11 (14.3)	10 (14.3)	0.02
ABI (≤0.9)	5 (4.0)	10 (13.0)	13 (18.6)	0.004

Values are expressed as mean ± SD or number with percentage. WML volume: median (interquartile range) presented due to skewed distribution. * p < 0.05 considered statistically significant: test for trend.

Table 2. Association between ABI (per SD decrease) and MRI markers

	Qualitative MRI markers			Quantitative MRI markers		
	OR			mean difference in volume		
	microbleeds	infarcts	intracranial stenosis	WML volume[1]	grey matter volume	white matter volume
Model 1	0.96 (0.73–1.25)	1.16 (0.84–1.60)	1.76 (1.21–2.56)	0.02 (–0.07 to 0.11)	–0.22 (–7.21 to 6.78)	–3.48 (–9.34 to 2.39)
Model 2	0.91 (0.68–1.22)	0.98 (0.66–1.45)	1.71 (1.13–2.59)	0.00 (–0.09 to 0.09)	–0.18 (–7.56 to 7.19)	–2.35 (–8.49 to 3.80)

Model 1: adjusted for age and gender. Model 2: adjusted for age, gender and vascular risk factors (smoking, hypertension, diabetes, hyperlipidemia and hs-CRP). Values in parentheses indicate 95% CI.
[1] Mean difference in log-transformed WML volume.

(4.0%) did not have cognitive impairment, 10 (13.0%) were CIND-mild and 13 (18.6%) CIND-moderate/dementia. Mean ± SD ABI across the cognitive categories was as follows: no cognitive impairment: 1.04 ± 0.09, CIND mild: 1.01 ± 0.12 and CIND moderate/dementia: 0.98 ± 0.12.

With respect to neuroimaging, of the 273 subjects, 16 did not consent to an MRI. Hence, a total of 257 subjects were included in the analysis on MRI markers. Infarcts were noted in 42 (16.3%) persons, of whom 7 (2.6%) had cortical infarcts. Furthermore, cerebral microbleeds were seen in 85 (33.2%) persons and intracranial stenosis in 21 (8.2%). A significant association was observed between ABI and intracranial stenosis (table 2). The mean difference in ABI between subjects with and without intracranial stenosis was –0.08 (95% CI: –0.13 to –0.03). No significant association was observed between ABI and other MRI markers, including markers of cerebral small vessel disease and atrophy (table 2).

Subjects with a low ABI were more likely to have CIND-moderate/dementia (multivariable adjusted odds ratio, OR, per SD decrease in ABI: 1.69, 95% CI: 1.00–

Table 3. Association between ABI (per SD decrease) and cognitive function

	CIND-mild (n = 77) OR[1]	CIND-moderate/dementia (n = 70) OR[1]	Global cognitive composite Z-score mean difference[2]
Model 1	1.49 (1.05–2.11)	1.82 (1.16–2.88)	–0.10 (–0.18 to –0.02)
Model 2	1.45 (1.00–2.11)	1.69 (1.00–2.85)	–0.07 (–0.15 to 0.01)
Model 3			
Infarcts	1.60 (1.06–2.40)	2.20 (1.12–4.32)	–0.09 (–0.17 to –0.02)
Cerebral microbleeds	1.53 (1.03–2.27)	1.93 (1.09–3.42)	–0.09 (–0.17 to –0.02)
WML volume	1.51 (1.02–2.24)	1.90 (1.07–3.37)	–0.09 (–0.16 to –0.01)
Intracranial stenosis	1.46 (0.98–2.15)	1.87 (1.04–3.36)	–0.08 (–0.15 to 0.00)
All MRI markers	1.54 (1.02–2.33)	2.26 (1.11–4.59)	–0.07 (–0.15 to 0.01)

Model 1: adjusted for age, gender and education. Model 2: adjusted for age, gender, education, vascular risk factors (smoking, hypertension, diabetes, hyperlipidemia, ischemic heart disease, history of stroke and hs-CRP) and GDS score. Model 3: model 2 additionally adjusted for individual MRI marker. Values in parentheses indicate 95% CI.
[1] Logistic regression. [2] Linear regression.

Table 4. Association between ABI (per SD decrease) and specific cognitive domains

	Attention	Language	Verbal memory	Visual memory	Visuoconstruction	Visuomotor speed	Executive function
Model 1	–0.02 (–0.12 to 0.08)	–0.08 (–0.18 to 0.03)	–0.14 (–0.23 to –0.05)	–0.09 (–0.18 to 0.00)	–0.08 (–0.17 to 0.01)	–0.07 (–0.15 to 0.01)	–0.12 (–0.22 to –0.02)
Model 2	–0.01 (–0.11 to 0.09)	–0.06 (–0.17 to 0.05)	–0.12 (–0.21 to –0.03)	–0.07 (–0.16 to 0.02)	–0.06 (–0.15 to 0.04)	–0.05 (–0.13 to 0.04)	–0.11] (–0.21 to –0.001)
Model 3	0.00 (–0.10 to 0.09)	–0.05 (–0.16 to 0.05)	–0.11 (–0.21 to –0.02)	–0.06 (–0.15 to 0.02)	–0.05 (–0.14 to 0.04)	–0.03 (–0.11 to 0.05)	–0.09 (–0.19 to 0.01)

Model 1: adjusted for age, gender and education. Model 2: adjusted for age, gender, education, vascular risk factors (hypertension, diabetes, dyslipidemia, ischemic heart disease, history of stroke and hs-CRP) and GDS score. Model 3: adjusted for age, gender, education, vascular risk factors (hypertension, diabetes, dyslipidemia, ischemic heart disease, history of stroke and hs-CRP), GDS score, infarcts, cerebral microbleeds, WML volume and intracranial stenosis. Values in parentheses indicate 95% CI.

2.85). Even after excluding the 4 cases with dementia, the association between ABI and CIND-moderate remained significant. ABI was significantly associated with the global cognitive composite Z-score, after adjusting for age, gender and education (table 3). The global cognitive composite score declined with a decrease in ABI (multivariable-adjusted mean difference in Z-score per SD decrease in ABI: –0.07, 95% CI: –0.15 to 0.01). To test whether the association of ABI and cognition was mediated by any of the MRI markers, additional adjustment for these markers was made (table 3). These associations remained largely unaltered after including markers of cerebral small vessel disease and atrophy. Finally, after adjusting for intracranial stenosis, the association between ABI and cognition attenuated, but remained statistically significant.

Table 4 shows the association between ABI and specific cognitive domains. In the fully adjusted models, there were no statistically significant associations between ABI and specific cognitive domains except verbal memory. However, when applying a Bonferroni-corrected significance level of 0.007 (approx. 0.05/7 domains) for the domain-specific analyses, none of these associations remained significant.

Discussion

In this Chinese cohort we showed that ABI was independently related to intracranial stenosis, suggesting that both these markers may reflect large artery atheroscle-

rotic disease, whereas no association was found with specific markers of cerebral small vessel disease on MRI. Furthermore, a low ABI was associated with cognitive impairment, independent of any marker of cerebral small vessel disease or large artery atherosclerotic disease, as reflected by intracranial stenosis.

Previous studies in Caucasian populations have shown that ABI is related to cognitive impairment [17, 29]. The Edinburgh artery study showed that a low ABI was predictive of poor performance in nonverbal reasoning, verbal fluency and information processing speed [30]. Furthermore, a review based on six cross-sectional and six prospective studies confirmed that a low ABI can be considered as a marker for cognitive impairment and dementia [15]. In non-Caucasians, a single study in elderly Chinese reported an association between ABI and MMSE scores [18]. In accordance with these findings, our results based on a comprehensive neuropsychological assessment confirmed an association between ABI and cognitive impairment.

As a low ABI is considered to be a marker of generalized atherosclerosis, it is possible that the relationship between ABI and cognitive impairment may be determined by the presence of cerebrovascular disease. In the present study, we found a significant association between a low ABI and the presence of intracranial stenosis, which suggests that both may be reflective of large artery atherosclerotic disease. In contrast, no association was found between ABI and other MRI markers such as WML volume, cerebral microbleeds and infarcts, which are considered to be markers of cerebral small vessel disease. Taken together, our findings suggest that ABI – although reflective of systemic atherosclerotic disease and hence related to intracranial stenosis – does not accurately reflect the burden of cerebral small vessel disease. In contrast, a previous study showed that a low ABI was associated with the presence of silent brain infracts [19]. That study was, however, limited to diabetic patients with a high prevalence of silent brain infarcts (>48%), while only 24.9% of our subjects were diabetic.

In our study, the association between ABI and cognition remained significant after additionally adjusting for MRI markers of cerebrovascular pathology, which include not only markers of cerebral small vessel disease but also intracranial stenosis. These findings suggest that other factors besides these MRI markers need to be considered, which may underlie the association between ABI and cognitive impairment. A possible explanation could be that a decrease in cerebral perfusion may be the underlying pathophysiological mechanism. Furthermore, cognitive impairment has previously been reported in patients with asymptomatic carotid artery stenosis [31, 32]. In patients with unilateral, asymptomatic carotid stenosis, lower performance in verbal fluency was related to impaired cerebrovascular reactivity [31]. Another study showed that patients with asymptomatic extracranial carotid stenosis had lower performance on cognitive function. This association was independent of the presence of other MRI lesions, including infarcts and WML [32]. This is concordant with our findings, and suggests that chronic cerebral hypoperfusion may underlie the decrease in cognitive performance.

Several methodological issues need to be discussed. First, the cross-sectional design did not allow us to make temporal inferences on the association between ABI and cognition. Second, approximately half of the screen-positive subjects declined to take part in phase II of the study. As extensively described previously [20], subjects excluded from these analyses were older and were more likely to have hypertension, which may have led to an underestimation of the prevalence of a low ABI. Furthermore, those who were excluded from this analysis may have had poorer cognitive function and this may have led to an underestimation of the effect sizes. Nevertheless, we found an association between ABI and cognition in the present study. Third, we did not have a sufficient number of subjects with dementia to examine the association between ABI and dementia separately. Fourth, it has previously been suggested that the effect of ABI on cognition may be mediated through the presence of depression [17]. Therefore, we adjusted for GDS score in our analysis, which did not affect the association between ABI and cognition. Finally, for the domain-specific analyses, we were not able to find significant associations after applying Bonferroni correction, probably due to the low power of our study. Strengths of our study include utilization of a validated comprehensive neuropsychological test battery for the evaluation of cognitive function and a multimodal MRI to visualize cerebrovascular disease burden.

In conclusion, in this Chinese cohort we showed that ABI was independently related to intracranial stenosis, suggesting that both may be indicative of large artery atherosclerotic disease. In contrast, no association was found with specific markers of cerebral small vessel disease on MRI. Furthermore, a low ABI was associated with cognitive impairment, independent of any marker of cerebral small vessel disease or even the presence of intracranial

stenosis. Future longitudinal studies are required to confirm these cross-sectional associations between ABI and cognition.

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Disclosure Statement

The authors declare that they have no conflict of interest.

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