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Short Report

Temporal trends in lipoprotein(a) testing among United States veterans from 2014 to 2023

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ABSTRACT

Objective: Lipoprotein (a) [Lp(a)] is a causal, genetically-inherited risk amplifier for atherosclerotic cardiovascular disease (ASCVD). Practice guidelines increasingly recommend broad Lp(a) screening among various populations to optimize preventive care. Corresponding changes in testing rates and population-level detection of elevated Lp(a) in recent years has not been well described.

Methods: Using Veterans Affairs electronic health record data, we performed a retrospective cohort study evaluating temporal trends in Lp(a) testing and detection of elevated Lp(a) levels (defined as greater than 50 mg/dL) from January 1, 2014 to December 31, 2023 among United States Veterans without prior Lp(a) testing. Testing rates were stratified based on demographic and clinical factors to investigate possible drivers for and disparities in testing: age, sex, race and ethnicity, history of ASCVD, and neighborhood social vulnerability.

Results: Lp(a) testing increased nationally from 1 test per 10,000 eligible Veterans (558 tests) in 2014 to 9 tests per 10,000 (4,440 tests) in 2023, while the proportion of elevated Lp(a) levels remained stable. Factors associated with higher likelihood of Lp(a) testing over time were a history of ASCVD, Asian race, and residing in neighborhoods with less social vulnerability.

Conclusion: Despite a 9-fold increase in Lp(a) testing among US Veterans over the last decade, the overall testing rate remains extremely low. The steady proportion of Veterans with elevated Lp(a) over time supports the clinical utility of testing expansion. Efforts to increase testing, especially among Veterans living in neighborhoods with high social vulnerability, will be important to reduce emerging disparities as novel therapeutics to target Lp(a) become available.

1. Introduction

Lipoprotein (a) [Lp(a)] is a highly atherogenic lipoprotein that is causally associated with atherosclerotic cardiovascular disease (ASCVD) [1]. Robust epidemiological and genetic data have established elevated Lp(a) level as an independent risk amplifier for ASCVD [2–4]. Furthermore, elevated Lp(a) is heritable and has been associated with certain genetic variants [3], which has implications for screening and expansion of testing. It is also more likely to be elevated in certain racial and ethnic groups, most notably among South Asian and Black individuals, especially those with African ancestry [5,6].

Increasingly, professional practice guidelines and statements have called for broad Lp(a) testing, particularly in high risk individuals, including those with personal or family history of premature ASCVD, LDL cholesterol ≥190 mg/dL, familial hypercholesterolemia, or South Asian ancestry [7–11]. The National Lipid Association and the European Society of Cardiology recommend that all adults receive one-time Lp(a) testing [10–12]. Although there are currently no approved treatments

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for Lp(a) lowering for the purpose of ASCVD risk reduction, prior work has found that testing for Lp(a) increases the use of other lipid-lowering therapies [13–15]. Testing trends have not yet been evaluated among United States (US) Veterans, despite higher risk of ASCVD compared to the general population and low rates of lipid lowering therapy among Veterans [16]. Evaluating temporal trends in Lp(a) testing among a Veteran population may reveal opportunities for identifying high-risk populations and guide future targeted therapies to improve preventive care. Lp(a) testing can help identify individuals who need more intensive risk factor management, prompt shared decision-making regarding therapies, and justify cascade screening for family members of Veterans with a known history of CV events. Because the Veterans Health Administration is a closed healthcare system, it provides a unique opportunity to reliably measure changes in testing practices over time.

2. Methods

We performed a retrospective cohort study using data from the Veterans Affairs (VA) electronic health record (EHR) to evaluate annual rates of Lp(a) testing from January 1, 2014 to December 31, 2023 among US Veterans across the country. This study was approved by the Institutional Review Board of Stanford University. Veterans in each year with at least 1 primary care or cardiology clinic visit, an active prescription filled, and no prior Lp(a) testing were included. Importantly, Lp(a) testing is covered by the VA and equally accessible to all Veterans. While test units (mg/dL or nmol/L) varied by site, all measurements were converted to mg/dL using a well-accepted conversion factor for uniformity [17]. Yearly testing rates were further stratified by various demographic and clinical factors: age, sex, race and ethnicity, history of ASCVD, and neighborhood social vulnerability index (SVI) scores [18] as employed by the Centers for Disease Control. This score is based on census data from the 5-year American Community Survey. It measures social vulnerability via measures of socioeconomic status, household characteristics, race and ethnicity, and transportation mode and creates a percentile rank from 0 % to 100 %, wherein higher percentiles reflect more vulnerability [18]. Lp(a) levels were additionally classified as being greater than 50 mg/dL, 70 mg/dL, and 90 mg/dL; these thresholds have been shown to be clinically meaningful and have been used as thresholds for ongoing outcomes trials with Lp(a) lowering therapies [19–21].

3. Results

Over the course of 9 years, Lp(a) testing increased across US Veterans from 1 test per 10,000 eligible Veterans (558 tests) in 2014 to 9 tests per 10,000 (4440 tests) eligible Veterans in 2023 (Fig. 1). Testing increased over time across Veterans of all ages, sexes, races and ethnicities, neighborhood SVI scores, and among those with and without a history of ASCVD.

Veterans with ASCVD were more likely to undergo Lp(a) testing over time: testing rose from 2 to 14 tests per 10,000 eligible Veterans with ASCVD from 2014 to 2023 (Fig. 1A). Among those without ASCVD, Lp(a) testing rose from 1 to 7 tests per 10,000 eligible Veterans (Fig. 1A). From 2014 to 2023, the proportion of Lp(a) testing increased less among those living in neighborhoods with high social vulnerability (from 1 to 8 tests per 10,000 eligible Veterans with SVI 75–100 %) compared with

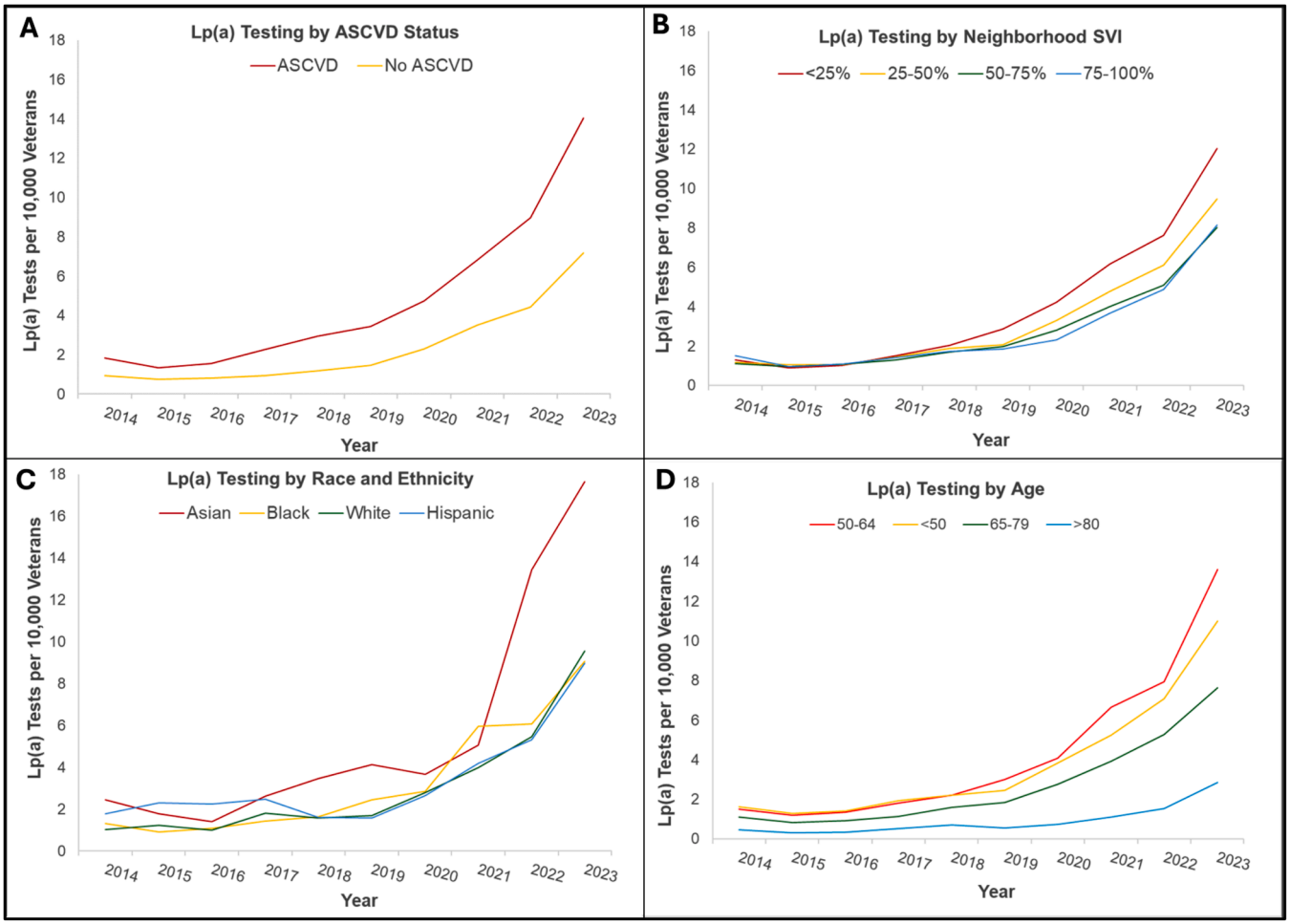

Fig. 1. Lipoprotein (a) [Lp(a)] testing by various demographic and clinical factors.

those in neighborhoods with low social vulnerability (from 1 to 12 tests per 10,000 eligible Veterans with SVI <25 %) (Fig. 1B). Over these years, there was a 9-fold increase in testing among those with SVI <25 % and a 5-fold increase in testing among those with SVI 75–100 %. Asian Veterans also had a more significant rise in the proportion of Lp(a) testing over time (2 to 18 tests per 10,000 eligible Veterans from 2014 to 2023) compared with White, Black, and Hispanic Veterans (from 1 to about 9 tests per 10,000 eligible veterans from 2014 to 2023 in each group) (Fig. 1C). Those Veterans aged 50–64 were more likely to receive Lp(a) testing over time compared with other age groups: testing rose from 2 to 14 tests per 10,000 eligible Veterans in this group (Fig. 1D). An exploratory multivariate regression analysis for these demographic variables and ASCVD history showed similar interactions across groups.

The proportion of Veterans tested who had elevated Lp(a) remained relatively stable over time, even across various clinical Lp(a) thresholds (Fig. 2). Among those tested, 20 % had Lp(a) levels >50 mg/dL in 2014 and 26 % had Lp(a) levels >50 mg/dL in 2023. This trend was also observed using higher Lp(a) thresholds. Lp(a) levels >70 mg/dL made up 14 % of tests in 2014 and 18 % of tests in 2023. Similarly, Lp(a) levels >90 mg/dL made up 9 % of tests in 2014 and 11 % of tests in 2023.

4. Discussion

Our analysis of Lp(a) testing among US Veterans showed a 9-fold increase in testing from 2014 to 2023. The stable frequency of elevated Lp(a) levels over this time demonstrates the clinical significance and widespread underuse of contemporary Lp(a) testing: broader testing increases detection of individuals with elevated Lp(a). This is the first study to report Lp(a) testing rates in a large US population of Veterans over time, as most prior studies evaluating temporal trends in Lp(a) testing in the US are limited to just one healthcare system [13,22]. Stratification by various clinical and demographic factors also provides helpful context for understanding potential inequities in testing.

Although Lp(a) testing increased steadily over time, the frequency of testing remained low. Increasingly, practice guidelines recommend screening among those with a history of ASCVD [9], with more recent guidelines recommending one-time testing for all adults [10–12]. Our work suggests that significant efforts will be necessary to identify Veterans with elevated Lp(a) due to remarkably low testing rates. An exploratory analysis showed that the number of sites with Lp(a) testing has also increased over time: in 1999, only 16 sites had at least one Lp(a) test performed compared to 97 sites in 2023. While testing availability is unconfirmed, this suggests that lack of institutional access to Lp(a) testing could be a barrier. The higher likelihood of testing among those with ASCVD that persisted over time is consistent with patients with ASCVD being more likely to have elevated Lp(a) [2–4]. However, testing for elevated Lp(a) may have greater impact on risk prevention decisions – such as target LDL – in a primary prevention population and may guide cascade screening among family members. We posit that the higher testing rate among younger Veterans may be because younger individuals, including those with premature ASCVD, could derive greater benefit from prevention therapies if initiated earlier in life. The lower likelihood of testing and slower rate of increase in testing among Veterans residing in neighborhoods with high social vulnerability is likely reflective of social barriers to care, as has been previously shown [23]. Racial and ethnic differences in Lp(a) testing, namely higher testing rates among Asian Veterans, may be related to well-established data suggesting South Asian individuals are more likely to have elevated Lp(a) [5,6]. Conversely, similar trends were not seen among Black Veterans, who are also more likely to have elevated Lp(a) [5,6]. Disaggregating racial and ethnic data among our cohort would be an important next step for further characterizing this trend.

Steady proportions of elevated Lp(a) tests across clinically meaningful thresholds demonstrates that further expansion of testing would likely help identify more patients at high risk for ASCVD. It is likely that the slight increase in elevated prevalence of elevated Lp(a) detected over time may reflect the higher likelihood of testing among higher risk groups over time. As has been shown previously, individuals who are found to have elevated Lp(a) are more likely to receive lipid-lowering therapies [13–15], further highlighting the benefit of wider testing. Efforts to broaden Lp(a) testing, especially among those residing in neighborhoods with high social vulnerability, will be integral in expanding preventive care and addressing disparities in the future. With the development of therapeutics to target Lp(a), equitable identification of elevated Lp(a) is paramount.

Limitations of this study include its retrospective nature, lack of disaggregated racial and ethnic data, and data collection limited to the VA EHR, which includes varied Lp(a) test units (mg/dL or nmol/L) requiring conversion for uniformity. Given the higher prevalence of elevated Lp(a) among South Asian populations, the lack of racial and ethnic disaggregation and low rates of South Asian Veterans in the US is another limiting factor. Veterans included in this study may have had Lp

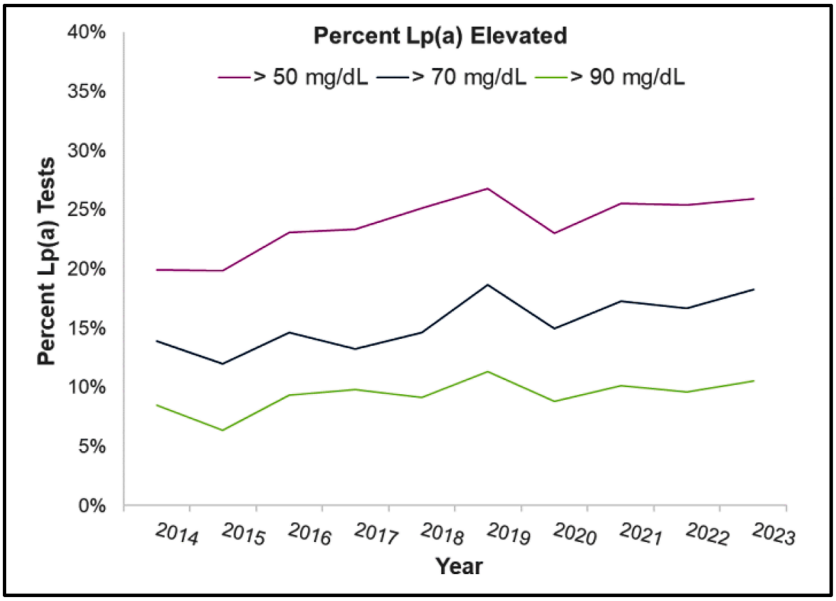

Fig. 2. Percent lipoprotein (a) [Lp(a)] tests at various clinically meaningful thresholds.

(a) testing performed at other institutions which would not be reflected in our results. Lastly, while this study included a broad population of US Veterans, participants did have one active prescription filled, which may limit generalizability to Veterans with at least one medical condition. Nevertheless, these findings remain valuable for assessing Lp(a) testing trends within the VA. Future efforts to correlate Lp(a) testing with cardiovascular outcomes will also be important to establish the clinical impact of Lp(a) testing.

5. Conclusion

Despite a 9-fold increase in Lp(a) testing among US Veterans nationally over the last 9 years, Lp(a) testing remains substantially low. The proportion of Veterans tested rose most among those with ASCVD, but increased across all demographic and clinical factors including neighborhood social vulnerability, race, ethnicity, and age. Veterans residing in neighborhoods with higher social vulnerability were less likely to receive testing and had a slower rise in Lp(a) testing over time. Efforts to expand testing, especially among these Veterans in neighborhoods with high social vulnerability, are critical to ensure equity with the advent of novel therapeutics to target Lp(a).

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Statement of authorship

Sofia E. Gomez, Jonathan Ward, Anthony Lozama, Alexander Sandhu, and Fatima Rodriguez participated in study design, writing, data analysis, data interpretation, and manuscript review. Adam Furst, Tania Chen, Natasha Din participated in study design, data analysis, data interpretation, and manuscript review. David Maron, Paul Heidenreich, Neil Kalwani, Shriram Nallamshetty participated in data interpretation and manuscript review.

CRediT authorship contribution statement

Sofia E. Gomez: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Adam Furst:** Writing – review & editing, Software, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Tania Chen:** Writing – review & editing, Validation, Resources, Methodology, Investigation, Data curation, Conceptualization. **Natasha Din:** Writing – review & editing, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **David J. Maron:** Writing – review & editing, Visualization, Validation, Supervision, Formal analysis. **Paul Heidenreich:** Writing – review & editing, Validation, Supervision, Formal analysis. **Neil Kalwani:** Writing – review & editing, Visualization, Validation, Formal analysis, Conceptualization. **Shriram Nallamshetty:** Writing – review & editing, Visualization, Validation, Methodology, Formal analysis, Conceptualization. **Jonathan H Ward:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Anthony Lozama:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Alexander Sandhu:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Fatima Rodriguez:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Alexander Sandhu, Fatima Rodriguez, Novartis employees Anthony Lozama and Jonathan Ward reports financial support was provided by Novartis Pharmaceuticals Corporation. This work was supported by Novartis Pharmaceutical Corporation. Mr. Ward and Doctor Lozama are employees of Novartis Pharmaceutical Corporation. Dr. Sandhu is supported by NHLBI and AHA. He also receives research funding from Reprieve Cardiovascular and has done consulting for Lexicon Pharmaceuticals. Dr. Rodriguez reports equity from Carta Healthcare and HealthPals, and consulting fees from HealthPals, Novartis, NovoNordisk, Esperion Therapeutics, Movano Health, Kento Health, Inclusive Health, Edwards, Arrowhead Pharmaceuticals, and HeartFlow outside the submitted work. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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