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Diagonal Earlobe Crease: A Warning Sign of Stroke

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Recommended Citation

Elyea, Matthew and Curran, Justin, "Diagonal Earlobe Crease: A Warning Sign of Stroke" (2019). *School of Physician Assistant Studies*. 660.

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Diagonal Earlobe Crease: A Warning Sign of Stroke

Abstract

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Background: The diagonal earlobe crease (DELC), commonly referred to as “Frank’s sign”, was first described in 1973 by an American physician as a crease in the earlobe that originates at the tragus and runs diagonally towards the outer, lower edge. Over the past half-century, research on this dermatologic finding has found a significant correlation between the presence of a DELC and coronary artery disease (CAD). Additionally, DELC has also been associated with other risk factors associated with both CAD and stroke, which include hypertension (HTN), diabetes mellitus (DM), and age. Despite this, skepticism has led to this physical exam finding being overlooked as a predictive marker. Therefore, the purpose of this systematic review was to analyze the association between the DELC and stroke risk.

Methods: An exhaustive search of available medical literature was conducted in MEDLINE-PubMed, CINAHL, and Google Scholar, using the search terms diagonal earlobe, Frank’s sign, stroke, cerebrovascular, and cerebral. References from relevant articles were also searched. Articles were included only after screening for relevance and if eligibility criteria were met. An assessment of quality was performed using the GRADE system.

Results: The initial literature search yielded 40 articles for review. After eliminating duplicates and screening for relevant articles, a total of 2 qualifying case-control studies remained. The quality of those studies was low, however the results of both studies were consistent. These studies support a positive correlation between the presence of DELC and stroke risk.

Conclusion: This systematic review determined there was a correlation between the presence of a DELC and an increased stroke risk. Based on the findings, visual examination of patients’ earlobes should be incorporated into routine physical evaluations and clinical assessments. Doing so may provide a clinician with an additional tool to recognize and provide earlier interventions, decreasing a patient’s risk of future cerebrovascular events.

Degree Type

Capstone Project

Degree Name

Master of Science in Physician Assistant Studies

Keywords

Diagonal earlobe crease, cardiovascular risk, cerebrovascular risk, stroke, Frank's sign

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Diagonal Earlobe Crease: A Warning Sign of Stroke

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Justin Curran**

**Pacific
University
Oregon**



*A Clinical Graduate Project Submitted to the Faculty of the
School of Physician Assistant Studies*

Pacific University

Hillsboro, OR

For the Masters of Science Degree, August 10, 2018

Faculty Advisors: Patrick Boyle, MD and Heather Porst, PA-C

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Biography

Matt Elyea is a veteran of the United States Air Force where he worked in the field of Aerospace Physiology. Matt received his Bachelors of Science Degree in Health Studies from Pacific University in Forest Grove, Oregon and his Masters of Science Degree from Pacific University's School of Physician Assistant Studies in Hillsboro, Oregon.

Justin Curran is a native of Oregon where he worked in the field of Medical Assisting and Radiology. Justin received his Bachelors of Science Degree in Health Studies from Pacific University in Forest Grove, Oregon and his Masters of Science Degree from Pacific University's School of Physician Assistant Studies in Hillsboro, Oregon.

Abstract

Background: The diagonal earlobe crease (DELC), commonly referred to as “Frank’s sign”, was first described in 1973 by an American physician as a crease in the earlobe that originates at the tragus and runs diagonally towards the outer, lower edge. Over the past half-century, research on this dermatologic finding has found a significant correlation between the presence of a DELC and coronary artery disease (CAD). Additionally, DELC has also been associated with other risk factors associated with both CAD and stroke, which include hypertension (HTN), diabetes mellitus (DM), and age. Despite this, skepticism has led to this physical exam finding being overlooked as a predictive marker. Therefore, the purpose of this systematic review was to analyze the association between the DELC and stroke risk.

Methods: An exhaustive search of available medical literature was conducted in MEDLINE-PubMed, CINAHL, and Google Scholar, using the search terms *diagonal earlobe*, *Frank’s sign*, *stroke*, *cerebrovascular*, and *cerebral*. References from relevant articles were also searched. Articles were included only after screening for relevance and if eligibility criteria were met. An assessment of quality was performed using the GRADE system.

Results: The initial literature search yielded 40 articles for review. After eliminating duplicates and screening for relevant articles, a total of 2 qualifying case-control studies remained. The quality of those studies was low, however the results of both studies were consistent. These studies support a positive correlation between the presence of DELC and stroke risk.

Conclusion: This systematic review determined there was a correlation between the presence of a DELC and an increased stroke risk. Based on the findings, visual examination of patients’ earlobes should be incorporated into routine physical evaluations and clinical assessments. Doing so may provide a clinician with an additional tool to recognize and provide earlier interventions, decreasing a patient’s risk of future cerebrovascular events.

Keywords: *Diagonal earlobe crease, cardiovascular risk, cerebrovascular risk, stroke, Frank’s sign*

Acknowledgements

To *our family and friends*: Thank you for the continuous support throughout our journey together through PA school. Our ability to succeed would have been far more challenging had we not had you there by our sides along the way.

To *our classmates*: Thank you for the support these past two years. No one understands what we have gone through more than ourselves. We have all grown together as a family and will continue on together through our journeys of being PAs.

To *our faculty*: We cannot express our profound gratitude for providing us with your unfailing support and continuous encouragement throughout the past two years. This accomplishment would not have been possible without you. Thank you.

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List of Abbreviations

CAD	Coronary Artery Disease
CT	Computed tomography
CVA	Cerebrovascular Accident
DELC	Diagonal Earlobe Crease
DM	Diabetes Mellitus
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HTN	Hypertension
MI	Myocardial infarction
RR	Relative Risk

Diagonal Earlobe Crease: A Warning Sign of Stroke

BACKGROUND

The diagonal earlobe crease (DELC) is commonly defined as a dermatologic crease of varying depths beginning at the tragus, and extending obliquely toward the inferolateral border of the earlobe (see Figure 1).¹⁻⁶ The DELC has long been associated with risk of coronary artery disease (CAD). One of the earliest accounts of the DELC was advocated by Dr. Robert B. Dickerson at Brooke Army Hospital in 1958; however, the first reported study² on the association between DELC and CAD in 1973 by Dr. Sanders T. Frank. Following Dr. Frank's publication, DELC is now often referred to as "Frank's Sign".^{1,3,4}

Over the course of the past half-century, determining the pathophysiologic correlation between the DELC and CAD has been challenging. There are a number of theories with researchers finding the most likely being associated to anatomical structure. Both the heart and the earlobe share terminal-artery blood supplies. A terminal artery only supplies blood to a portion of tissue, and additionally has an inability to provide collateral circulation.^{2,4} In addition to circulation, both the ear and the heart are composed of elastin fibers. The elastin degeneration in the ear may mirror changes that occur within the

elastin found in cardiac vasculature, leading to sclerosis of the vessels.^{1,2,5-7}

Classic cardiovascular and cerebrovascular risk factors are similar to one another. These risk factors include age, gender,^{1,8} hypertension (HTN), diabetes mellitus (DM),¹ common carotid artery intima thickness,^{4,6} and more. While previous research was focused on determining the correlation between DELC and CAD,^{2,6} the aim of this study was to examine the relationship between DELC and cerebrovascular accidents (CVA).

METHODS

An exhaustive literature search was performed using the following search engines: MEDLINE PubMed, PubMed Central, CINAHL, PMC, and Google Scholar, and the following search terms: diagonal earlobe, Frank's Sign, stroke, cerebrovascular, and cerebral. The references from relevant articles were also searched. Studies were included if they were published in English within the past 30 years and studied populations consisting of adults who had experienced an acute stroke and had unilateral or bilateral creases of varying depths. Other inclusion criteria required additional cardiac risk factors, which included age, gender, HTN, DM, and hypercholesterolemia. The quality of relevant articles was evaluated using the Grading of

Recommendations Assessment, Development and Evaluation (GRADE) Working Group guidelines.⁹

RESULTS

The initial literature search yielded 40 articles for review. After eliminating duplicates and screening for relevant articles using the eligibility criteria, a total of 2 qualifying case-control studies remained (see Figure 2). The quality of those included was low due to their inherent nature of being observational studies (see Table 1).

|| Levine and Daly ||

This prospective observational study⁸ was published in 1993 and aimed to explore the potential relationship between diagonal earlobe creases and patients who presented with ischemic strokes. The authors gathered data over the course of a year from the medical records of Caucasian patients who had suffered an ischemic stroke. Patient stroke data was included only after the authors examined the data, and then subsequently entered it into the University of Wisconsin Hospitals Stroke Data Bank. Data consisting of the total number of patients screened were not mentioned; however, after applying exclusion criteria (non-Caucasian, disagreement between physicians on DELC presence, ischemic stroke absence on computed tomography [CT], patients with a transient ischemic attack [TIA], reversible

ischemic neurological deficits, hemorrhagic strokes, and evident cerebral embolization), 116 ischemic stroke patients remained eligible for the study. To maintain low statistical variability, the authors removed age and gender from the study by including neurological patient controls from a population of patients on the Neurology Ward or Consultation Services. The controls were chosen on a 2:1 non-stroke control to ischemic stroke patient basis, and matched precisely for age and gender, resulting in a control count of 232 patients.⁸

In order to determine if patients qualified for this study, DELC were scored as present or absent by both physicians (authors), who had to be in agreement; however, data on the degree, extent, and bilateral or unilateral presence were not included. Additionally, the diagnosis of ischemic stroke was based on clinical impression in accordance with the results of a CT. Diagnostic imaging results were either normal or showed an ischemic lesion appropriate for the diagnosis, further separated into lacunar or large-vessel types, and evidently a result of thrombosis. Furthermore, the medical charts of all patients were reviewed for evidence of additional risk factors for CVA, including CAD, HTN, DM, hypercholesterolemia, and history of prior ischemic stroke, with additional risk factors lacking enough available data to include in the study. Of those risk factors mentioned, each were clearly defined

by specific criteria that must have been met in order to be included as well.⁸

Analysis of the data was performed using datasets generated for the 116 stroke victims and the 232 controls (see Table 2). Two-by-two contingency tables were studied using either Chi-square or Fisher exact tests. Further definitions of the Chi-square values were determined by computing relative risk (RR) for each characteristic. The authors also computed cumulative incidences of CAD, HTN, DM, and hypercholesterolemia for DELC-present stroke patients. Analysis using the Mantel-Haenszel test was also used to assign Z-scores and *p*-values for strokes with DELC versus non-strokes with DELC, and comparisons of age between subgroups was also performed using the Wilcoxon two-sample rank test.⁸

The authors found that there was a steady, increased likelihood of DELC with each decade of age within the study's 348 patient population; however, age was not a factor that distinguished those with a DELC from those without. Overall, within the total population the authors found more patients did not have a DELC compared to those who did, 61% vs. 39% respectively. It appeared that among the entire population, the presence of DELC was significantly related to male gender, CAD, HTN, DM, and ischemic strokes (RR 1.19, 2.98, 1.93, and 2.38, respectively).⁸

When analyzing the data collected from the subgroup of 116 ischemic stroke patients, 59% had a DELC, while 41% did not. They determined DELC was significantly related to CAD and DM (RR 1.48 and 3.10, respectively). Interestingly, patients who had suffered a lacunar stroke were more likely to not have a DELC (RR 3.12) and demonstrated a frequency that was triple that of those who suffered a lacunar stroke who did have a DELC. While lack of a DELC was related to lacunar strokes, analysis revealed that 47% of patients were also free of CAD, which was also significantly related to non-lacunar strokes (RR 1.42). Regarding the subgroup of 232 non-stroke patients, the authors determined that DELC was present in 29% of patients, whereas 71% had an absent DELC (see Figure 3). Of those who had a DELC, there was a significant relationship to HTN, DM, and CAD (RR 1.95, 3.00, 3.27, respectively). Calculations of cumulative incidences of CAD ($Z = 4.7$, $p = 0.001$), HTN ($Z = 4.3$, $p = 0.001$), DM ($Z = 3.3$, $p = 0.005$), and hypercholesterolemia ($Z = 2.17$, $p = 0.015$) were also determined and used to characterize DELC presence among stroke and non-stroke patients.⁸

|| Nazzal et al ||

This prospective observational study¹ was published in 2017 and explored the association between Frank's Sign and the development of ischemic stroke. The authors collected data from male and female

patients over the age of 18 years, who were consecutively admitted with an acute ischemic stroke. To have been included in the study, patients had to also sign consent. To determine if a patient qualified for the study, the diagnosis of an acute ischemic stroke had to be confirmed in the first 24 hours by a senior neurologist. Authors also obtained the medical histories and performed physical exams for all patients included, and the presence of Frank's sign was determined in both ears. Data consisting of the time frame in which patients were selected for this study was not mentioned; however, after applying exclusion criteria (less than 18 years old, unconfirmed diagnosis of an ischemic stroke, and lack of consent), 241 consecutive patients were eligible and thus recruited.¹

Upon recruitment, authors segregated patients based on their clinical and CT findings. Two subgroups were created, one consisting of 153 patients who suffered a TIA, and the other consisting of 88 with a CVA (see Table 3). With the addition of the patients' medical histories, clinical data also included age, gender, type 2 DM, and HTN. Analysis of the data was performed using categorical variables and determining frequencies by using the Kolmogorov-Smirnov test if quantitative data was normally distributed. In the event data was not normally distributed, data was presented as median and interquartile ranges. To compare categorical data, authors used the χ^2 test, whereas

quantitative data was compared using the *t*-test and Mann-Whitney *U*-test for data with normal distributions and abnormal distributions respectively.¹

The authors found that among the patients who suffered a TIA, 112 patients (73.2%), and of those with a CVA, 78 patients (88.6%)(see Table 3), all were positive for a Frank's sign ($p < 0.1$). Upon review of the patients' medical records, the authors also looked at the correlations between other risk factors and the presence of DELC. Of those examined, 66 patients had a prior myocardial infarction (MI), and of them 59 (89.3%) also had Frank's sign, whereas out of the remaining 175 patients without a prior MI, 131 (74.9%) had a Frank's sign present (see Table 4).¹

In addition to prior ischemic heart diseases and/or MI, the authors also looked at HTN, type 2 DM, gender, and age. They found that 163 stroke patients also suffered from HTN, and of them 142 (87%) had Frank's sign, while of the remaining 78 patients without HTN, 48 (61.5%) were positive as well. There were a total of 115 stroke patients who were also type 2 diabetics, whereas 126 were not, and of them 103 (87%) and 87 (69%) had Frank's sign, respectively (see Table 4). Surprisingly, upon comparing gender and age, the authors determined no significant differences among gender, but a significant difference between age. Patients with a positive Frank's sign

were older (70 ± 12.51 years), compared to younger patients (55.2 ± 14.67 years, $p < 0.01$), who were more likely to have a negative Frank's sign.¹

According to the data acquired through the authors' research, there was an increased frequency of a positive Frank's sign in patients, if the patient had classic risk factors for cardiovascular events, including prior MIs, HTN, type 2 DM, and age. It was also discovered that Frank's sign was more prevalent in patients who had suffered a CVA than those with a TIA, when comparing the number of patients presenting with a positive Frank's sign and had suffered either a CVA or TIA. Gender was the only risk factor that evidently demonstrated no significant correlation to the presence of Frank's sign.¹

DISCUSSION

Traditionally, medicine has used the physical examination to effectively evaluate and assess patients. However, modern day medicine has become increasingly reliant on diagnostic techniques to identify underlying cardiovascular and/or cerebrovascular risk factors. Research on DELC and the connection to CAD has been studied extensively¹⁻⁸; however, the association between DELC and stroke is in its infancy. To date, there are only a few select studies that have examined this possible relationship. Among the studies included in this review, each agreed that there was an association between the

presence of DELC and cerebrovascular risk factors linked to the development of stroke.

Levine and Daly⁸ found a significant relationship between DELC, age, and classic cardiovascular risk factors, such as CAD, HTN, DM, and hypercholesterolemia. Specifically, the findings from this study results in a sensitivity of 50.3% and specificity of 77.5%; additionally, a LR+ of 2.24 and LR- of 0.654 can be calculated. These numbers imply that the presence of DELC can increase the suspicion for stroke risk but the lack of DELC shouldn't drastically decrease suspicion of that risk. Since the frequency of DELC and advancing age was already established by previous research,² age was removed as an important statistical variable. By removing age as a confounding variable, researchers found that DELC was significantly higher in patients who had experienced an ischemic stroke. Furthermore, when controlling for CAD, the study found DELC to be significantly related to non-lacunar ischemic strokes specifically.⁸

Nazzal et al¹ expanded on the Levine and Daly⁸ study; however, they expanded their patient population to include only patients who had suffered an ischemic stroke, with fewer exclusion criteria. A significant difference in this study¹ compared to Levine and Daly⁸ was the lack of a non-stroke comparison group (inhibiting the ability to calculate sensitivity, specificity, and likelihood ratios), as this study¹

focused specifically on an acute stroke cohort that also included TIA. In doing so, researchers were able to analyze and establish a stronger association between DELC and type of stroke. Although DELC was present in patients with a TIA and CVA, the finding was more prevalent in those with a CVA. In addition to confirming the associations found by Levine and Daly,⁸ Nazzal et al¹ also found an increased rate of DELC in patients admitted for an acute stroke and had suffered a past MI.

In reviewing and appraising the evidence presented in each study,^{1,8} the Levine and Daly⁸ study was found to be limited by the cohort the data was collected from. This data limitation was attributed to the small sample size due to extensive exclusion criteria, which included type of stroke and ethnicity. Levine and Daly⁸ limited their study to include only ischemic strokes and data collected from a Caucasian-only cohort. Due to the specifics implemented, a larger multi-ethnic study is recommended as it may provide researchers with additional information. In addition, there was a lack of follow up with study participants.⁸ Had follow up occurred, it would have been interesting to see how many patients within the non-stroke control group who presented with a DELC, later experienced a stroke.

Since the DELC has been found to have a strong relationship with CAD,¹⁻⁸ it makes sense that it could also have a similar relationship with stroke risk, as cardiovascular risk factors and

cerebrovascular risk factors are quite similar. This commonality reinforces the importance of DELC and what it can tell a healthcare provider during a physical examination. The DELC does not mean the patient has CAD or suffered a stroke. The DELC is a non-modifiable risk factor that simply provides a clinician with a visible physical exam finding that should initiate a response to begin evaluation for modifiable risk factors. Adding the detection of the DELC to a healthcare providers routine physical examination and assessment should be considered.

CONCLUSION

The DELC is a physical exam finding that has been found to be an independent early warning sign of underlying cerebrovascular risk factors associated with stroke. The development of this dermatologic finding has also been linked to the natural progression of the aging process, making it difficult for previous studies to attribute the DELC specifically to underlying pathology. Since both advancing age and modifiable risk factors associated with the development of stroke share this external finding, it is important that providers not overlook it. Although age, a non-modifiable risk factor for the development of stroke, has been thoroughly studied, research on other non-modifiable risk factors such as ethnicity and race have not been sufficiently established. Ethnicity is an important confounding variable in medicine

that must be accounted for, therefore additional studies analyzing the relationship and prevalence of DELC across multiple ethnicities must be performed.

Identification of the modifiable risk factors associated with stroke is critical. Without the use of expensive diagnostic tools, the DELC may be the only outward sign available to a provider in any setting as a predictor of stroke in an otherwise healthy appearing patient. Based on the findings in this review, adding the presence of a DELC to a provider's routine physical examination is recommended as an additional mode of stroke prevention.

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Table 1. Quality Assessment of Reviewed Articles

Study	Design	Downgrade Criteria					Upgrade Criteria	Quality
		Limitations	Indirectness	Inconsistency	Imprecision	Publication bias		
Levine and Daly ⁸	Case control	Serious ^a	Not serious	Not Serious	Not Serious	Unlikely	None	Very Low
Nazzal et al ²	Case control	Serious ^b	Not serious	Not Serious	Not Serious	Unlikely	None	Very Low
^a Lack of follow up ^b Lacked a non-stroke comparison group								

Table 2. Cerebrovascular risk factors and the presence of a Diagonal Earlobe Crease (DEL C)

Risk Factor	DEL C		No DEL C	
	Number	Percentage	Number	Percentage
Gender				
Male	101	74.8	134	62.9
Female	34	25.2	79	37.1
Total	135	38.8	213	61.2
CAD	66	48.9	40	18.8
Hypertension	73	54.1	64	30.0
Diabetes Mellitus	31	23.0	13	6.1
Hypercholesterolemia	11	8.1	10	4.7
Ischemic Stroke				
Nonlacunar Stroke	65	95.6	42	87.5
Lacunar Stroke	3	4.4	6	12.5
Total	68	50.4	48	22.5

Table 3. Transient Ischemic Attacks (TIA) and Cerebrovascular Accidents (CVA) among patients with and without the presence of a Diagonal Earlobe Crease (DELIC)

Variable	TIA		CVA		Total	
	Number	Percentage	Number	Percentage	Number	Percentage
DELIC	112	58.9	78	41.1	190	78.8
No DELIC	41	80.4	10	19.6	51	21.2
Total	153	63.5	88	36.5	241	100

Table 4. Presence of cardiovascular risk factors among patients with and without the presence of a Diagonal Earlobe Crease (DELIC) experiencing an ischemic cerebrovascular event

Variable	Ischemic Heart Disease		Hypertension		Diabetes Mellitus	
	Number	Percentage	Number	Percentage	Number	Percentage
DELIC	59	89.4	142	87.1	103	89.6
No DELIC	7	10.6	21	12.9	12	10.4
Total	66	100	163	100	115	100



Figure 1. Diagonal earlobe crease

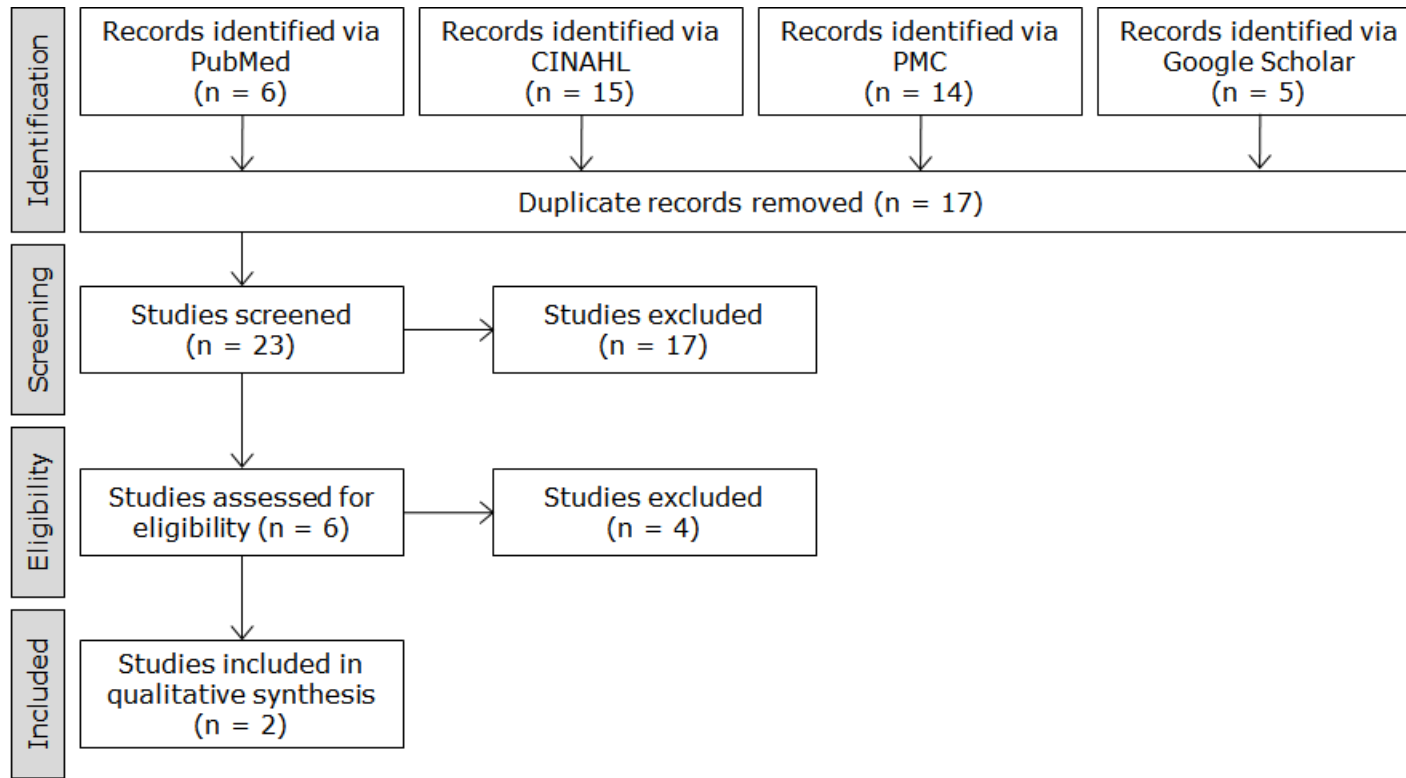


Figure 2. Study search and selection

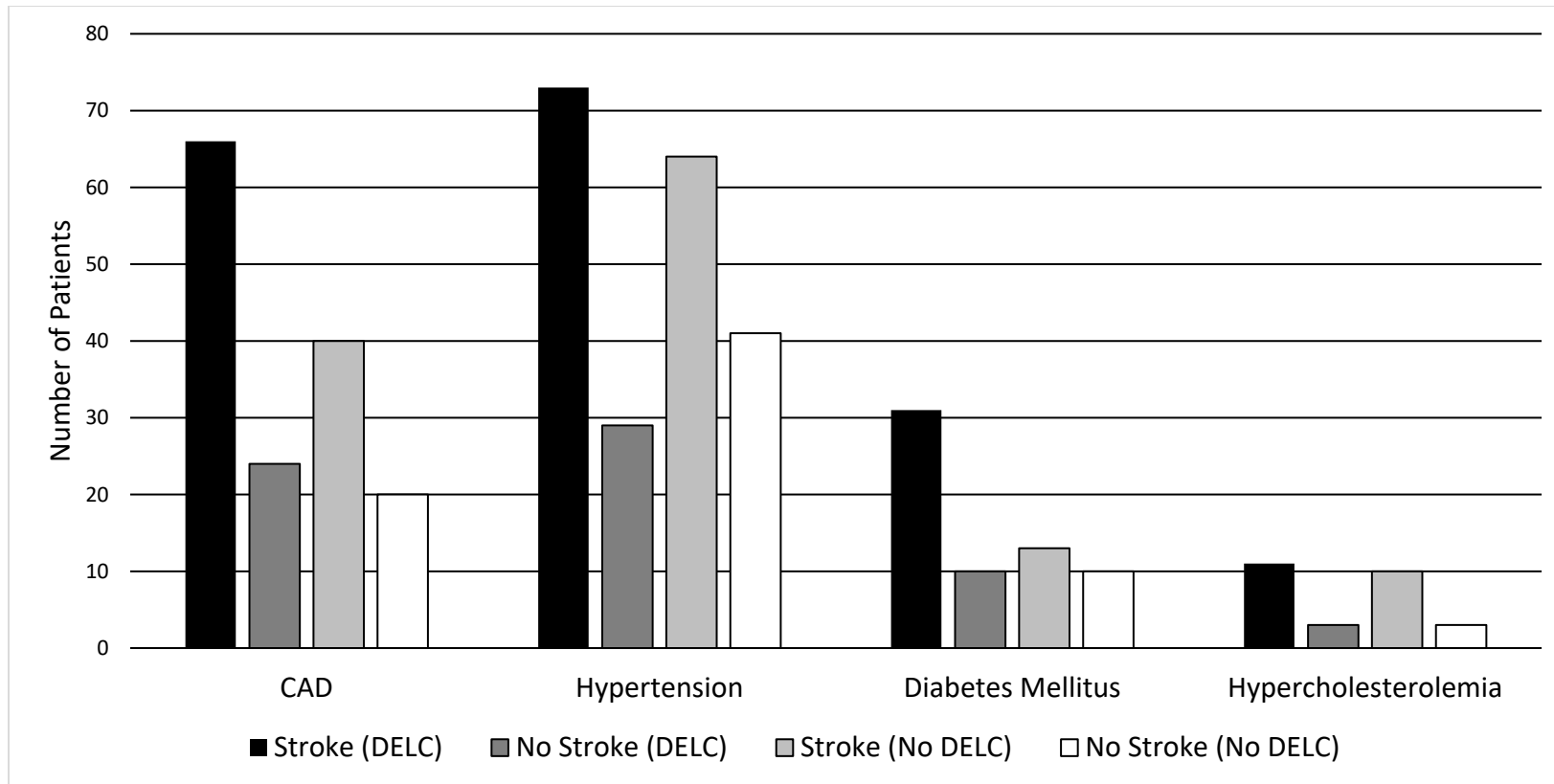


Figure 3. Comparison of the presence of diagonal earlobe creases and cerebrovascular risk factors.