Original Article



"Mild", "Moderate", or "Severe" Carpal Tunnel Syndrome? Depends on Who You Ask: Analysis of Existing Classification Systems in 665 Hands

Nathan J. Savage¹, John S. McKell²

¹Department of Physical Therapy, Winston-Salem State University, USA; ²Department of Physical Therapy, McKell Therapy Group, LLC, USA

Abstract

Objectives: Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy in the body and impacts approximately 5% of the U.S. population costing nearly \$5 billion/year. Electrodiagnostic (EDX) testing is considered the gold standard for CTS diagnosis. Classification systems exist that categorize CTS severity based on EDX findings. This investigation evaluated EDX findings across consecutive CTS severity categories within existing classification systems and *consolidated* classifications. **Methods**: This retrospective study analyzed 665 hands from 468 patients undergoing EDX testing for suspected CTS. Complete classification systems and *consolidated* classifications were evaluated for discrimination capability across consecutive CTS severity categories based on EDX findings. Additional analysis evaluated the relationship of sex and age factors and CTS severity. **Results**: *Consolidated* classification system used. Demographic factors significantly influenced EDX findings and categorization of CTS severity. **Conclusions**: This study underscores the value of *consolidated* classifications for enhancing discrimination between consecutive CTS severity categories based on EDX findings. This study underscores the value of *consolidated* classifications for enhancing discrimination between consecutive CTS severity categories based on EDX findings for the purpose of categorizing CTS severity. Future research should refine existing classification systems and explore additional factors influencing CTS severity used to inform medical management.

Keywords: Carpal Tunnel Syndrome, Classification, Electrodiagnostic, Electromyography, Nerve Conduction

Introduction

Median neuropathy at the wrist, commonly referred to as carpal tunnel syndrome (CTS), is the most common entrapment neuropathy in the body with an incidence of approximately 5% in the United States¹ and associated costs estimated around \$5 billion/year². Electrodiagnostic (EDX) testing, comprised of peripheral sensory and motor nerve

Edited by: G. Lyritis Accepted 1 February 2024 conduction testing and needle electromyography (EMG), has long been considered the gold standard test for diagnosing neuropathic changes in the peripheral nervous system³⁻⁹. In patients presenting with symptoms suggesting CTS, EDX testing is routinely performed to confirm the presence of median neuropathy at the wrist while ruling out competing diagnoses and helping inform selection of interventions based on severity of the nerve lesion¹⁰⁻¹⁴.

Systems classifying the relative severity of CTS based on EDX findings have been proposed by Padua et al¹², Bland¹⁴, and Greathouse et al (GEHS)¹⁵. The specific EDX criteria used by each of these classification systems to categorize CTS severity are summarized in Figure 1. All of these classification systems assume a linear relationship between the progression of median neuropathy and severity of EDX findings, namely early sensory-only conduction abnormalities followed by motor conduction abnormalities and eventually progressing to sensory and motor nerve



The authors have no conflict of interest.

Corresponding author: Nathan J. Savage, PhD, DPT, Department of Physical Therapy, Winston-Salem State University, 601 S. Martin Luther King Jr. Drive, 336 F.L. Atkins Building, Winston-Salem, NC 27110, USA E-mail: savagenj@wssu.edu





axonopathy^{10,12,14,15}. The criteria used by each of these classification systems to categorize CTS severity includes median distal sensory latency/conduction velocity, including more sensitive comparison studies (eg, superficial radial vs median at the thumb or trans-carpal conduction)^{16,17}, and median distal motor latency. These classification systems largely ignore median sensory and motor amplitude, with the lone exception being Bland's consideration of distal motor amplitude in their "Extremely Severe" category. Notably, the GEHS classification system is unique in consideration of EMG findings in the abductor pollicis brevis (APB) muscle^{11,15,18}.

Previous studies have investigated the relationship between clinical symptoms and severity of CTS;^{9,10,12-14} however, no studies were found investigating the ability of existing classification systems to discriminate between consecutive categories of CTS severity based on EDX significantly different across consecutive CTS severity categories within existing classification systems. Additionally, a direct comparison of existing classification systems has not been conducted, including analysis of the proportion of hands that can be correctly categorized based on proposed criteria. Sasaki et al¹⁹ recently compared the Padua and Bland classification systems in 1120 hands and found that "boundary values" likely prevented accurate categorization of CTS severity, which occurred in 15% of hands in their study under the Padua classification. When EDX findings do not meet the specified criteria of a particular CTS severity category within a classification system, the clinician is left to determine severity based on the data before them, which can introduce subjectivity and variability across clinicians. Similarly, Sucher¹⁰ argued that classification systems with

findings. In other words, it is unknown if EDX findings are

multiple categories of CTS severity are likely problematic because of the inherent variability of sensory and motor conduction findings (ie, non-linear neuropathic changes) and that more complex classification systems are likely to be met with resistance by clinicians resulting in limited use and ultimately limited value as a diagnostic aid. Alternatively, Sucher argued that using 3 primary categories of severity (ie, "Mild", "Moderate", or "Severe") is more likely to be adopted by clinicians and less likely to have borderline values preventing accurate categorization.

The primary purpose of this investigation was to evaluate EDX findings across consecutive CTS severity categories within existing classification systems. We hypothesized that EDX findings would poorly discriminate between consecutive CTS severity categories within existing classification systems and that consolidating multiple categories into 3 primary categories would improve discrimination capability of all existing classification systems. Additionally, we hypothesized that *consolidated* classifications would significantly differ from one another and that categorization of "Mild", "Moderate", or "Severe" CTS would be highly dependent on the classification system used.

Materials and Methods

In this retrospective study of cross-sectional patient data, the primary outcome was categorization of CTS severity. Study participants were patients undergoing EDX testing and ultrasound imaging for suspected CTS in the Department of Physical Therapy, Therapy West Physical Therapy & Sports Medicine Centers located in Richfield and Gunnison, Utah. Participating patients provided written informed consent prior to testing and every effort was made to ensure their rights were protected, including handling of personal and health-related information.

Examiners & EDX Testing

EDX testing was performed by two examiners (NJS and JSM), but the final EDX impression was determined by the principal investigator (NJS) who is Board Certified in Clinical Electrophysiology by the American Board of Physical Therapist Specialties with over 17 years of experience performing and teaching EDX testing. Ultrasound imaging was performed by a single examiner (NJS) who is Registered in Musculoskeletal[®] sonography by the Alliance for Physician Certification & Advancement with over 7 years of experience performing and teaching neuromusculoskeletal ultrasound imaging. Sierra Wave and Sierra Summit devices (Cadwell: Kennewick, WA) were used for all EDX testing. Upper extremity nerve conduction studies were performed with patients seated and skin temperature maintained ≥32°C. Sensory and motor nerve conduction studies followed the standardized setup and performance described by Buschbacher¹⁶, including analysis of distal latencies, conduction velocities, and amplitudes based on normative values considering patient sex and age. Needle EMG was performed with patients

in supine using monopolar needle electrodes evaluating insertional and resting activity followed by volitional muscle activation to analyze morphology and recruitment pattern of observed motor unit potentials (MUP).

Antidromic superficial radial and median distal sensory latencies (DSL1) were obtained by wrist stimulation and thumb recording over 10 cm. Antidromic median and ulnar distal sensory latencies were obtained by wrist and palm stimulation and middle (DSL3) and little finger recordings over 14 cm and 7 cm, respectively. Orthodromic median and ulnar distal motor latencies (DML) were obtained by wrist stimulation and abductor pollicis brevis (APB) and abductor digiti minimi muscle recording over 8 cm, respectively. Needle EMG of muscles in the upper extremity representing C5-T1 nerve roots and all primary peripheral motor nerves were used to evaluate for axonal loss at rest and/or neuropathic MUP during volitional activation. Needle EMG of the APB muscle was routinely included in hands with median motor conduction abnormalities, but rarely included in hands with median sensory-only findings.

A final EDX impression was determined for all hands and used the following categorization of median neuropathy at the wrist: "Normal", "Mild", "Moderate", or "Severe". In general, "Mild" involved sensory-only findings, "Moderate" involved sensory and motor findings, including volitional EMG abnormalities when present, and "Severe" involved absent sensory responses, prolonged/absent motor responses, and EMG evidence of axonopathy in the APB muscle at rest.

Classification Systems

Hands were categorized according to CTS severity based on criteria defined in the Padua¹², Bland¹⁴, and GEHS¹⁵ classification systems. Notably, each classification system utilizes different cut-off values for determining abnormalities in median DSL and DML, which also differ from the normative values described by Buschbacher that are organized by sex and age categories¹⁶. For the purposes of analysis, and consistent with clinical practice, hands not meeting a specified criteria for a particular CTS severity category within a classification system were placed in the category that best fit the available EDX findings. Additionally, because Padua describes 5 categories and Bland and GEHS describe 6 categories of CTS severity, each classification system was consolidated into 3 primary categories ("Mild", "Moderate", or "Severe") for statistical comparison.

Statistical Analysis

IBM[®] SPSS[®] Statistics, version 28.0.1.0. (Armonk, NY, USA) was used for all data analysis. Descriptive statistics summarized characteristics of participating patients and hands tested. Multiple analysis of variance (MANOVA) was used to compare EDX findings across CTS severity categories within each classification system and within each *consolidated* classification²⁰. Chi Square analysis was used to compare *consolidated* classifications. Additional analyses



were performed using MANOVA and Chi Square to investigate the relationship between EDX findings, sex, age category, and CTS severity categories within complete and *consolidated* classification.

Results

Participants

Data was collected from December 2019 through July 2023 on 468 patients (54.6±16.8 years; 67.0±3.9 inches; 59% female) referred for EDX testing for suspected CTS (50% PA/NP; 49% MD/DO; 1% Other) that contributed 665 hands (51% right). EDX testing was completed by two examiners (78% NJS; 22% JSM), but the final EDX impression for all hands was determined by the principal investigator (NJS). After consideration of median sensory and motor latencies, amplitudes, and EMG of the APB muscle (when included in the examination), the final EDX impression resulted in the

following categorizations: 171 hands "Normal" (26%), 91 hands "Mild" (14%), 316 hands "Moderate" (48%), and 87 hands "Severe" (13%) for median neuropathy at the wrist.

Classification Systems

Based on a strict application of criteria used for each CTS severity category, the Padua classification system categorized 658 of 665 hands (99%), the Bland system categorized 625 of 665 hands (94%), and the GEHS system categorized 318 of 665 hands (48%). Because the GEHS system is unique in considering EMG findings, the percentage strictly categorized rises to 69% when analyzing only the 464 hands that included needle EMG of the APB muscle. For the purposes of analysis, and consistent with clinical practice, hands not meeting the criteria for a particular CTS severity category were placed in the category best fitting the EDX findings (Figure 2).

CTS Severity	N	Category Comparison	DSL1 (ms)	Mean Δ	p value	DSL3 (ms)	Mean Δ	p value
Normal	50		2.39 ± 0.14			2.97 ± 0.11		
*Minimal	1	NA	NA	NA	NA	NA	NA	NA
Mild	133	Mild v Norm	2.79 ± 0.27	0.41	.256	3.49 ± 0.41	0.52	<.001
Moderate	337	Mod v Mild	3.42 ± 1.12	0.62	<.001	4.61 ± 0.82	1.12	<.001
Severe	120	Sev v Mod	0.90 ± 1.77	-2.51	<.001	0.00 ± 0.00	-4.61	<.001
Extreme	24	Ext v Sev	0.17 ± 0.84	-0.73	.034	0.85 ± 1.95	-0.85	<.001
CTS Severity	N	Category Comparison	DML (ms)	Mean Δ	p value	DMA (mV)	Mean Δ	p value
Normal								
Normai	50		$\textbf{3.23} \pm \textbf{0.29}$			9.54 ± 3.03		
*Minimal	50 1	NA	3.23 ± 0.29 NA	NA	NA	9.54 ± 3.03 NA	NA	NA
*Minimal Mild	50 1 133	NA Mild v Norm	3.23 ± 0.29 NA 3.59 ± 0.26	NA 0.36	NA .604	9.54 ± 3.03 NA 8.68 ± 2.94	NA -0.86	NA .591
*Minimal Mild Moderate	50 1 133 337	NA Mild v Norm Mod v Mild	3.23 ± 0.29 NA 3.59 ± 0.26 5.09 ± 0.92	NA 0.36 1.50	NA .604 <.001	9.54 ± 3.03 NA 8.68 ± 2.94 6.76 ± 2.66	NA -0.86 <i>-1.92</i>	NA .591 <.001
*Minimal Mild Moderate Severe	50 1 133 337 120	NA Mild v Norm Mod v Mild Sev v Mod	3.23 ± 0.29 NA 3.59 ± 0.26 5.09 ± 0.92 7.45 ± 2.24	NA 0.36 1.50 2.35	NA .604 <.001 <.001	9.54 ± 3.03 NA 8.68 ± 2.94 6.76 ± 2.66 4.66 ± 2.53	NA -0.86 -1.92 -2.09	NA .591 <.001 <.001
*Minimal Mild Moderate Severe Extreme	50 1 133 337 120 24	NA Mild v Norm Mod v Mild Sev v Mod Ext v Sev	3.23 ± 0.29 NA 3.59 ± 0.26 5.09 ± 0.92 7.45 ± 2.24 0.00 ± 0.00	NA 0.36 1.50 2.35 -7.45	NA .604 <.001 <.001 <.001	9.54 ± 3.03 NA 8.68 ± 2.94 6.76 ± 2.66 4.66 ± 2.53 0.00 ± 0.00	NA -0.86 -1.92 -2.09 -4.66	NA .591 <.001 <.001 <.001

 Table 1. MANOVA of nerve conduction parameters across categories of CTS severity in the Padua classification system (A) and consolidated

 Padua classification (B).

p<0.0125 for post hoc comparisons. *Combined with "Mild" to conduct MANOVA

(B) Consolidated Padua									
CTS Severity	N	Category Comparison	DSL1 (ms)	Mean Δ	p value	DSL3 (ms)	Mean Δ	p value	
Negative	50		2.39 ± 0.14			2.97 ± 0.11			
Mild	134	Mild v Neg	2.79 ± 0.27	0.41	.159	3.49 ± 0.41	0.52	<.001	
Moderate	337	Mod v Mild	3.42 ± 1.12	0.62	<.001	4.61 ± 0.82	1.12	<.001	
Severe	144	Sev v Mod	0.78 ± 1.67	-2.64	<.001	0.14 ± 0.84	-4.47	<.001	
CTS Severity	N	Category Comparison	DML (ms)	Mean Δ	p value	DMA (mV)	Mean Δ	p value	
Negative	50		$\textbf{3.23} \pm \textbf{0.29}$			9.54 ± 3.03			
Mild	134	Mild v Neg	3.59 ± 0.26	0.36	1.00	8.68 ± 2.94	-0.86	.376	
Moderate	337	Mod v Mild	5.09 ± 0.92	1.50	<.001	6.76 ± 2.66	-1.92	<.001	
Severe	144	Sev v Mod	6.21 ± 3.45	-1.11	<.001	3.89 ± 2.89	-2.88	<.001	

p<0.0167 for post hoc comparisons. DSL1: distal sensory latency to thumb; DSL3: distal sensory latency to middle finger; DML: distal motor latency; DMA: distal motor amplitude; Norm: Normal; Mod: Moderate; Sev: Severe; Ext: Extreme; ms: milliseconds; mV: millivolts; NA: not applicable

Nerve Conduction Parameters

A significant moderate correlation was found between DSL1 and DSL3 (r=0.65, p<.001) with all other parameters having small or insignificant correlations. Because the "Minimal" CTS severity category in the Padua classification system contained only 1 hand it was combined with the "Mild" CTS severity category to allow for statistical analysis. In the Padua classification system, significant differences were found across CTS severity categories for DSL1 (F=144.5, df=4, p<.001), DSL3 (F=997.2, df=4, p<.001), DML (F=320.8, df=4, p<.001), and DMA (F=87.2, df=4, p<.001). Effect sizes were large ranging from η^2 =.35 for DMA to η^2 =.86 for DSL3 (Table 1A). In the consolidated Padua classification, significant differences were found across CTS severity categories for DSL3

for DSL1 (F=187.6, df=3, *p*<.001), DSL3 (F=1267.8, df=3, *p*<.001), DML (F=68.9, df=3, *p*<.001), and DMA (F=88.2, df=3, *p*<.001). Effect sizes were large ranging from η^2 =.24 for DML to η^2 =.85 for DSL3. DSL3 provided the best discrimination between consecutive CTS severity categories in the complete classification system and consolidated classification at 100% (4 of 4 and 3 of 3 comparisons, respectively). Overall, the complete classification system and *consolidated* classification performed equally, discriminating 75% (12 of 16 and 9 of 12 comparisons, respectively) of CTS severity categories (Table 1B).

In the Bland classification system, significant differences were found across CTS severity categories for DSL1 (F=100.8, df=6, *p*<.001), DSL3 (F=665.4, df=6, *p*<.001),

(A) Bland									
CTS Severity	N	Category Comparison	DSL1 (ms)	Mean Δ	p value	DSL3 (ms)	Mean Δ	p value	
Normal	138		2.57 ± 0.23			3.20 ± 0.22			
V Mild	12	V Mild v Norm	3.06 ± 0.19	0.49	1.00	3.40 ± 0.15	0.19	1.00	
Mild	134	Mild v V Mild	3.09 ± 0.49	0.04	1.00	3.82 ± 0.81	0.42	1.00	
Moderate	241	Mod v Mild	3.51 ± 1.29	0.42	.011	4.87 ± 0.80	1.05	<.001	
Severe	38	Sev v Mod	1.45 ± 2.05	-2.06	<.001	0.00 ± 0.00	-4.87	<.001	
V Severe	78	V Sev v Sev	0.61 ± 1.57	-0.84	.003	0.00 ± 0.00	0.00	1.00	
E Severe	24	E Sev v V Sev	0.17 ± 0.84	-0.43	1.00	0.85 ± 1.95	0.85	<.001	
CTS Severity	N	Category Comparison	DML (ms)	Mean Δ	p value	DMA (mV)	Mean Δ	p value	
Normal	138		3.49 ± 0.37			8.94 ± 3.08			
V Mild	12	V Mild v Norm	3.75 ± 0.22	0.26	1.00	8.58 ± 2.73	-0.36	1.00	
Mild	134	Mild v V Mild	4.00 ± 0.34	0.26	1.00	8.05 ± 2.75	-0.53	1.00	
Moderate	241	Mod v Mild	5.45 ± 0.85	1.44	<.001	6.34 ± 2.52	-1.71	<.001	
Severe	38	Sev v Mod	5.44 ± 0.51	-0.02	<.001	5.59 ± 2.83	-0.74	1.00	
V Severe	78	V Sev v Sev	8.58 ± 1.96	3.15	1.00	4.12 ± 2.22	-1.47	.104	
E Severe	24	E Sev v V Sev	0.00 ± 0.00	-8.58	<.001	0.00 ± 0.00	-4.12	<.001	

Table 2. MANOVA of nerve conduction parameters across categories of CTS severity in the Bland classification system (A) and *consolidated* Bland classification (B).

p<0.0083 for post hoc comparisons.

CTS Category	N	Category Comparison	DSL1 (ms)	Mean ∆	p value	DSL3 (ms)	Mean Δ	p value
Normal	138		2.57 ± 0.23			3.20 ± 0.22		
Mild	146	Mild v Norm	3.09 ± 0.47	0.53	.001	3.79 ± 0.79	0.59	<.001
Moderate	241	Mod v Mild	3.51 ± 1.29	0.42	.002	4.87 ± 0.80	1.08	<.001
Severe	140	Sev v Mod	0.76 ± 1.67	-2.75	<.001	0.15 ± 0.86	-4.72	<.001
CTS Category	N	Category Comparison	DML (ms)	Mean Δ	p value	DMA (mV)	Mean Δ	p value
Normal	138		3.49 ± 0.37			8.94 ± 3.08		
Mild	146	Mild v Norm	3.99 ± 0.34	0.49	.082	8.09 ± 2.74	-0.84	.063
Moderate	241	Mod v Mild	5.45 ± 0.85	1.47	<.001	6.34 ± 2.52	-1.76	<.001
_		a b b	6.26 . 2.40	0.01		2 0 2 1 2 0 0	2.52	1001

p<0.0167 for post hoc comparisons. DSL1: distal sensory latency to thumb; DSL3: distal sensory latency to middle finger; DML: distal motor latency; DMA: distal motor amplitude; V: Very; E: Extremely; Norm: Normal; Mod: Moderate; Sev: Severe; Ext: Extreme; ms: milliseconds; mV: millivolts.

DML (F=453.1, df=6, p<.001), and DMA (F=63.4, df=6, p<.001). Effect sizes were large ranging from η^2 =.37 for DMA to η^2 =.86 for DSL3. DSL3 and DML provided the best discrimination between consecutive CTS severity categories in the complete classification system at 50% (3 of 6 comparisons, respectively) (Table 2A). In the *consolidated* Bland classification, significant differences were found across CTS severity categories for DSL1 (F=188.1, df=3, p<.001), DSL3 (F=1264.7, df=3, p<.001), DML (F=84.4, df=3, p<.001), and DMA (F=94.4, df=3, p<.001). Effect sizes were large ranging from η^2 =.28 for DML to η^2 =.85 for DSL3. DSL1 and DSL3 provided the best discrimination between

consecutive CTS severity categories in the *consolidated* classification at 100% (3 of 3 comparisons, respectively). Overall, the *consolidated* classification outperformed the complete classification system, discriminating 83% (10 of 12 comparisons) compared to 42% (10 of 24 comparisons) of CTS severity categories, respectively (Table 2B).

In the GEHS classification system, significant differences were found across CTS severity categories for DSL1 (F=20.1, df=6, *p*<.001), DSL3 (F=21.1, df=6, *p*<.001), DML (F=59.4, df=6, *p*<.001), and DMA (F=57.2, df=6, *p*<.001). Effect sizes were large ranging from η^2 =.16 for DSL1 to η^2 =.35 for DML. DSL3, DML, and DMA provided the best discrimination

(A) GEHS									
CTS Severity	N	Category Comparison	DSL1 (ms)	Mean Δ	p value	DSL3 (ms)	Mean Δ	p value	
Normal	134		2.56 ± 0.23			3.20 ± 0.22			
V Mild	13	V Mild v Normal	3.05 ± 0.19	0.49	1.00	3.45 ± 0.22	0.25	1.00	
Mild(s)	100	Mild(s) v V Mild	3.05 ± 0.42	-0.05	1.00	3.85 ± 0.62	0.41	1.00	
Mild(s/m)	124	Mild(s/m) v Mild(s)	3.33 ± 0.73	0.28	1.00	4.13 ± 0.91	0.27	1.00	
Moderate	230	Mod v Mild(s/m)	2.53 ± 2.04	-0.80	<.001	3.08 ± 2.58	-1.04	<.001	
Mod/Sev	18	Mod/Sev v Mod	2.03 ± 2.23	-0.50	1.00	3.64 ± 2.67	0.56	1.00	
Severe	46	Sev v Mod/Sev	0.84 ± 1.97	-1.19	.500	0.95 ± 2.12	-2.69	<.001	
CTS Severity	N	Category Comparison	DML (ms)	Mean Δ	p value	DMA (mV)	Mean Δ	p value	
Normal	134		3.46 ± 0.34			9.05 ± 3.05			
V Mild	13	V Mild v Normal	3.75 ± 0.21	0.29	1.00	8.16 ± 3.03	-0.89	1.00	
Mild(s)	100	Mild(s) v V Mild	3.89 ± 0.30	0.13	1.00	8.19 ± 2.81	0.03	1.00	
Mild(s/m)	124	Mild(s/m) v Mild(s)	4.61 ± 0.19	0.72	.019	7.13 ± 2.49	-1.06	.073	
Moderate	230	Mod v Mild(s/m)	6.33 ± 1.43	1.72	<.001	5.57 ± 2.57	-1.56	<.001	
Mod/Sev	18	Mod/Sev v Mod	6.42 ± 0.25	0.09	1.00	5.37 ± 2.59	-0.20	1.00	
Severe	46	Sev v Mod/Sev	4.57 ± 5.18	-1.86	<.001	1.72 ± 2.33	-3.65	<.001	
10,000,000									

 Table 3. MANOVA of nerve conduction parameters across categories of CTS severity in the GEHS classification system (A) and consolidated

 GEHS classification (B).

p<0.0083 for post hoc comparisons.

(B) Consolidated GEHS										
CTS Severity	N	Category Comparison	DSL1 (ms)	Mean Δ	p value	DSL3 (ms)	Mean A	p value		
Normal	134		2.56 ± 0.23			3.20 ± 0.22				
Mild	113	Mild v Norm	3.19 ± 0.61	0.64	<.001	3.97 ± 0.79	0.77	<.001		
Moderate	354	Mod v Mild	2.53 ± 2.04	-0.67	<.001	3.08 ± 2.58	-0.89	<.001		
Severe	64	Sev v Mod	1.17 ± 2.09	-1.36	<.001	1.71 ± 2.57	-1.37	<.001		
CTS Severity	N	Category Comparison	DML (ms)	Mean Δ	p value	DMA (mV)	Mean ∆	p value		
Normal	138		3.46 ± 0.34			9.05 ± 3.05				
Mild	146	Mild vs Norm	4.26 ± 0.44	0.79	<.001	7.63 ± 2.70	-1.42	<.001		
Moderate	279	Mod vs Mild	6.33 ± 1.43	2.07	<.001	5.57 ± 2.57	-2.07	<.001		
Severe	102	Sev vs Mod	5.09 ± 4.46	-1.24	<.001	2.74 ± 2.90	-2.82	<.001		

p<0.0167 for post hoc comparisons. DSL1: distal sensory latency to thumb; DSL3: distal sensory latency to middle finger; DML: distal motor latency; DMA: distal motor amplitude; V: Very; s: sensory only; s/m: sensory & motor; Norm: Normal; Mod: Moderate; Sev: Severe; ms: milliseconds; mV: millivolts.

between consecutive CTS severity categories in the complete classification system at 33% (2 of 6 comparisons, respectively) (Table 3A). In the *consolidated* GEHS classification, significant differences were found across CTS severity categories for DSL1 (F=35.8, df=3, p<.001), DSL3 (F=29.6, df=3, p<.001), DML (F=104.6, df=3, p<.001), and DMA (F=98.9, df=3, p<.001). Effect sizes were moderate to large ranging from η^2 =.12 for DSL3 to η^2 =.32 for DML. All nerve conduction parameters provided 100% discrimination (3 of 3 comparisons, respectively) between consecutive CTS severity categories in the *consolidated* classification. Overall, the *consolidated* classification outperformed the

complete classification system, discriminating 100% (12 of 12 comparisons) compared to 29% (7 of 24 comparisons) of CTS severity categories, respectively (Table 3B).

Comparing nerve conduction parameters across the Padua and Bland classification systems, a single significant difference was found in DMA (F=7.6, df=2, *p*<.001) with a small effect size (η^2 =.02). Comparing nerve conduction parameters across the Padua and GEHS classification systems, significant differences were found in DSL3 (F=3.4, df=6, *p*=.003) and DML (F=3.2, df=6, *p*=.005) with small effect sizes of η^2 =.03, respectively. Comparing nerve conduction parameters across the Bland and GEHS classification systems, significant



differences were found in DSL1 (F=4.2, df=5, *p*<.001), DSL3 (F=21.1, df=5, *p*<.001), and DML (F=6.9, df=5, *p*<.001) with small to large effect sizes ranging from η^2 =.03 for DSL1 to η^2 =.14 for DSL3.

Needle EMG

A total of 454 hands (68%) underwent needle EMG of the APB muscle in this study. Among those hands, 42% were "Negative", 44% had volitional MUP abnormalities, and 14% had abnormalities at rest with or without volitional MUP abnormalities. Significant differences were found between EMG findings and all nerve conduction parameters including DSL1 (F=21.6, df=3, *p*<.001), DSL3 (F=18.3, df=3, *p*<.001), DML (F=36.4, df=3, *p*<.001), and DMA (F=67.3, df=3, *p*<.001) with medium to large effect sizes ranging from η^2 =.08 for DSL3 to η^2 =.23 for DMA. On average, sensory and motor latencies were slower/absent and motor amplitudes were lower/absent in the presence of EMG abnormalities at rest.

Planned comparisons revealed that only DML and DMA discriminated between all consecutive EMG categories

significant differences finding between "Volitional abnormalities" and "Normal" (1.38 ms, p<.001 and -1.8 mV, p<.001, respectively) and "Resting abnormalities" and "Volitional abnormalities" (-0.8 ms, p=.016 and -2.4 mV, p<.001). Significant differences were also found between "Resting abnormalities" and "Volitional abnormalities" in DSL1 (-1.2 ms, p<.001) and DSL3 (-1.6 ms, p<.001). Linear regression analysis revealed that age (β =-0.3, *p*=.022), DML (β=-4.4, p<.001), and DMA (β=3.2, p<.001) were significantly correlated with EMG findings, with the overall model explaining about 16% of the variance. Chi Square analysis revealed significant differences between EMG findings and CTS severity in the final EDX impression and all consolidated classifications (EDX Impression, χ^2 =430.3, p<.001; Padua, χ²=234.8, p<.001; Bland, χ²=258.7, p<.001; GEHS, χ^2 =564.9, p<.001). On average, volitional EMG abnormalities were more prevalent in "Mild" and "Moderate" CTS categories and EMG abnormalities at rest were more prevalent in the "Severe" CTS category regardless of classification used.

Consolidated Classifications

For the final EDX impression, significant differences were found across categories of median neuropathy at the wrist for DSL1 (F=91.7, df=3, *p*<.001), DSL3 (F=104.8, df=3, *p*<.001), DML (F=74.8, df=3, *p*<.001), and DMA (F=99.2, df=3, *p*<.001). Effect sizes were large ranging from η^2 =.25 for DML to η^2 =.32 for DSL3. DSL1, DML, and DMA provided the best discrimination between consecutive categories of median neuropathy at the wrist at 67% (2 of 3 comparisons, respectively). Overall, the final EDX impression discriminated 58% (7 of 12 comparisons) of consecutive categories of median neuropathy at the wrist.

The *consolidated* Padua classification resulted in the following categorizations: 50 hands "Normal" (8%), 134 hands "Mild" (20%), 337 hands "Moderate" (51%), and 144 hands "Severe" (22%) for CTS. The *consolidated* Bland classification resulted in the following categorizations: 138 hands "Normal" (21%), 146 hands "Mild" (22%), 241 hands "Moderate" (36%), and 140 hands "Severe" (21%) for CTS. The consolidated GEHS classification resulted in the following categorizations: 134 hands "Normal" (20%), 237 hands "Mild" (36%), 230 hands "Moderate" (35%), and 64 hands "Severe" (10%) for CTS (Figure 3). Chi Square analysis revealed significant differences between all consolidated classifications (Padua vs Bland, χ^2 =1114.7, *p*<.001; Padua vs GEHS, χ^2 =621.4, *p*<.001; Bland vs GEHS, χ^2 =1043.4, *p*<.001).

Comparison of nerve conduction parameters across consolidated Padua and Bland classifications found a single significant difference in DMA (F=11.9, df=1, p<.001) with a small effect size (η^2 =.02). Comparison of nerve conduction parameters across consolidated Padua and GEHS classifications found significant differences in DSL3 (F=5.5, df=3, p<.001), DML (F=16.9, df=3, p<.001), and DMA (F=4.7, df=3, p<.001) with small to medium effect sizes ranging from η^2 =.01 for DSL3 to η^2 =.09 for DML. Comparison of nerve conduction parameters across consolidated Bland and GEHS classifications found significant differences in DSL3 (F=31.9, df=3, p<.001) and DML (F=17.7, df=3, p<.001) with medium effect sizes ranging from η^2 =.08 for DML to η^2 =.13 for DSL3.

Additional Analyses

A significant moderate correlation was found between age and DMA (r=-0.49, *p*<.001) with all other variables having small or insignificant correlations. Sex-specific analysis revealed significant differences between men and women in all nerve conduction parameters including DSL1 (F=5.2, df=1, *p*=.023), DSL3 (F=8.7, df=1, *p*=.003), DML (F=13.4, df=1, *p*<.001), and DMA (F=22.4, df=1, *p*<.001) with small to medium effect sizes ranging from η^2 =.01 for DSL1 to η^2 =.03 for DMA. On average, women had slower DSL1/DSL3, faster DML, and larger DMA. In the Padua classification system, significant differences were found between men and women in DSL3 (F=4.1, df=4, *p*=.003) and DML (F=2.8, df=4, *p*=.026) with small effect sizes of η^2 =.02, respectively. On average, women had slower DSL3, faster DML, and more normality with less overall severity. In the Bland classification system, a single significant difference was found between men and women in DSL3 (F=2.9, df=6, p=.009) with a small effect size ($n^2=.03$). On average, women had slower DSL3 but more normality with less overall severity. In the GEHS classification system, no significant differences were found between men and women in any nerve conduction parameter. In the Padua and Bland consolidated classifications, significant differences were found between men and women only in DMA (F=3.6, df=3, p=.013 and F=3.6, df=3, p=.014, respectively) with small effect sizes of n²=.02, respectively. On average, women had larger DMA and more normality with less overall severity. In the GEHS consolidated classification, no significant differences were found between men and women in any nerve conduction parameter. Chi Square analysis revealed significant differences between men and women in CTS severity comparing consolidated classifications (Padua, χ²=44.4, *p*<.001; Bland, χ²=37.1, *p*<.001; GEHS, χ²=37.7, p<.001). On average, women had a higher proportion of normality with a lower proportion of overall severity.

Age categories used in this study were based on those commonly used in normative data sets and included <50 years and ≥50 years for DSL1, DSL3, and DML and <40 years, 40-59 years, and ≥60 years for DMA. Age categoryspecific analysis revealed significant differences between age categories in all nerve conduction parameters including DSL1 (F=7.4, df=1, p=.007), DSL3 (F=8.9, df=1, p=.003), DML (F=16.8, df=1, p<.001), and DMA (F=79.2, df=1, p<.001). Effect sizes were small to large ranging from η^2 =.01 for DSL1 to η^2 =.19 for DMA. On average, patients \geq 50 years had faster DSL1/DSL3 (likely associated with a higher proportion of absent responses reflected in larger standard deviations), slower DML, and smaller DMA. Because DMA includes 3 age categories, a significant difference was found comparing patients ≥60 years with those 40-59 years (-2.72 mV, p<.001) but not found comparing patients 40-59 years with those <40 years (-0.49 mV, *p=.346*). Only the Bland classification system found a significant difference based on age category, and that was only in DSL3 (F=2.2, df=6, p=.043) with a small effect size (η^2 =.02). On average, patients ≥50 years had slower DSL3 and less normality with more overall severity. Only the consolidated Bland and GEHS classifications found significant differences based on age category, both in DSL3 (F=3.6, df=3, p=.013 and F=3.6, df=3, *p=.014*, respectively) with small effect sizes of η^2 =.01, respectively. On average, patients ≥50 years had slower DSL3 and less normality with more overall severity. Chi Square analyses revealed significant differences between age category and consolidated classifications, whether analyzed using 2 or 3 age categories (Padua, χ^2 =80.4 to 87.3, *p*<.001; Bland, χ^2 =67.1 to 74.3, *p*<.001; GEHS, χ^2 =37.7, *p<.001*). On average, patients \geq 50 years had a lower proportion of normality and a higher proportion of overall severity.

Discussion

This study evaluated the value of common EDX findings to discriminate across consecutive CTS severity categories within existing classification systems. The results support the use of consolidated classifications to improve discrimination capability between consecutive CTS severity categories regardless of classification system used. In addition, significant differences were found in EDX findings and categorization of CTS severity when comparing complete classification systems and consolidated classifications, which is clinically significant considering the implications of CTS severity diagnosis on the subsequent medical management and selection of interventions^{10,11}. While the Padua classification showed the highest discrimination capability between consecutive CTS severity categories at 75%, it should be remembered that because only a single hand was categorized as "Minimal" it had to be combined with the "Mild" category for statistical analysis, resulting in a true discrimination capability to 60%. Similarly, while the consolidated GEHS classification showed the higher discrimination capability between consecutive CTS severity categories at 100%, it should be remembered that only 48% of hands could be strictly classified, which improved to just 69% when analyzed only in hands including needle EMG of the APB muscle. Having to determine the CTS severity category best fitting the EDX findings in nearly 1 out of 3 hands may limit the clinical utility of the GEHS systems and potentially introducing large variability across clinicians.

Because the final EDX impression used by the examiners in this investigation discriminated just 58% of CTS severity categories, the value of EMG findings and/or the evaluation of median sensory and motor amplitudes to inform categorization of CTS severity should be considered^{18,21}. Although only one of the classification systems in this study considers EMG findings in the APB muscle^{11,15}, inclusion of needle EMG in patients with suspected CTS appears (when appropriate) appears warranted based on the results of this investigation. Among the 68% of hands undergoing needle EMG of the APB muscle in this study, the most common finding was volitional MUP abnormalities, a finding that was most prevalent in hands categorized as "Mild" or "Moderate" CTS regardless of the classification system used. An abnormal EMG finding in the presence of otherwise "Normal" or "Mild" sensory-only findings presents a diagnostic challenge for a clinician who is seeking to accurately categorize CTS severity. Alternatively, the findings of this investigation were consistent with prior studies demonstrating the relationship between EMG abnormalities at rest are more severe CTS^{11,18,21}. Additionally, DML and DMA provided the best discrimination between categories of EMG findings and were most predictive of the presence of EMG abnormities in general.

While none of the existing classification systems evaluated in this study use sex or age-specific criteria, sex and age category-specific analysis revealed significant differences related to CTS severity. Significant differences were found in all nerve conduction parameters, with women generally exhibiting slower sensory latencies, faster motor latencies, and larger motor amplitudes. Significant differences were found between men and women in the distribution of CTS severity categories regardless of classification system used, with women exhibiting a higher proportion of normality and lower proportion of overall severity. Age category-specific analysis demonstrated significant differences in all nerve conduction parameters, with patients \geq 50 years generally exhibiting slower sensory and motor latencies and smaller motor amplitudes. Significant differences were found between age categories in the distribution of CTS severity categories regardless of classification system used, with patients \geq 50 years exhibiting a lower proportion of normality and higher proportion of overall severity. Additionally, age was among the predictive factors of EMG findings generally. These findings suggest that sex and age may be important factors to consider when interpreting EDX findings for the purpose of categorizing CTS severity.

This original study contributes significant insights into the evaluation of existing classification systems describing categories of CTS severity through a comprehensive analysis of EDX findings. This investigation found that *consolidated* classifications provide superior discrimination capability between consecutive CTS severity categories within existing classification systems based on EDX findings. These results also highlight the importance of considering demographic factors when interpreting EDX findings for the purposes of categorizing CTS severity. Future research is needed to further refine existing classification systems and explore additional factors that may influence the categorization of CTS severity for the purposes of enhancing diagnosis and improving selection of interventions.

Ethics approval

All study-related procedures were approved by the Institutional Review Board at Winston-Salem State University (IRB-FY2023-37).

References

- Joshi A, Patel K, Mohamed A, et al. Carpal Tunnel Syndrome: Pathophysiology and Comprehensive Guidelines for Clinical Evaluation and Treatment. Cureus 2022;14(7):e27053.
- 2. Hubbard ZS, Law TY, Rosas S, Jernigan SC, Chim H. Economic benefit of carpal tunnel release in the Medicare patient population. Neurosurg Focus 2018;44(5):E16.
- Kimura J. Electrodiagnosis in Diseases of Nerve and Muscle: Principles and Practice. Oxford University Press, USA; 2001:1024.
- Dumitru D. Electrodiagnostic Medicine. Hanley & Belfus; 2001:1524.
- 5. Preston DC, Shapiro B. Electromyography and Neuromuscular Disorders: Clinical-Electrophysiologic Correlations. Butterworth-Heinemann; 2005:704.
- Liveson JA. Peripheral Neurology: Case Studies. Oxford University Press, USA; 2000:528.
- 7. Katirji B. Electromyography in Clinical Practice: A Case

Study Approach. 2 ed. Mosby; 2007:432.

- Werner RA. Electrodiagnostic evaluation of carpal tunnel syndrome and ulnar neuropathies. Pm r 2013;5(5 Suppl):S14-21.
- 9. Graham B. The value added by electrodiagnostic testing in the diagnosis of carpal tunnel syndrome. J Bone Joint Surg Am 2008;90(12):2587-93.
- 10. Sucher BM. Grading severity of carpal tunnel syndrome in electrodiagnostic reports: why grading is recommended. Muscle Nerve 2013;48(3):331-3.
- Ernst G, Shaffer SW, Halle JS, Greathouse DG. Utilization of Neurophysiological Classification Systems in Determining Interventions for Patients with Carpal Tunnel Syndrome. Med J (Ft Sam Houst Tex) 2022;(Per 22-01/02/03):33-40.
- Padua L, LoMonaco M, Gregori B, Valente EM, Padua R, Tonali P. Neurophysiological classification and sensitivity in 500 carpal tunnel syndrome hands. Acta Neurol Scand 1997;96(4):211-7.
- Aulisa L, Tamburrelli F, Padua R, Romanini E, Lo Monaco M, Padua L. Carpal tunnel syndrome: indication for surgical treatment based on electrophysiologic study. J Hand Surg Am 1998;23(4):687-91.
- 14. Bland JD. A neurophysiological grading scale for carpal

tunnel syndrome. Muscle Nerve 2000;23(8):1280-3.

- Greathouse DG, Ernst G, Halle JS, Shaffer SW. GEHS Neurophysiological Classification System for Patients with Carpal Tunnel Syndrome. US Army Med Dep J 2016:60-7.
- Buschbacher RM, Kumbhare DA, Robinson LR. Buschbacher's manual of nerve conduction studies. Third edition. ed. Demos Medical; 2016:xiv, 299 pages.
- Jazayeri SM, Ashraf A, Karimian H, Moghari A, Azadeh A. Test-retest reliability of transcarpal sensory NCV method for diagnosis of carpal tunnel syndrome. Ann Indian Acad Neurol 2015;18(1):60-2.
- Chang CW, Lee WJ, Liao YC, Chang MH. Which nerve conduction parameters can predict spontaneous electromyographic activity in carpal tunnel syndrome? Clin Neurophysiol 2013;124(11):2264-8.
- Sasaki T, Koyama T, Kuroiwa T, et al. Evaluation of the Existing Electrophysiological Severity Classifications in Carpal Tunnel Syndrome. J Clin Med 2022;11(6).
- 20. Tabachnick BG, Fidell LS. Using Multivariate Statistics (5th Edition). Allyn & Bacon; 2006:1008.
- Rubin DI, Dimberg EL. Needle EMG of Thenar Muscles in Less Severe Carpal Tunnel Syndrome. J Clin Neurophysiol 2018;35(6):481-484.

Supplementary file. STROBE Statement—Checklist of items that should be included in reports of cross-sectional studies.

Initial of the second		Itom No.	Decommondation	Dago No
Title and abstract Introduction Introdu		Item No	Recommendation	Page No 216
This dimonstration The abstrate and informative and balances summary of max was done and packground/rationale 216 Introduction Explain the scientific background and rationale for the investigation being reported 216-218 Objectives 3 State specific objectives, including any prespecified hypotheses 218 Study design 4 Present key elements of study design early in the paper 218-219 Setting 5 Describe the setting, locations, and relevant dates, including periods of recruitment, compours, following, and data collection 218-219 Participants 6 (a) Give the eligibility criteria, and the sources and methods of selection of participants 218-219 Data sources/f 8* for each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group 218-219 Data sources/f 8* for each variable of interest, give sources of data and details of methods of assessment (b) Describe and statistical methods, including those used to control for confounding 218-219 Bats sources/f 0 Describe any efforts to address potential sources of bas NA Statistical methods 11 Explain how quantitative variables were handled in the analyses. If applicable, describe w	Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title of the abstract	210
Introduction Value Background/rationale 2 Explain the scientific background and rationale for the investigation being reported 216-218 Methods 3 State specific objectives. Including any prespecified hypotheses 218 Study design 4 Present key elements of study design early in the paper 218 Study design 6 (a) Give the eligibility criteria, and the sources and methods of selection of participants 218 Variables 7 Clearly define all outcomes, exposures, predictors, potential confounders, and effect 218-219 Data sources/ measurement 8* For each variable of interest, give sources of data and details of methods of assessment measurement Duscribe any ardiorts to address potential sources of bias NA Study size 10 Explain how the study size wara barrived at 218-219 Quantitative variables 11 Explain how quantitative variables were handled in the analyses. If applicable, describe arrived rescribe all statistical methods, including those used to control for confounding 218-219 Variables 11 Explain how missing data were addressed NA Statistical methods 12 (c) Describe any stratigy essinty analyses NA <t< td=""><td></td><td></td><td>what was found</td><td>216</td></t<>			what was found	216
Background/rationale 2 Explain the scientific background and rationale for the investigation being reported 216-218 Objectives 3 State specific objectives, including any prespecified hypotheses 218 Setting 5 Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection 218-219 Participants 6 (a) Give the eligibility criteria, and the sources and methods of selection of participants 218-219 Data sources/ 8 For each variable of interest, give sources of data and details of methods of assessment methods if there is more than one group or oup or oup aroup 218-219 Bias 9 Describe any efforts to address potential sources of bias NA Study size 10 Explain how quantitative variables were handled in the analyses. If applicable, describe any efforts to address potential sources of bias NA Quantitative variables 11 Explain how quantitative variables were handled in the analyses. If applicable, describe any efforts to address potential sources of bias NA Statistical methods 11 Explain how quantitative variables were handled in the analyses. If applicable, describe any efforts to address potential sources of bias NA Outreating statistical methods taking account of sampl	Introduction			
Objectives3State specific objectives, including any prespecified hypotheses218Methods1Setting4Present key elements of study design early in the paper218Setting5Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection218-219Participants6(c) Give the eliapility criteria, and the sources of data and details of methods of assessment methods if assessm	Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	216-218
MethodSludy design4Present key elements of study design early inte paper218Setting5Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection218-219Participants60 Gi Vert en eligibility criteria, and the sources and methods of selection of participants218Variables7Clearly define all outcomes, exposures, predictors, potential confounders, and effect218-219Data sources/ measurement8For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group218-219Bias9Describe any efforts to address potential sources of biasNAStudy size101Explain how the study size was arrived at which groupings were chosen and why218-219Quantitative variable(a) Describe any efforts to address potential sources of biasNA(b) Describe any efforts to address potential sources of biasNA(c) Describe any methods used to examine studyroups and interactionsNA(d) flopplicable, describe analytical methods, including these used to control for confounding (d) flopplicable, describe analytical methods taking account of sampling strategy (a) flopplicable, describe analytical methods including the study, completing follow-up, and analysed219Participants16(b) Give characteristics of study participants (e) demographic, clinical, scola) and (d) flopplicable, describe on study and to reaction data of each strateging study and to reaction data of each strateging st	Objectives	3	State specific objectives, including any prespecified hypotheses	218
Study design4Present key elements of study design early in the paper218Setting0Describe the setting, locations, and relevant dates, including periods of recuritment exposure, follow-up, and data collection218-219Participants6(a) Ever the eligibility criteria, and the sources and methods of selection of participants218Variables7Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable218-219Data sources/ measurement)8rFor each variable of interest, give sources of data and details of methods of assessment methods if there is more than one group218-219Bias9Describe any efforts to address potential sources of biasNAStudy size101Explain how the study size was arrived at which groupings were chosen and why218-219Quantitative variables10Explain how methods, including those used to control for confounding (d) Describe any methods used to examine subgroups and interactionsNAStatistical methods(d) Explain how missing data were addressedNA(d) Describe any sensitivity analysesNAResults(d) Report numbers of individuis at each stage of study-eng numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, an analysed219-222Outcome data15Report numbers of outcome events or summary measures219-222Main results(d) Give tracesons for non-participation at each stageNAOutcome data15Report numbers	Methods			
Setting S Describe the setting, locations, and relevant dates, including periods of recruitment, seposure, follow-up, and data collection 218-219 Participants 6 (a) Give the eligibility criteria, and the sources and methods of selection of participants 218 Variables 7 Clearly define all outcomes, exposures, ordicitors, potential confounders, and effect in dispation defines, if explicable 218-219 Data sources/ measurement 8° For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. 218-219 Bias 90 Describe any efforts to address potential sources of bias NA Quantitative variables 10 Explain how quantitative variables were handled in the analyses. If applicable, describe with conguings were chosen and why 218-219 Statistical methods 12 (a) Describe and ynthical methods, including those used to control for confounding 218-219 Statistical methods 12 (b) Describe and ynthical methods taking account of sampling strategy NA (b) Describe and ynthical methods taking account of sampling strategy NA (c) Explain how missing data were addressed NA Statistical methods 10 (c) Expl	Study design	4	Present key elements of study design early in the paper	218
Participants 6 (o) Cive the eligibility criteria, and the sources and methods of selection of participants 218 Variables 7 Clearly define all outcomes, exposures, predictors, potential contounders, and effett modifiers. Give diagnostic criteria, if applicable 218-219 Data sources/ measurement 8* For each variable of interest, give sources of data and details of methods of assessment measurement 218-219 Diagnostic 9 Describe any efforts to address potential sources of bias NA Study size 10 Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why 218-219 Quantitative variables (a) Describe any efforts to address potential sources of bias NA (b) Describe any methods used to examine subgroups and interactions NA (c) Catapain how missing data were addressed NA (d) drapplicable, describe analytical methods taking account of sampling strategy NA (d) Give reasons for non-participation at each stage of study—eq numbers potentially eligible. (d) Consider used of simularity, confirmed eligible, included in the study, completing follow-up, and analysed 219-222 Outcome data 15* Report numbers of individuals at each stage of study—eq numbers potentiallay eligible. (d) Give reasons for non-participat	Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	218-219
Variables 7 Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Cive diagnostic criteria, if applicable. 218-219 Data sources/ measurement B* For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group 218-219 Bias 9 Describe any efforts to address potential sources of blas NA Study size 10 Explain how the study size was arrived at 218-219 Quantitative variables 11 Explain how tauty size was arrived at 218-219 Quantitative variables 11 Explain how tauty size was arrived at 218-219 Quantitative variables 11 Explain how maintitative variables were handled in the analyses. If applicable, describe and its stutical methods taking account of sampling strategy NA (a) Describe any methods used to examine subgroups and interactions NA NA (b) Describe any methods used to examine subgroups and interactions NA (c) Explain how missing data were addressed (c) Go ive characteristics of study participants (end moty analysed NA Participants 14* (a) Report numbers of individuals at each stage of study, completing follow-up, and information	Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	218
Data sources/ measurement8*For each variable of interest, give sources of data and details of methods of assessment group218-219Bias9Describe any efforts to address potential sources of biasNAStudy size10Explain how the study size was arrived at218-219Quantitative variables11Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why218-219Quantitative variables(a) Describe any methods used to examine subgroups and interactionsNA(b) Explain how missing data were addressedNA(c) Explain how missing data were addressedNA(d) for applicable, describe analytical methods, including those used to control for confounding218-219(d) for applicable, describe analytical methods taking account of sampling strategyNA(e) Describe any sensitivity analysesNA(e) Describe any sensitivity analysesNA(f) frapplicable, describe analytical methods included in the study, completing follow-up, and analysed219-219Participants14*(a) Geport numbers of individuals at each stage of study –eq numbers potentially eligible, (b) Give creasons for non-participation at each stageNADescriptive data15*(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential contounders219-222Outcome data15*(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential contounders219-222Main results	Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	218-219
Bias9Describe any efforts to address potential sources of biasNAStudy size10Explain how the study size was arrived at218Quantitative variables11Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why218-219Statistical methods12Explain how musicing data were addressed (d) applicable, describe any sethodo used to examine subgroups and interactionsNAStatistical methods12(e) Explain how missing data were addressed (d) applicable, describe any sethodo used to examine subgroups and interactionsNAResults(e) Explain how missing data were addressed (d) applicable, describe any sethodo used to examine subgroups and interactionsNAResults(e) Explain how missing data were addressed (d) applicable, describe any sethodo used to examine dupNAResults(e) Explain how missing data were addressed (d) applicable, describe any sethodo used to examine dupNAResults(e) Correader unmers of individuals at each stage of study—eq numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed219Descriptive data14*(o) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders219-222Outcome data15*Report numbers of outcome events or summary measures219-222Main results(o) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eq, 95% confidence intervat). Make clear which confoun	Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	218-219
Study size10Explain how the study size was arrived at218Quantitative variables11Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why218-219Statistical methods11(D Describe and statistical methods, including those used to control for contounding (D) Describe and statistical methods, including those used to control for contounding (D) Explain how missing data were addressedNAStatistical methods(D Explain how missing data were addressed (D) Explain how missing data were addressedNARewults(D) Explain how missing data were addressedNA(D) Give characteristics of study participants (eg demographic, clinical, social) and (D) Indicate number of participants with missing data for each variable of interest219-222Outcome data15*Report numbers of outcome events or summary measures219-222Main results(D) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their meristical methods which confinued with the were includedNAOutcome data17*Report other analyses done—eg analyses of subgroups and interact	Bias	9	Describe any efforts to address potential sources of bias	NA
Quantitative variables 11 Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why 218-219 Statistical methods (a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions NA Statistical methods (c) Explain how missing data were addressed NA (d) If applicable, describe analytical methods taking account of sampling strategy NA (e) Describe any sensitivity analyses NA Results	Study size	10	Explain how the study size was arrived at	218
Statistical methods (a) Describe all statistical methods, including those used to control for confounding 218-219 (b) Describe any methods used to examine subgroups and interactions NA (c) Explain how missing data were addressed NA (d) If applicable, describe analytical methods taking account of sampling strategy NA (e) Describe any sensitivity analyses NA Results (d) Report numbers of individuals at each stage of study—eq numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed 219 Participants (a) Report numbers of individuals at each stage of study—eq numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed 219 Descriptive data (b) Give characteristics of study participants (eg demographic, clinical, social) and (o) linicate number of participants with missing data for each variable of interest 219-222 Outcome data 15* Report numbers of outcome events or summary measures 219-224 Main results (d) Give unadjusted estimates and, if applicable, confounder sever adjusted for precision (eq, 95% confidence interval). Make clear which confounder sever adjusted for precision (eq, 95% confidence interval). Make clear which confounder sever adjusted for analyses 219-224 Other analyses 18	Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	218-219
Statistical methods [b] Describe any methods used to examine subgroups and interactions NA Statistical methods [c] Explain how missing data were addressed NA (c) Explain how missing data were addressed NA (c) Describe any sensitivity analyses NA Results (d) Roport numbers of individuals at each stage of study—eng numbers potentially eligible, included in the study, completing follow-up, and analysed 219 Participants (a) Roport numbers of individuals at each stage of study—eng numbers potentially eligible, included in the study, completing follow-up, and analysed NA Describe any sensitivity analyses NA 219 (b) Give reasons for non-participation at each stage of study, completing follow-up, and information on exposures and potential confounders NA Outcome data 15* Report numbers of outcome events or summary measures 219-222 Outcome data 15* Report numbers of outcome events or summary measures 219-222 Main results (d) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for NA 219-224 Main results (17 Report to ther analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Statistical methods		(a) Describe all statistical methods, including those used to control for confounding	218-219
Statistical methods12 (c) Explain how missing data were addressedNA (d) If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analysesNAResults(a) Report numbers of individuals at each stage of study—eq numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagramNADescriptive data14*(a) Report numbers of individuals at each stage 		12	(b) Describe any methods used to examine subgroups and interactions	NA
(d) If applicable, describe analytical methods taking account of sampling strategy NA Results (e) Describe any sensitivity analyses NA Participants 13* (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed 219 Participants 13* (a) Report numbers of individuals at each stage NA (b) Give reasons for non-participation at each stage NA NA (c) Consider use of a flow diagram NA NA (b) Indicate number of participants (eg demographic, clinical, social) and information on exposures and potential confounders 219-222 Outcome data 15* Report numbers of outcome events or summary measures 219-222 Outcome data 15* Report number of participants (eg demographic, clinical, social) and individuals at each stage (i) Rive unadjusted for each variable of interest 219-222 Main results 16* Report numbers of outcome events or summary measures 219-224 (c) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and heir precision (e.g. 5%) confidence interval). Make clear which confounders were adjusted for an meaningful time period 219-224 Other analyses 17 Report other analyses done—eg analyses of s			(c) Explain how missing data were addressed	NA
ResultsNAResults(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed219Participants13*(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed219Descriptive data14*(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders219-222Outcome data15*Report number of participants with missing data for each variable of interest219-222Outcome data15*Report numbers of outcome events or summary measures219-222Anan results(b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time periodNAOther analyses18Summarise key results with reference to study objectives225Limitations19Discuss both direction and magnitude of any potential bias or imprecision. Discuss both direction and magnitude of any potential bias, and other relevant evidence Biscuss both direction and magnitude of any potential bias, and other relevant evidence225Umitations20Give a cautious overall interpretation of results considering objectives, imitations, multiplicity of analyses, results from similar studies, and other relevant evidence225Umitations22Give the source of funding and the role of the funders for the present study and, i			(d) If applicable, describe analytical methods taking account of sampling strategy	NA
Participants (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed 219 Participants 13* (b) Give reasons for non-participation at each stage NA (c) Consider use of a flow diagram NA NA Descriptive data 14* (d) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders 219-222 Outcome data 15* Report numbers of outcome events or summary measures 219-222 Main results (d) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for an why they were included 219-224 Main results 17 Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses NA Other analyses 17 Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses done—eg analyses, results (pot endities, and other relevant evidence 225 Limitations 19 Discuss both direction and magnitude of any potential bias 225 Limitations 21 Discus both direction and magnitude of any potential bias 225 Give a cautious overa			(e) Describe any sensitivity analyses	NA
Participants(a) Report numbers of individuals at each stage of study—eq numbers potentially eligible, analysed21913*analysed(b) Give reasons for non-participation at each stageNA(c) Consider use of a flow diagramNA0Give characteristics of study participants (eg demographic, clinical, social) and (b) Indicate number of participants with missing data for each variable of interest219-222Outcome data15*Report numbers of outcome events or summary measures219-222Outcome data15*Report numbers of outcome events or summary measures219-222Main results(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for ensingful time period219-224Other analyses17Report category boundaries when continuous variables were categorized219-224(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time periodNADiscussion225Limitations19Discuss limitations of the study, taking into account sources of potential bias or imprecision. multiplicity of analyses, results from similar studies, and other relevant evidence225Cherration20Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence225Cherration20Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other rele	Results			
(b) Give reasons for non-participation at each stageNA(c) Consider use of a flow diagramNADescriptive data14*(a) Give characteristics of study participants (eq demographic, clinical, social) and information on exposures and potential confounders219Outcome data15*Report numbers of outcome events or summary measures219-222Outcome data15*Report numbers of outcome events or summary measures219-224Main results(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eq, 95% confidence interval). Make clear which confounders were adjusted for (b) Report category boundaries when continuous variables were categorized219-224(b) Give the analyses(b) Report category boundaries of relative risk into absolute risk for a meaningful time periodNAOther analyses17Report other analyses done—eq analyses of subgroups and interactions, and sensitivity piscuss both direction and magnitude of any potential biasNADiscussion225Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence225Interpretation20Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence225Other information22Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is basedNA	Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	219
IndexInterpretationInterpretationNADescriptive data14*(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders219Outcome data15*Report numbers of outcome events or summary measures219-222Outcome data15*Report numbers of outcome events or summary measures219-222(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included219-224(b) Report category boundaries when continuous variables were categorized219-224(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time periodNAOther analyses17Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analysesNADiscussion225Simmarise key results with reference to study objectives225Limitations19Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias225Generalisability21Discuss the generalisability (external validity) of the study results. 			(b) Give reasons for non-participation at each stage	NA
Descriptive data14*(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders219Outcome data15*Report number of participants with missing data for each variable of interest219-222Outcome data15*Report numbers of outcome events or summary measures219-222Main results16*Report numbers of outcome events or summary measures219-224Image: data for each variable destimates and, if applicable, confounder-adjusted estimates and their precision (eg. 95% confidence interval). Make clear which confounders were adjusted for and why they were included219-224Image: data for each variables were categorized219-224Image: data for each variable sere for each variable sere categorized			(c) Consider use of a flow diagram	NA
InterpretationInterpretation(b) Indicate number of participants with missing data for each variable of interest219-222Outcome data15*Report numbers of outcome events or summary measures219-222Main resultsImage: Second Contexperiment of the study analyses(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg., 95% confidence interval). Make clear which confounders were adjusted of and why they were included219-224Main results16*Report category boundaries when continuous variables were categorized219-224(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time periodNAOther analyses17Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analysesNADiscussion225225Limitations19Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential biasNAInterpretation20Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results (external validity) of the study results, and other relevant evidence225Other information21Discuss the generalisability (external validity) of the study results of the present study and, if applicable, for the original study on which the present article is basedNA	Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	219
Outcome data15*Report numbers of outcome events or summary measures219-222Main results15*(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included219-224Main results16(b) Report category boundaries when continuous variables were categorized219-224(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time periodNAOther analyses17Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analysesNADiscussion18Summarise key results with reference to study objectives225Limitations19Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias225Generalisability21Discuss the generalisability (external validity) of the study results225Other information22Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is basedNA			(b) Indicate number of participants with missing data for each variable of interest	219-222
Main results(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included219-224Main results16(b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time periodNAOther analyses17Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analysesNADiscussion18Summarise key results with reference to study objectives Discuss both direction and magnitude of any potential bias or imprecision. Discuss both direction and magnitude of any potential biasNAInterpretation20Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence225Other information22Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is basedNA	Outcome data	15*	Report numbers of outcome events or summary measures	219-222
Main results16(b) Report category boundaries when continuous variables were categorized219-224(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time periodNAOther analyses17Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analysesNADiscussionKey results18Summarise key results with reference to study objectives225Limitations19Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential biasNAInterpretation20Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence225Other information22Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is basedNA			(<i>a</i>) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	219-224
(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time periodNAOther analyses17Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analysesNADiscussionKey results18Summarise key results with reference to study objectives225Limitations19Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential biasNAInterpretation20Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence225Other information22Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is basedNA	Main results	16	(b) Report category boundaries when continuous variables were categorized	219-224
Other analyses17Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analysesNADiscussionVVVVKey results18Summarise key results with reference to study objectives225Limitations19Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential biasNAInterpretation20Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence225Generalisability21Discuss the generalisability (external validity) of the study results225Other information22Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is basedNA			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
DiscussionKey results18Summarise key results with reference to study objectives225Limitations19Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential biasNAInterpretation20Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence225Generalisability21Discuss the generalisability (external validity) of the study results225Other information22Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is basedNA	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Key results18Summarise key results with reference to study objectives225Limitations19Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential biasNAInterpretation20Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence225Generalisability21Discuss the generalisability (external validity) of the study results225Other information22Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is basedNA	Discussion			
Limitations19Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential biasNAInterpretation20Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence225Generalisability21Discuss the generalisability (external validity) of the study results225Other information22Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is basedNA	Key results	18	Summarise key results with reference to study objectives	225
Interpretation20Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence225Generalisability21Discuss the generalisability (external validity) of the study results225Other information22Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is basedNA	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	NA
Generalisability21Discuss the generalisability (external validity) of the study results225Other informationFunding22Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is basedNA	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	225
Other information Funding 22 Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based NA	Generalisability	21	Discuss the generalisability (external validity) of the study results	225
Funding22Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is basedNA	Other information			
	Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	NA

*Give information separately for exposed and unexposed groups.