


Efficacy and safety of vasopressin and terlipressin in preterm neonates: a protocol for a systematic review

Abdulrahman Salim Alsaadi ¹, Katelyn Sushko,² Vivian Bui,³ John Van Den Anker,^{4,5,6} Abdul Razak,^{7,8} Samira Samiee-Zafarghandy ¹

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ABSTRACT

Background The use of vasoactive agents like arginine vasopressin (AVP) and terlipressin to treat hypotension or persistent pulmonary hypertension in critically ill preterm neonates is increasing. Therefore, a systematic review of the available data on dosing, efficacy and safety of AVP and terlipressin in this patient population appears beneficial.

Methods We will conduct a systematic review of the available evidence on the use of AVP and terlipressin for the treatment of hypotension or persistent pulmonary hypertension in preterm neonates. We will search Ovid MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, Web of Science and Google Scholar from inception to March 2021. Two reviewers will independently screen titles and abstracts, review the full text of eligible studies, extract data, assess the risk of bias and judge the certainty of the evidence. Our primary outcome will be an (1) improvement of end-organ perfusion after initiation of AVP or terlipressin and (2) mortality prior to discharge. Our secondary outcomes will include (1) major neurosensory abnormality and (2) the occurrence of adverse events.

Discussion The currently available evidence on the efficacy and safety of AVP and terlipressin in preterm neonates is limited. Yet, evidence on the pharmacology of these drugs and the pathophysiology of vasoplegic shock support the biological plausibility for their clinical effectiveness in this population. Therefore, we aim to address this gap concerning the use of vasopressin and terlipressin among critically ill preterm neonates.

Trial registration This protocol has been submitted for registration to the international database of prospectively registered systematic reviews (PROSPERO, awaiting registration number).

INTRODUCTION

Arginine vasopressin (AVP) is a potent endogenous peptide hormone that regulates extracellular volume and renal water excretion via vasopressin receptor 2 (V2R).¹ At supraphysiologic concentrations, AVP exerts moderate vasoconstrictor effects via vasopressin receptor 1 (V1R).² The contradictory actions of vasopressin, however, appear to be mainly related to the distribution pattern and function of receptors (vasoconstriction via V1R in vascular smooth muscle and vasodilation via

What is already known on this topic?

- Arginine vasopressin (AVP) and terlipressin are potent systemic vasoconstrictors and pulmonary vasodilators.
- The efficacy of AVP and terlipressin to treat septic shock and haemodynamic instability in adult and paediatric patients is well established.
- There is a lack of data on how to treat refractory shock, a leading cause of morbidity and mortality, in preterm neonates.

What this study hopes to add?

- Data on the efficacy of AVP and terlipressin for the treatment of hypotension and persistent pulmonary hypertension in critically ill preterm neonates.
- Data on the safety of AVP and terlipressin for the treatment of hypotension and persistent pulmonary hypertension in critically ill preterm neonates.
- Data on important evidence gaps in need of future research for optimal use of AVP and terlipressin in critically ill neonates with hypotension and persistent pulmonary hypertension.

V2R expressed in endothelium by NO formation).^{3–6}

The use of AVP to restore vascular tone in vasoplegic shock was described for the first time in 1997.⁷ Since then, a number of studies have illustrated the efficacy of AVP in catecholamine-resistant shock in adults and children, with limited data available for the use of AVP to treat neonatal catecholamine-resistant septic, cardiogenic shock and refractory persistent pulmonary hypertension.^{8–10} In 2006, Meyer *et al* reported the first use of AVP in six extremely low birthweight infants with catecholamine-refractory shock and acute renal injury.¹⁰ Following the administration of AVP, investigators observed a substantial increase in arterial blood pressure and urine output among three infants with septic shock and a



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For numbered affiliations see end of article.

Correspondence to

Dr Abdulrahman Salim Alsaadi; dr-abdul-alsaadi@hotmail.com



mortality rate of one out of three. However, among the infants with non-septic shock, blood pressure and urine output only improved briefly, and the mortality rate was three out of three.¹⁰

Similar to AVP, terlipressin, a synthetic long-acting analogue of vasopressin, has potent vasoconstrictor properties. Terlipressin, however, selectively binds to V1R and has a longer half-life and duration of action. Currently available data demonstrate that vasopressin has an elimination half-life of ≤ 10 min with onset of its pressor effect within 15 min that fades within 20 min after stopping the infusion. For terlipressin, the estimated half-life is up to 3 hours with time to peak plasma concentration of approximately 2 hours and duration of action of 4–6 hours.¹¹ Among adults and children with septic shock, terlipressin improves haemodynamic parameters and reduces the use of catecholamines. However, reports have also highlighted the controversial effects of terlipressin on survival, and also described tissue ischaemia as a possible adverse event.^{12–15}

In premature neonates treated in neonatal intensive care units (NICUs), fluid-refractory catecholamine-resistant shock remains a leading cause of morbidity and mortality.¹⁶ Hence, there is an immediate need for pharmacotherapeutic options that can target the intractable vasoplegia via alternative pathways. Evidence suggests that AVP and terlipressin have favourable haemodynamic profiles as they lead to a minimal decline in cardiac output, induce limited vasoconstriction in the pulmonary circulation and cause selective constriction of renal efferent over afferent arterioles.^{17–19} This data, along with reports of low levels of circulating AVP in patients with refractory shock, provide a biologic plausibility and support the use of these drugs by NICU clinicians.²⁰ This has resulted in a considerable increase in the use of AVP and its analogues in preterm neonates.^{21–22} Despite the promising outlook, the evidence on the efficacy and safety of AVP and its analogues remains controversial, particularly regarding the short-term and long-term adverse effects in preterm neonates.^{23–26} Reports of serious adverse events such as decreased cardiac index, peripheral cyanosis and digital ischaemia are among complications that require further investigation.²⁶ A recent systematic review and meta-analysis that examined the role of vasopressin and terlipressin in refractory shock in paediatric patients, reported improvements in haemodynamic indices but lack of benefit on mortality or length of hospital stay with a trend towards a higher risk for tissue ischaemia.²⁴ In critically ill preterm neonate with complex and poorly understood hormonal dysfunction, the risk of such undesired short-term and long-term adverse effects is of serious concern.^{21–23} In view of the increasing use of AVP and terlipressin in neonates of NICUs and high risk of serious adverse events, the need for enhancement of data on efficacy and safety of these drugs in this vulnerable population becomes clear.

Objective

We aim to conduct a systematic review of the available evidence on the dosing, efficacy, and safety of AVP and terlipressin in preterm neonates with hypotension or persistent pulmonary hypertension (box 1).

METHODS

Protocol registration

The protocol for this systematic review has been submitted to the international database of prospectively registered systematic reviews (PROSPERO, awaiting registration number). The development and reporting of the protocol followed the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol (PRISMA-P) guidelines.²⁷ The final review will also be reported according to the PRISMA guidelines.

Data sources and search strategy

We developed a search strategy in consultation with a professional librarian to comprehensively search Ovid MEDLINE (1964 to February 2021), EMBASE (1974 to March 2021), Web of Science (1900 to March 2021) and the Cochrane Central Register of Controlled Trials (CENTRAL) (online supplemental appendix A). This search strategy, containing database-specific subject headings and text word terms for concepts, was first developed in MEDLINE (Ovid interface) and was translated as appropriate for the other databases. We also plan to search the bibliographies of any relevant studies for additional references. Using Google Scholar, we will also seek out relevant studies that are not commercially published, such as conference abstracts, dissertations,

Box 1 PICO framework

Population: Preterm neonates born at less than 37 weeks' gestation with hypotension (defined as mean blood pressure less than gestational age or hypotension requiring fluid or vasoactive therapy) or persistent pulmonary hypertension.

Intervention: Arginine vasopressin or terlipressin administered intravenously, initiated at any time and for any duration as a primary or rescue treatment for hypotension or persistent pulmonary hypertension.

Comparator: Standard treatment, placebo or any other vasoactive agent.

Outcomes: (1) Improvement in end-organ perfusion defined as an increase in mean, diastolic or systolic blood pressure within 1 hour of the start of treatment, or an increase in urine output, a decrease in the need for inotropes, or a reduction in serum lactate within 12 hours of treatment initiation as identified in the primary studies, (2) mortality prior to discharge. Our secondary outcomes (1) major neurosensory disability defined as moderate to severe motor or cognitive impairment or severe visual or hearing impairment as identified in the primary study; and (2) the occurrence of adverse events defined as reports of peripheral tissue ischaemia, gastrointestinal events (occurrence of perforation, necrotising enterocolitis or gastrointestinal bleed), hepatic events, renal events or hyponatraemia as identified in the primary studies. (table 2).

Table 1 Data extraction form for primary studies

Study ID	
Title	
Author	
Country of study conduct	USA UK Canada Australia Other
Study characteristics	
Aim	
Design	Randomised controlled trial Non-randomised experimental study Cohort study Cross-sectional study Case-control study Case series Case report Other
Start date	
End date	
Funding source	
Conflict of interest	
Participant characteristics	
Population description	
Inclusion criteria	
Exclusion criteria	
Sample size (n)	
Birth weight (grams)	
Gestational age (weeks)	
Postnatal age (weeks)	
Underlying condition	
Comorbidities	
Concurrent medications	
Intervention/exposure details	
AVP or terlipressin dosing (mg/kg/dose)	
AVP or terlipressin treatment duration (days)	
AVP or terlipressin route of administration	
Control details	
Pharmacotherapy	Dopamine Dobutamine Epinephrine Norepinephrine Placebo Other
Outcomes	
Primary outcomes	
Improvement in end organ perfusion details	<ul style="list-style-type: none"> ▶ SBP ▶ DBP ▶ MBP ▶ Urine output ▶ Inotropic support ▶ Serum lactate
Mortality	▶ Death before discharge

Continued

Table 1 Continued

Study ID	
Secondary outcomes*	
Major neurosensory disability	Neurosensory disability <ul style="list-style-type: none"> ▶ Moderate to severe motor or cognitive impairment ▶ Severe visual or hearing impairment
Occurrence of adverse events	Adverse events <ul style="list-style-type: none"> ▶ Peripheral tissue ischaemia ▶ Gastrointestinal events ▶ Renal events ▶ Hepatic events ▶ Hyponatraemia

*The secondary outcomes will be defined as reported in the primary studies. AVP, arginine vasopressin; DBP, diastolic blood pressure; MBP, mean blood pressure; SBP, systolic blood pressure.

policy documents and book chapters. We will not apply any language or study design limitations. Animal studies and duplicate studies will be excluded. A peer-review of our strategy using the Peer Review for Electronic Search Strategies guideline was completed by a professional librarian²⁸ (online supplemental appendix B).

Eligibility criteria

All interventional and observational original research studies, including randomised controlled trials (RCTs), quasi RCTs, prospective and retrospective cohort studies, descriptive studies, case series and case reports and conference abstracts describing the use of AVP or terlipressin as primary or rescue treatment for hypotension or persistent pulmonary hypotension in hospitalised preterm neonates born at less than 37 weeks' gestation will be eligible for inclusion. We will include studies with mixed populations (term and preterm neonates) as long as separate data for preterm neonates are available. Studies will be included irrespective of the dose, administration frequency and duration of AVP or terlipressin treatment. In studies with a control group, the provided intervention(s), placebo or standard practice will be the comparator. In studies with no comparator group, the observational report of the dosing, efficacy and safety of AVP or terlipressin during the study will be recorded. Studies reporting the use of AVP or terlipressin for indications other than hypotension or persistent pulmonary hypotension will be excluded.

Study selection and data extraction

We will use Covidence as the primary screening and data extraction tool. The titles and abstracts of retrieved studies will be screened by two independent reviewers (ASA and KS) to assess their eligibility. The eligible studies will then be reviewed in duplicate at the full-text level by the same reviewers. A PRISMA flow diagram will be created to illustrate the study selection process. Two reviewers (ASA and KS) will independently conduct data extraction from the full-text studies meeting the inclusion criteria using



a standardised data extraction form developed in Covidence (table 1). Any disagreements throughout the study selection and data extraction process will be resolved through discussion with a third reviewer (SS-Z).

Assessment of risk of bias and certainty of evidence

Two independent reviewers (ASA and KS) will conduct a duplicate qualitative assessment of studies using a standardised risk of bias assessment tool appropriate for each study design. The Cochrane risk-of-bias assessment tool for randomised trials (RoB 2), the Newcastle-Ottawa Quality Assessment Scale for cohort and case-control studies and the modified Newcastle-Ottawa scale for cross-sectional studies will be used as appropriate.^{29 30} The quality of descriptive studies and case reports will be evaluated using the Checklist for Analytical Cross-Sectional Studies and Case Reports by the Joanna Briggs Institute.³¹ The same independent reviewers will judge the certainty of the evidence using the Cochrane Grading of Recommendations Assessment, Development, and Evaluation approach.³² Any disagreement will be solved through discussion with a third reviewer (SS-Z).

Patient and public involvement

Patients are not directly involved in the design or conduct of this study. We will plan for public involvement mostly concerned with the dissemination of the results of the review and knowledge translation on the completion of our review, to contribute to wider dissemination of the review to patients and public. We will plan to provide clear explanation of the concept and develop a glossary of research terms specific to our review. We will also provide detailed explanation of the purpose of patient and public involvement and the expectations of their roles.³³

Outcomes and variables

Our primary outcomes are (1) improvement in end-organ perfusion defined as an increase in mean, diastolic or systolic blood pressure within 1 hour of the start of treatment, or an increase in urine output, a decrease in the need for inotropes or a reduction in serum lactate within 12 hours of treatment initiation, as defined by the authors in the primary studies, and (2) mortality prior to discharge. Our secondary outcomes are (1) major neurosensory disability defined as moderate to severe motor or cognitive impairment or severe visual or hearing impairment as identified in the primary study; and (2) the occurrence of adverse events defined as peripheral tissue ischaemia, gastrointestinal events (occurrence of perforation, necrotising enterocolitis or gastrointestinal bleed), hepatic events, renal events or hyponatraemia as identified in the primary studies (table 2).

DISCUSSION

The increased use of AVP and terlipressin in preterm neonates illustrates the need for alternative pharmacotherapeutic options for critically ill neonates. The currently available evidence on the pharmacology of

Table 2 Primary and secondary outcome variables

Primary outcomes	
Primary outcomes	Primary outcome variables
Improvement in end organ perfusion	<ul style="list-style-type: none"> ▶ SBP ▶ DBP ▶ MBP ▶ Urine output ▶ Inotropic support ▶ Serum lactate
Mortality	▶ Death before discharge
Secondary outcomes	
Major neurosensory disability	Neurosensory disability
	<ul style="list-style-type: none"> ▶ Moderate to severe motor or cognitive impairment ▶ Severe visual or hearing impairment
Occurrence of adverse events	Adverse events <ul style="list-style-type: none"> ▶ Peripheral tissue ischaemia ▶ Gastrointestinal events ▶ Renal events ▶ Hepatic events ▶ Hyponatraemia

The secondary outcomes will be defined as reported in the primary studies.
DBP, diastolic blood pressure; MBP, mean blood pressure; SBP, systolic blood pressure.

these drugs and the pathophysiology of vasoplegic shock support the biological plausibility for their clinical effectiveness in critically ill preterm neonates. Nevertheless, the available data on the efficacy and safety of AVP and terlipressin in preterm neonates remain limited and in need for a comprehensive review. A systematic review using explicit and reproducible methods helps to produce rigorous and high-quality evidence synthesis and identify evidence gaps that could be the subject of future research. The difficulty in performing clinical trials in preterm neonates limits their evidence-based pharmacological treatment. We aim to complete a high-quality synthesis of the entirety of available data concerning the use of vasopressin and terlipressin among this vulnerable population in order to further the evidence on this important topic.

Author affiliations

¹Department of Pediatrics, McMaster University, Hamilton, Ontario, Canada

²Faculty of Health Sciences, School of Nursing, McMaster University, Hamilton, Ontario, Canada

³Department of Pharmacy, Hamilton, Ontario, Canada

⁴Department of Pediatrics and Pharmacology and Pharmacometric, University Children's Hospital Basel, Basel, Switzerland

⁵Division of Clinical Pharmacology, Children's National Hospital, Washington, DC, USA

⁶Intensive Care and Department of Pediatric Surgery, Erasmus MC Sophia Children's Hospital, Rotterdam, Netherlands

⁷Department of Pediatrics, Princess Norah Bint Abdulrahman University, Riyadh, Saudi Arabia

⁸Division of Neonatology, Department of Pediatrics, King Abdullah bin Abdulaziz University Hospital, King Abdullah bin Abdulaziz University Hospital, Riyadh, Saudi Arabia

Contributors ASA and SS-Z contributed to the conception and design of the protocol. ASA, KS, AR, JVDA and SS-Z contributed to planning the search strategy. AR, SS-Z and JVDA contributed to the critical review of the protocol and review of its scientific content.

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Competing interests I know one of the authors personally and professionally (JVDA). My relationship with this author had no influence on my review.

Patient consent for publication Not required.

Ethics approval No ethical approval is required as this review will be based on the analysis of publicly available evidence. No personal data of patients will be required. The results of the review will be submitted to a peer-reviewed journal, focusing on paediatrics or neonatology, for publication. We also plan to present results at academic conferences.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository.

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ORCID iDs

Abdulrahman Salim Alsaadi <http://orcid.org/0000-0002-2161-1965>

Samira Samiee-Zafarghandy <http://orcid.org/0000-0001-8385-0657>

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California's T21 Law and Adolescents' Tobacco and Nicotine Use: Appendix 1

1

Appendix 1

Associations of California's T21 Law with Changes in Trends in Adolescents' Tobacco and Nicotine Use

(California Healthy Kids Survey Details and Supplemental Tables)

California Health Kids Survey

We analyzed data from a statewide sample of 7th, 9th, and 11th graders from public schools in California that participated in the California Healthy Kids Survey (CHKS) from 2010-11 to 2017-18. For a given school, the CHKS data are collected every other school year. Data collection is staggered, however, such that it occurs in approximately half the schools each school year. Data are collected in the fall each school year for some schools and in the spring for others. CHKS is managed by WestEd, a non-profit research organization, in collaboration with the California Department of Education (CDE).[1] School districts were formerly required to participate in CHKS to comply with the No Child Left Behind Act, Title IV, and are now required to participate if they receive funding under the State Tobacco Use Prevention Education Program. Otherwise CHKS participation is voluntary. Minimum CHKS requirements include participation by students in 7th, 9th, and 11th grades with a targeted response rate of 70% using passive or active parental consent. Based on CDE data, we estimate for the 2017-2018 and 2018-2019 survey years that 71% of schools with 7th, 9th, and 11th grades participated. To get complete student response rates would require us to access individual school reports for each year across all the years and schools. However, using a random sample of high schools from 48 school districts in 19 counties across several years we found the average response rates were 73% for 9th graders and 68% for 11th graders, with an overall rate of 71%.

Sample characteristics. The study sample includes data collected from 2,956,054 students who provided complete data on tobacco and nicotine use and other study variables. Because the survey did not include items about e-cigarette use until 2013, fewer students are included in those analyses (N = 2,069,487). Of CHKS participants in the study sample, 51% were female, 49% were Latinx, 22% identified as non-Latinx White, 1% as American

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Indian/Alaska Native, 2% as Native Hawaiian/Pacific Islander, 11% as Asian American, 4% as Black or African American, and 12% as more than one race or unknown race/ethnicity. About 34% of participating students in the study sample were in 7th grade, 35% in 9th grade, and 31% in 11th grade.

Measures

Cigarette smoking. Students were asked how many times they had smoked a whole cigarette in their lifetime with 6 responses from “0 times” to “7 or more times”. They were also asked how many days they smoked cigarettes in the past 30 days, with 6 responses from “0 days” to “20 to 30 days”. Because of the skewed distribution of the responses, we dichotomized these measures (1 = any lifetime/past month use).

Smokeless tobacco use. Students were asked how many times in their lifetime they used smokeless tobacco and on how many days they used smokeless tobacco or snuff in the past 30 days using the same scales as for cigarette smoking. These measures were dichotomized (1 = any lifetime/past month use).

E-cigarette use. From the school year 2013-2014 onward, students were asked how many times they had used electronic cigarettes in their lifetime and past 30-days using the same scales as for cigarette smoking and smokeless tobacco use. We dichotomized these measures for the analyses (1 = any lifetime/past month use).

Demographics. Students were asked their sex, grade, race, and ethnicity. Sex was coded as a dummy variable (1 = Female). Grade was coded into two dummy variables, with 7th grade as the reference group. Race/ethnicity was coded as a series of dummy variables, with non-Latinx White as the reference group.

California's T21 Law and Adolescents' Tobacco and Nicotine Use: Appendix 1

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Table S1 Results of Mixed Effects Logistic Regressions Testing Associations Between California's T21 Law and Cigarette Smoking: Changes in Slopes (OR, 95% CI)

Predictor	Lifetime Smoking		Past 30-Day Smoking	
	Model 1	Model 2	Model 1	Model 2
T21	0.85 (0.73, 0.98)*	0.93 (0.69, 1.26)	1.26 (1.01, 1.56)*	1.73 (1.13, 2.64)**
Survey year	0.82 (0.81, 0.82)***	0.85 (0.84, 0.85)***	0.82 (0.81, 0.82)***	0.84 (0.83, 0.84)***
9 th Grade ¹	3.35 (3.21, 3.51)***	3.35 (3.21, 3.50)***	2.17 (2.06, 2.27)***	2.16 (2.06, 2.27)***
11 th Grade ¹	5.93 (5.68, 6.20)***	5.94 (5.68, 6.20)***	3.29 (3.13, 3.45)***	3.28 (3.13, 3.44)***
Female	0.77 (0.76, 0.78)***	0.77 (0.76, 0.78)***	0.722 (0.71, 0.73)***	0.72 (0.71, 0.73)***
American Indian/Alaska Native ²	1.62 (1.57, 1.68)***	1.65 (1.52, 1.79)***	1.70 (1.63, 1.78)***	1.57 (1.43, 1.73)***
Native Hawaiian/Pacific Islander ²	1.12 (1.09, 1.15)***	1.42 (1.32, 1.52)***	1.12 (1.08, 1.17)***	1.32 (1.20, 1.45)***
Asian American ²	0.47 (0.46, 0.48)***	0.57 (0.54, 0.59)***	0.49 (0.48, 0.50)***	0.59 (0.55, 0.62)***
African American ²	0.89 (0.87, 0.91)***	1.06 (1.00, 1.12)*	1.08 (1.05, 1.11)***	1.12 (1.05, 1.20)***
Multi-racial/unknown ²	1.10 (1.08, 1.12)***	1.26 (1.21, 1.30)***	1.08 (1.06, 1.10)***	1.14 (1.09, 1.19)***
Latinx ²	1.14 (1.13, 1.16)***	1.42 (1.38, 1.45)***	1.07 (1.05, 1.09)***	1.22 (1.18, 1.26)***
T21 x Survey Year	1.02 (1.00, 1.04)*	1.01 (0.97, 1.05)	0.97 (0.94, 1.00)*	0.93 (0.88, 0.98)**
T21 x American Indian/Alaska Native	–	3.11 (0.94, 10.32)	–	2.92 (0.61, 13.86)
T21 x Native Hawaiian/Pacific Islander	–	0.85 (0.25, 2.81)	–	1.31 (0.24, 7.23)
T21 x Asian American	–	0.78 (0.38, 1.60)	–	0.44 (0.16, 1.23)
T21 x African American	–	1.42 (0.61, 3.30)	–	1.88 (0.61, 5.75)
T21 x Multi-racial/unknown	–	1.06 (0.63, 1.80)	–	0.84 (0.40, 1.77)
T21 x Latinx	–	0.89 (0.62, 1.26)	–	0.60 (0.36, 1.00)*
Survey Year x American Indian/Alaska Native	–	1.00 (0.98, 1.02)	–	1.02 (1.00, 1.05)

Table Continues

California's T21 Law and Adolescents' Tobacco and Nicotine Use: Appendix 1

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Predictor	Lifetime Smoking		Past 30-Day Smoking	
	Model 1	Model 2	Model 1	Model 2
Survey Year x Native Hawaiian/Pacific Islander	–	0.94 (0.92, 0.95)***	–	0.95 (0.93, 0.98)***
Survey Year x Asian American	–	0.95 (0.94, 0.96)***	–	0.95 (0.93, 0.96)***
Survey Year x African American	–	0.96 (0.94, 0.97)***	–	0.99 (0.98, 1.01)
Survey Year x Multi-racial/unknown	–	0.97 (0.96, 0.98)***	–	0.99 (0.97, 1.00)*
Survey Year x Latinx	–	0.95 (0.94, 0.96)***	–	0.97 (0.96, 0.98)***
T21 x Survey Year X American Indian/Alaska Native	–	0.86 (0.73, 1.01)	–	0.86 (0.70, 1.06)
T21 x Survey Year X Native Hawaiian/Pacific Islander	–	1.05 (0.89, 1.23)	–	0.99 (0.79, 1.24)
T21 x Survey Year X Asian American	–	1.05 (0.95, 1.15)	–	1.14 (1.00, 1.31)
T21 x Survey Year X African American	–	0.95 (0.85, 1.07)	–	0.91 (0.78, 1.05)
T21 x Survey Year X Multi-racial/unknown	–	0.99 (0.93, 1.07)	–	1.02 (0.92, 1.13)
T21 x Survey Year X Latinx	–	1.02 (0.97, 1.07)	–	1.07 (1.00, 1.14)

¹Reference category is 7th grade.

²Reference category is non-Latinx White.

* $p < 0.05$ ** $p < .01$ *** $p < 0.001$

California's T21 Law and Adolescents' Tobacco and Nicotine Use: Appendix 1

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Table S2 Results of Mixed Effects Logistic Regressions Testing Associations of California's T21 Law with Tobacco and Nicotine Use by Race and Ethnicity: Change in Slopes¹

Racial/Ethnic Group	Lifetime Smoking		Past 30-Day Smoking	
	OR	95% CI	OR	95% CI
Non-Latinx White	1.01	0.97, 1.05	0.93**	0.88, 0.98
American Indian/Alaska Native	0.87	0.74, 1.01	0.80*	0.65, 0.98
Native Hawaiian/Pacific Islander	1.06	0.91, 1.24	0.92	0.74, 1.14
Asian American	1.06	0.97, 1.15	1.06	0.94, 1.20
African American	0.96	0.86, 1.07	0.84*	0.73, 0.97
Multi-Racial/Unknown	1.00	0.95, 1.06	0.95	0.87, 1.03
Latinx	1.03	1.00, 1.05	0.99	0.96, 1.03
	Lifetime Smokeless Use		Past Month Smokeless Use	
	OR	95% CI	OR	95% CI
Non-Latinx White	0.93**	0.89, 0.98	0.90**	0.84, 0.97
American Indian/Alaska Native	0.96	0.80, 1.14	0.84	0.67, 1.06
Native Hawaiian/Pacific Islander	0.94	0.77, 1.15	0.90	0.69, 1.17
Asian American	1.04	0.92, 1.18	1.00	0.86, 1.17
African American	1.01	0.89, 1.14	0.80**	0.69, 0.93
Multi-Racial/Unknown	0.99	0.92, 1.06	0.86**	0.78, 0.96
Latinx	1.01	0.97, 1.04	0.99	0.94, 1.04
	Lifetime E-Cigarette Use		Past Month E-Cigarette Use	
	OR	95% CI	OR	95% CI
Non-Latinx White	1.17***	1.14, 1.21	1.88***	1.81, 1.96
American Indian/Alaska Native	0.97	0.85, 1.09	1.67***	1.42, 1.97
Native Hawaiian/Pacific Islander	1.08	0.97, 1.19	1.85***	1.60, 2.14
Asian American	1.09**	1.03, 1.15	1.98***	1.82, 2.16
African American	0.88***	0.82, 0.94	1.39***	1.25, 1.54
Multi-Racial/Unknown	1.04*	1.00, 1.08	1.75***	1.65, 1.85
Latinx	1.02	1.00, 1.04	1.79***	1.74, 1.83

¹All models controlled for survey year, grade in school, race, ethnicity, and sex. The individual group effects of T21 were estimated using models with the race/ethnicity x T21 product terms, but no T21 x survey year term.

* $p < 0.05$ ** $p < .01$ *** $p < 0.001$.

California's T21 Law and Adolescents' Tobacco and Nicotine Use: Appendix 1

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Table S3 Results of Mixed Effects Logistic Regressions Testing Associations Between California's T21 Law and Smokeless Tobacco Use: Changes in Slopes (OR, 95% CI) (OR, 95% CI)

Predictor	Lifetime Smokeless Use		Past Month Smokeless Use	
	Model 1	Model 2	Model 1	Model 2
T21	1.10 (0.91, 1.33)	1.59 (1.11, 2.28)*	1.46 (1.12, 1.91)**	1.91 (1.12, 3.26)*
Survey year	0.88 (0.88, 0.89)***	0.90 (0.89, 0.90)***	0.88 (0.88, 0.89)***	0.90 (0.90, 0.91)***
9 th Grade ¹	1.86 (1.78, 1.94)***	1.85 (1.78, 1.94)***	1.54 (1.47, 1.61)***	1.54 (1.47, 1.61)***
11 th Grade ¹	2.95 (2.83, 3.08)***	2.95 (2.83, 3.08)***	1.99 (1.90, 2.08)***	1.99 (1.90, 2.08)***
Female	0.45 (0.44, 0.45)***	0.45 (0.44, 0.45)***	0.44 (0.43, 0.45)***	0.44 (0.43, 0.45)***
American Indian/Alaska Native ²	1.65 (1.59, 1.72)***	1.67 (1.52, 1.84)***	1.98 (1.88, 2.08)***	1.89 (1.67, 2.13)***
Native Hawaiian/Pacific Islander ²	0.98 (0.94, 1.03)	1.06 (0.96, 1.17)	1.20 (1.14, 1.27)***	1.27 (1.12, 1.45)***
Asian American ²	0.40 (0.39, 0.41)***	0.48 (0.45, 0.52)***	0.50 (0.48, 0.52)***	0.59 (0.54, 0.65)***
African American ²	1.04 (1.01, 1.07)*	1.14 (1.07, 1.23)***	1.54 (1.48, 1.59)***	1.72 (1.58, 1.87)***
Multi-racial/unknown ²	0.95 (0.93, 0.97)***	0.97 (0.92, 1.01)	1.02 (1.00, 1.05)	1.07 (1.00, 1.14)*
Latinx ²	0.93 (0.91, 0.94)***	1.01 (0.97, 1.04)	1.07 (1.05, 1.10)***	1.22 (1.16, 1.27)***
T21 x Survey Year	0.98 (0.96, 1.01)	0.93 (0.89, 0.98)**	0.94 (0.90, 0.98)***	0.90 (0.84, 0.97)**
T21 x American Indian/Alaska Native	–	0.84 (0.21, 3.29)	–	1.56 (0.25, 9.44)
T21 x Native Hawaiian/Pacific Islander	–	1.02 (0.21, 4.84)	–	1.14 (0.15, 8.77)
T21 x Asian American	–	0.52 (0.20, 1.38)	–	0.59 (0.17, 2.12)
T21 x African American	–	0.57 (0.21, 1.53)	–	2.56 (0.74, 8.81)
T21 x Multi-racial/unknown	–	0.64 (0.33, 1.24)	–	1.40 (0.55, 3.57)
T21 x Latinx	–	0.60 (0.39, 0.92)*	–	0.54 (0.29, 1.01)
Survey Year x American Indian/Alaska Native	–	1.00 (0.97, 1.02)	–	1.02 (0.98, 1.05)

Table Continues

California's T21 Law and Adolescents' Tobacco and Nicotine Use: Appendix 1

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Predictor	Lifetime Smokeless Use		Past Month Smokeless Use	
	Model 1	Model 2	Model 1	Model 2
Survey Year x Native Hawaiian/Pacific Islander	–	0.98 (0.95, 1.01)	–	0.98 (0.95, 1.02)
Survey Year x Asian American	–	0.95 (0.93, 0.96)***	–	0.95 (0.92, 0.97)***
Survey Year x African American	–	0.98 (0.96, 0.99)**	–	0.97 (0.95, 0.99)*
Survey Year x Multi-racial/unknown	–	1.00 (0.98, 1.01)	–	0.99 (0.97, 1.01)
Survey Year x Latinx	–	0.98 (0.97, 0.98)***	–	0.97 (0.95, 0.98)***
T21 x Survey Year X American Indian/Alaska Native	–	1.03 (0.86, 1.23)	–	0.93 (0.73, 1.19)
T21 x Survey Year X Native Hawaiian/Pacific Islander	–	1.01 (0.82, 1.24)	–	1.00 (0.76, 1.31)
T21 x Survey Year X Asian American	–	1.12 (0.98, 1.27)	–	1.11 (0.94, 1.31)
T21 x Survey Year X African American	–	1.08 (0.95, 1.23)	–	0.89 (0.75, 1.05)
T21 x Survey Year X Multi-racial/unknown	–	1.06 (0.97, 1.16)	–	0.96 (0.85, 1.09)
T21 x Survey Year X Latinx	–	1.08 (1.02, 1.14)*	–	1.10 (1.01, 1.20)*

¹Reference category is 7th grade.

²Reference category is non-Latinx White.

* $p < 0.05$ ** $p < .01$ *** $p < 0.001$

California's T21 Law and Adolescents' Tobacco and Nicotine Use: Appendix 1

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Table S4 Results of Mixed Effects Logistic Regressions Testing Associations Between California's T21 Law and E-Cigarette Use: Changes in Slopes (OR, 95% CI)

Predictor	Lifetime E-Cigarette Use		Past Month E-Cigarette Use	
	Model 1	Model 2	Model 1	Model 2
T21	0.48 (0.44, 0.54)***	0.24 (0.20, 0.30)***	0.01 (0.01, 0.02)***	0.01 (0.01, 0.02)***
Survey year	1.00 (0.99, 1.00)	1.01 (1.00, 1.02)*	0.80 (0.80, 0.81)***	0.85 (0.84, 0.87)***
9 th Grade ¹	2.65 (2.57, 2.74)***	2.66 (2.57, 2.75)***	2.13 (2.05, 2.22)***	2.14 (2.06, 2.22)***
11 th Grade ¹	4.20 (4.06, 4.34)***	4.21 (4.07, 4.35)***	2.84 (2.73, 2.96)***	2.85 (2.74, 2.97)***
Female	0.90 (0.90, 0.91)***	0.90 (0.90, 0.91)***	0.84 (0.83, 0.84)***	0.84 (0.83, 0.84)***
American Indian/Alaska Native ²	1.27 (1.23, 1.32)***	1.80 (1.40, 2.32)***	1.38 (1.32, 1.44)***	2.08 (1.52, 2.84)***
Native Hawaiian/Pacific Islander ²	1.24 (1.20, 1.28)***	1.44 (1.17, 1.76)**	1.20 (1.15, 1.24)***	1.93 (1.48, 2.52)***
Asian American ²	0.48 (0.47, 0.49)***	0.58 (0.52, 0.66)***	0.45 (0.44, 0.46)***	0.72 (0.60, 0.85)***
African American ²	0.92 (0.90, 0.94)***	0.94 (0.80, 1.09)	0.90 (0.87, 0.92)***	1.53 (1.25, 1.87)***
Multi-racial/unknown ²	1.12 (1.11, 1.14)***	1.25 (1.13, 1.38)***	1.05 (1.03, 1.07)***	1.33 (1.17, 1.52)***
Latinx ²	1.31 (1.30, 1.32)***	1.62 (1.51, 1.73)**	1.17 (1.15, 1.18)***	2.10 (1.92, 2.29)***
T21 x Survey Year	1.06 (1.04, 1.07)***	1.17 (1.14, 1.21)***	1.81 (1.78, 1.86)***	1.88 (1.81, 1.96)***
T21 x American Indian/Alaska Native	–	4.59 (1.85, 11.40)***	–	2.21 (0.65, 7.52)
T21 x Native Hawaiian/Pacific Islander	–	1.81 (0.84, 3.92)	–	1.16 (0.38, 3.48)
T21 x Asian American	–	1.72 (1.11, 2.67)*	–	0.70 (0.35, 1.38)
T21 x African American	–	6.91 (4.03, 11.85)***	–	8.57 (3.87, 18.96)***
T21 x Multi-racial/unknown	–	2.22 (1.57, 3.14)***	–	1.57 (0.96, 2.56)
T21 x Latinx	–	2.51 (1.98, 3.19)***	–	1.34 (0.96, 1.86)
Survey Year x American Indian/Alaska Native	–	0.94 (0.89, 0.99)*	–	0.94 (0.88, 1.00)

Table Continues

California's T21 Law and Adolescents' Tobacco and Nicotine Use: Appendix 1

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Predictor	Lifetime E-Cigarette Use		Past Month E-Cigarette Use	
	Model 1	Model 2	Model 1	Model 2
Survey Year x Native Hawaiian/Pacific Islander	–	0.98 (0.94, 1.02)	–	0.92 (0.87, 0.97)**
Survey Year x Asian American	–	0.97 (0.95, 0.99)**	–	0.92 (0.89, 0.96)***
Survey Year x African American	–	1.01 (0.98, 1.04)	–	0.92 (0.89, 0.96)***
Survey Year x Multi-racial/unknown	–	0.99 (0.97, 1.01)	–	0.97 (0.95, 1.00)*
Survey Year x Latinx	–	0.98 (0.96, 0.99)***	–	0.90 (0.89, 0.93)***
T21 x Survey Year X American Indian/Alaska Native	–	0.82 (0.73, 0.93)**	–	0.89 (0.75, 1.05)
T21 x Survey Year X Native Hawaiian/Pacific Islander	–	0.92 (0.83, 1.02)	–	0.98 (0.84, 1.14)
T21 x Survey Year X Asian American	–	0.93 (0.88, 0.99)*	–	1.05 (0.96, 1.15)
T21 x Survey Year X African American	–	0.75 (0.70, 0.81)***	–	0.74 (0.66, 0.82)***
T21 x Survey Year X Multi-racial/unknown	–	0.89 (0.85, 0.93)***	–	0.93 (0.87, 0.99)*
T21 x Survey Year X Latinx	–	0.87 (0.84, 0.89)***	–	0.95 (0.91, 0.99)*

¹Reference category is 7th grade.

²Reference category is non-Latinx White.

* $p < 0.05$ ** $p < .01$ *** $p < 0.001$

California's T21 Law and Adolescents' Tobacco and Nicotine Use: Appendix 1

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Reference

California Department of Education. California Healthy Kids Survey 2020.
<https://www.cde.ca.gov/ls/he/at/chks.asp>