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Child-resistant and tamper-resistant packaging: A systematic review to inform tobacco packaging regulation

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Abstract

Objective—We aimed to investigate the effects of special packaging (child-resistant, adult-friendly) and tamper-resistant packaging on health and behavioral outcomes in order to identify research gaps and implications for packaging standards for tobacco products.

Methods—We searched seven databases for keywords related to special and tamper-resistant packaging, consulted experts, and reviewed citations of potentially relevant studies. 733 unique papers were identified. Two coders independently screened each title and abstract for eligibility. They then reviewed the full text of the remaining papers for a second round of eligibility screening. Included studies investigated a causal relationship between type of packaging or packaging regulation and behavioral or health outcomes and had a study population composed of consumers. Studies were excluded on the basis of publication type, if they were not peer-reviewed, and if they had low external validity. Two reviewers independently coded each paper for study and methodological characteristics and limitations. Discrepancies were discussed and resolved.

Results—The review included eight studies: four assessing people's ability to access the contents of different packaging types and four evaluating the impact of packaging requirements on health-related outcomes. Child-resistant packaging was generally more difficult to open than non-child-resistant packaging. Child-resistant packaging requirements have been associated with reductions in child mortality.

Conclusions—Child-resistant packaging holds the expectation to reduce tobacco product poisonings among children under six.

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Keywords

Child safety; Child-resistant; Product packaging; Special packaging; Tamper-resistant

1. Introduction

Every year in the United States there are an average of 50,000 cases of unintentional poisonings among children under age six years (Centers for Disease Control and Prevention, 2013), and a significant proportion of these poisonings are related to tobacco products. From 2006 through 2008, the National Poison Data System reported 13,705 cases of tobacco product ingestion by children under six (Connolly et al., 2010). During these years, ingested tobacco products included cigarettes, smokeless tobacco (chewing tobacco and snuff), and cigars (Connolly et al., 2010).

The marketplace of tobacco products is ever changing, and novel tobacco products such as dissolvables, snus, and electronic cigarettes (e-cigarettes or ENDS – electronic nicotine delivery devices) have raised new concerns about poisoning, given their potential appeal to children.

Some dissolvable products, like Camel Orbs®, have a candy-like appearance and come in flavors like mint and cinnamon (Wilson, 2010). Snus, another oral tobacco product, is available in flavors like “frost” and “winterchill” (TobaccoProducts.Org, 2010). Snus is a traditional Swedish smokeless tobacco product made from moist, finely ground tobacco and sold in small sachets or in loose form (National Cancer Institute, 2014). E-liquids, or the liquids used in e-cigarette devices, are offered in fruit and sweet flavors (e.g., strawberry banana smoothie, pink lemonade, caramel apple fritter) (Popular E-Liquid, 2016). These tobacco products have all been linked to poisonings in children (Connolly et al., 2010; Forrester, 2015; Vakkalanka et al., 2014).

E-liquids and other e-cigarette components have received particular attention, given the growing popularity of e-cigarettes (Arrazola et al., 2015; Pepper and Brewer, 2014), the April 2015 U.S. death of a toddler due to e-liquid ingestion (Clukey, 2015), and the rapid increase in poisoning cases due to e-cigarette exposure (Forrester, 2015; Vakkalanka et al., 2014; Chatham-Stephens et al., 2014). Chatham-Stephens et al. (2014) analyzed e-cigarette and cigarette-related calls made to U.S. poison centers from 2010 to 2014. E-cigarette exposures represented a growing proportion of these calls, from 0.3% in September 2010 to about 42% in 2014. Most e-cigarette exposures have been reported as ingestions (Forrester, 2015; Durmowicz, 2014) and for children under six years (Vakkalanka et al., 2014; Chatham-Stephens et al., 2014; Ordonez et al., 2015). Negative health effects associated with e-cigarette exposure have included vomiting, nausea, eye irritation, headaches, and dizziness (Chatham-Stephens et al., 2014; Ordonez et al., 2015). The U.S. Food and Drug Administration’s adverse event database, which includes consumers’ complaints associated with e-cigarettes, has also reported the death of an infant due to choking on an e-cigarette cartridge (Durmowicz, 2014).

In response to this public health threat, some manufacturers of e-cigarettes, dissolvables, and snus have voluntarily packaged their products in child-resistant containers (Wilson, 2010; Buettner-Schmidt et al., 2016; Nikitin et al., 2016; Rosetta, 2009). E-cigarette liquids have been reported to include press-and-turn closures resembling those used for aspirin (Buettner-Schmidt et al., 2016; Nikitin et al., 2016). At least one tobacco product manufacturer has claimed that its dissolvable packaging is child-resistant (Connolly et al., 2010). In general though, e-liquids have been sold in containers that are not considered child-resistant (Chatham-Stephens et al., 2016; Kamboj et al., 2016).

Policymakers at the local, state, federal, and global levels have also begun implementing legislation requiring child-resistant packaging for liquids and occasionally gels, cartridges, or other e-cigarette paraphernalia (114th Congress, 2015; Frey and Tilburg, 2016; Bear River Board of Health, 2014; European Parliament and the Council of the European Union, 2014). In July 2015 the U.S. Food and Drug Administration issued an Advance Notice of Proposed Rulemaking soliciting information to guide regulatory development around child-resistant packaging for nicotine liquid and other tobacco products (e.g., gels, dissolvables) (U.S. Department of Health and Human Services, 2015). In January 2016 *special packaging* standards, which had been in place for household substances, were expanded to include liquid nicotine through the Child Nicotine Poisoning Prevention Act (114th Congress, 2015). Special packaging is defined as packaging that is “significantly difficult for children under 5 years of age to open or obtain a toxic or harmful amount of the substance contained therein within a reasonable time and not difficult for normal adults to use properly” (Code of Federal Regulations, 1973).

Another dimension of packaging distinct from special packaging but potentially relevant to packaging standards for tobacco products is resistance to tampering. Tamper-resistant packaging, which is required for over-the-counter drugs, aims to prevent the post-manufacture altering of products and to enable consumers to determine easily whether or not their product may have been altered (e.g., seal is missing from medication container) (Code of Federal Regulations, 2016). In contrast to special packaging, tamper-resistant packaging, to our knowledge, has not been mentioned in news stories or policies related to tobacco products. However, given the poor quality control exhibited by some e-cigarette manufacturers (Cobb et al., 2010; Lisko et al., 2015), policymakers may want to consider including tamper-resistant design features as one way to address quality control in packaging.

To help inform ongoing and future legislative and regulatory efforts, we conducted a systematic review to investigate the effects of special and tamper-resistant packaging on the health and behavioral outcomes of individuals. We aimed to identify research gaps and implications for packaging standards for tobacco products. For the purpose of this review, we use the terms “child-resistant” and “special packaging” interchangeably.

2. Methods

2.1. Search strategy

We developed two search strings, one containing keywords related to special packaging and one containing words related to tamper-resistant packaging. Through an iterative process, we analyzed the results generated by each string and added to and refined the strings to capture relevant articles and to reduce the number of irrelevant articles. We used and adapted, as necessary, the search strings to search for literature in seven databases: Academic Search Complete, Business Source Complete, CINAHL Plus with Full Text, Embase, PubMed, SciFinder, and Web of Science. The search strings for each database and the overall review protocol are available from the corresponding author. An example of a final PubMed search string is ((Child-resistant[TIAB] OR "child resistant"[TIAB] OR child-proof[TIAB] OR childproof[TIAB] OR "child proof"[TIAB] OR "safety packaging"[TIAB] OR "special packaging"[TIAB] OR "safety caps"[TIAB] OR "safety cap"[TIAB]) AND ("Poisoning/prevention and control"[MH] OR "drug packaging"[TIAB] OR "packaging materials"[TIAB] OR "abuse deterrent"[TIAB] OR "abuse liability"[TIAB] OR abuse-deterrent[TIAB] OR "Drug Packaging"[MH] OR "Consumer Product Safety"[MH] OR "consumer product safety"[TIAB] OR "Product Packaging"[MH] OR "product packaging"[TIAB] OR "Poison Prevention Packaging Act"[TIAB] OR "Food Packaging"[MH] OR "food packaging"[TIAB] OR "blister pack"[TIAB] OR "blister packs"[TIAB])). Our searches included all studies, regardless of date published, geography, and language. Searches were conducted between July 8, 2014 and July 18, 2014.

Our database searches resulted in 944 records (see Fig. 1). We identified an additional 46 records by contacting experts in packaging and by reviewing the citations of 10 potentially-relevant articles. Records were imported into reference managing software.

2.2. Eligibility criteria

Included studies investigated a causal relationship between type of packaging or packaging regulation (a measured or manipulated variable) and a behavioral or health outcome. Note that this criterion, by definition, excluded descriptive studies. Included studies also had a study population of consumers as opposed to a non-consumer population, like health care professionals. Non-English studies were included and translated in-house.

Non-peer-reviewed articles were excluded, as were conference abstracts, case studies, and articles for which full text was not available. We excluded review articles since we assumed our search strings would have captured any relevant studies that reviews would have reported. We excluded studies if they had low external validity or lacked data to assess external validity (e.g., country of data collection not reported). Studies were marked as having low external validity if they (1) took place in a country outside of the United States and provided minimal detail about the packaging being tested or regulation being implemented or (2) included only data collected before 1985. Results from studies meeting these criteria were challenging to interpret for the U.S. context, given the wide variety of child-resistant packaging available globally and the major developments in packaging over the past 30 years.

2.3. Eligibility coding

After de-duplicating the records, the first and second authors independently screened the 733 papers for eligibility in two phases. In the first phase, they reviewed titles and abstracts independently and resolved all coding discrepancies through discussion. If agreement could not be reached, they consulted the third and last authors.

After this phase of screening, 132 papers remained as potentially meeting eligibility criteria. These records included those for which eligibility could not be determined from the title and abstract alone (e.g., abstract was missing or vague). The first and second authors independently reviewed the full text of these articles for eligibility, discussed and resolved coding discrepancies, and consulted the third and last authors, as necessary. One hundred twenty-four records were excluded during this phase, leaving eight studies for inclusion in qualitative synthesis.

2.4. Data abstraction

The first and second authors independently coded the articles for study and methodological characteristics, using a data abstraction form. Discrepancies were discussed and resolved. Study characteristics included the study population, country in which the study took place, data collection dates, types of products involved (e.g., oblong tablets, mouthwash), and financial disclosures (i.e., industry, government, not reported). Methodological characteristics included the study design and the independent and dependent variables. Independent variables fell into two categories: (1) packaging design features or (2) the implementation of packaging rules or requirements. For studies investigating packaging design features, we captured details about the packaging tested, including the type of opening and size of the packaging or container, if available. For studies involving packaging rules or requirements, we noted when the policy came into place. Dependent variables represented dimensions of functional ability (e.g., ability to empty a package or not, time required to open) and health outcomes resulting from poisoning ingestions. We reported the direction of results and results of sub-group analyses conducted, if any. We further coded for whether or not randomization took place or an a priori power analysis was conducted.

Based on a scan of quality assessment tools and resources (Deeks et al., 2003; Institute of Medicine, 2011; Committee to Review the IRIS Process, 2014; Sanderson et al., 2007; National Toxicology Program Office of Health Assessment and Translation, 2015; Turner et al., 2013; West et al., 2002; Whiting et al., 2004; Zaza et al., 2000), we identified four categories of study limitations that we considered to be relevant to the included studies and feasible to assess: limitations with regard to *study description*, *sampling*, *measurement*, and *interpretation of results*. *Study description* limitations included the lack of a clear research question and lack of details regarding where and when the study took place and who participated in the study (i.e., age, sex). For structured observational studies, we additionally tracked if the study lacked detail on the study procedure (e.g., what behaviors were being observed). We coded for *sampling* limitations if the sampling frame or screening criteria for study eligibility were not reported, if a non-probability sample was taken, and if the participation rate was under 80%.

Measurement limitations primarily focused on reliability and validity. Reliability issues included failure to mention procedures to estimate some form of reliability, such as internal consistency or test-retest reliability. If reported, we looked for reliability coefficients of at least 0.70 (Kline, 2011). We also noted if authors qualitatively described any reliability issues. For validity, we tracked when the definitions of the independent or dependent variables were unclear. For example, if packaging type was the independent variable, we sought a description of the size and opening mechanism of the packages. We coded the lack of such descriptions as limitations. Other validity issues were the failures to use multiple measures to assess the outcome and to provide evidence of construct validity (e.g., demonstration of convergent or discriminant validity) of measured variables. For studies involving an intervention, like the implementation of packaging rules or requirements, we additionally considered lack of a controlled exposure to the intervention to be a measurement limitation.

The next category of limitations related to the *interpretation of results*. These limitations included the failure to discuss potential confounders. If discussed, we noted attempts to control for and potential biases resulting from these confounders (e.g., instrumentation bias resulting from a change in a measure used in a study). Another limitation was reporting high attrition (i.e., over 20%) without explaining why attrition occurred or how it could have affected the results. When non-randomized studies included control or comparison groups, we assessed if the groups were appropriate (i.e., groups were similar on age, sex, or other demographic characteristics). Studies with inappropriate groups were coded as having a limitation since selection bias could have occurred. For structured observational studies, we noted if the stimuli were presented to participants in random, varying (non-random), or fixed order. Presenting stimuli in a fixed order was considered to be a limitation since it could result in order effects. Lastly, we reviewed characteristics of the study samples. For example, a sample being disproportionately composed of a certain demographic could affect the interpretation of results. We opted not to provide a quality score given the variability in design and outcomes across the studies and the limited value of assigning weights to disparate dimensions of quality. Instead, we report the limitations identified for each study and summarize key findings.

3. Results

The eight studies included in this review were published from 1988 to 2013. All but one study took place in the United States (Keram and Williams, 1988; Lovegrove et al., 2013; Massey and Shulman, 2006; Meyer and Schuna, 1989; Mrvos and Krenzelok, 2007; Rodgers, 1996; Rodgers, 2002). The non-US study took place in Germany (Muhlfeld et al., 2012). Four studies involved structured observations, where researchers assessed participants' ability to open different types of packaging, using a test protocol (Keram and Williams, 1988; Lovegrove et al., 2013; Meyer and Schuna, 1989; Muhlfeld et al., 2012). The remaining four studies had an interrupted time series design, where the interruption was a policy or regulation related to special packaging (Massey and Shulman, 2006; Mrvos and Krenzelok, 2007; Rodgers, 1996; Rodgers, 2002). Three structured observational studies involved persons over the age of sixty (Keram and Williams, 1988; Meyer and Schuna, 1989; Muhlfeld et al., 2012), while one structured observational study involved children

under the age of six (Lovegrove et al., 2013). All four interrupted time series studies involved children under six (Massey and Shulman, 2006; Mrvos and Krenzelok, 2007; Rodgers, 1996; Rodgers, 2002). Sample size ranged from 50 to 141 participants for the structured observational studies and 10 to 29 time points for the interrupted time series studies. One study involved randomization (Lovegrove et al., 2013). This same study was the only study to report conducting an a priori power analysis (Lovegrove et al., 2013). Of the studies reporting their funding source (k = 4), two reported receiving industry funding (i.e., funding from and/or equipment and materials provided by a private company). One reported government funding, and one reported government funding and funding from an undisclosed source. See Supplementary Table 1 for study characteristics.

Several limitations were either identified in the manuscripts or through the review. Two studies failed to report when the study was conducted (Keram and Williams, 1988; Meyer and Schuna, 1989). Seven studies used non-probability sampling (Keram and Williams, 1988; Lovegrove et al., 2013; Massey and Shulman, 2006; Mrvos and Krenzelok, 2007; Rodgers, 1996; Rodgers, 2002; Muhlfeld et al., 2012), which limits our ability to draw conclusions about their respective target populations: children (Lovegrove et al., 2013) and the elderly for the structured observational studies and time periods for the interrupted time series studies (Keram and Williams, 1988; Mrvos and Krenzelok, 2007; Muhlfeld et al., 2012). One study failed to report study eligibility criteria (Muhlfeld et al., 2012).

None of the studies discussed issues related to reliability, provided reliability estimates, or provided evidence of construct validity (Keram and Williams, 1988; Lovegrove et al., 2013; Massey and Shulman, 2006; Meyer and Schuna, 1989; Mrvos and Krenzelok, 2007; Rodgers, 1996; Rodgers, 2002; Muhlfeld et al., 2012). Other validity limitations included the lack of clear definitions of the type of packaging assessed (Keram and Williams, 1988) and the failure to use more than one measure to assess the dependent variable (Massey and Shulman, 2006; Meyer and Schuna, 1989; Mrvos and Krenzelok, 2007). The four interrupted time series studies assessed the impact of an intervention, that is, packaging rules or requirements, on health or behavioral outcomes. These studies had the additional validity limitation of failing to control exposure to the intervention, although this is to be expected, given that the interventions were environmental variables (Massey and Shulman, 2006; Mrvos and Krenzelok, 2007; Rodgers, 1996; Rodgers, 2002).

Regarding the interpretation of results, a key limitation among structured observational studies was the failure to mention the order in which stimuli were presented to participants (Keram and Williams, 1988; Meyer and Schuna, 1989). Another limitation was the composition of study samples. Three structured observational studies had disproportionate numbers of males to females in the samples (Keram and Williams, 1988; Meyer and Schuna, 1989; Muhlfeld et al., 2012).

Interrupted time series studies generally reported and, in differing degrees, discussed or attempted to control for the impact of potential sources of bias. Common sources of bias included instrumentation (Mrvos and Krenzelok, 2007; Rodgers, 1996; Rodgers, 2002), history (e.g., change in number of poison reporting centers) (Mrvos and Krenzelok, 2007; Rodgers, 1996; Rodgers, 2002), and maturation (e.g., increase in reporting of

overingestions) (Massey and Shulman, 2006; Mrvos and Krenzelok, 2007; Rodgers, 1996; Rodgers, 2002; Done et al., 1971). Another common limitation was the failure to report whether pre- and post-intervention groups were well-matched with regard to demographic characteristics, which could suggest selection bias (Massey and Shulman, 2006; Rodgers, 1996; Rodgers, 2002).

3.1. Structured observational studies

Studies assessed packaging for medications in tablet (k = 3) (Keram and Williams, 1988; Meyer and Schuna, 1989; Muhlfeld et al., 2012), liquid (k = 2) (Keram and Williams, 1988; Lovegrove et al., 2013), and/or patch form (k = 1) (Keram and Williams, 1988). See Supplementary Table 2 for detailed descriptions of the designs tested and study results. Muhlfeld et al. (2012) compared five different types of blister designs on the usability and preferences of older adults. The one child-resistant design tested required the participant to peel-off the polyethylene terephthalate layer of the foil covering the blister and to push through the remaining aluminum foil layer (Muhlfeld et al., 2012). The other designs required the participant to peel off or push through the lidding foil. Study authors measured five outcomes: level of difficulty associated with opening the blister, participants' overall assessment of the package (i.e., good, intermediate, bad), whether or not participants experienced pain when opening, whether or not participants gave up trying to open the package, and the number of tablets removed. Of all designs, the child-resistant design was found to be the least accessible and the most negatively assessed. More participants rated it as being "very difficult" to open than any other design, and it received the highest number of negative overall ratings (Muhlfeld et al., 2012). Pain was reported by the highest proportion of participants trying to open the child-resistant design (Muhlfeld et al., 2012). Relative to all other designs tested, a higher proportion of participants gave up when trying to open the child-resistant design and failed to remove four tablets from the pack (Muhlfeld et al., 2012). Female participants, older participants (i.e., aged 86+), and participants with diseases like rheumatism, stroke, arthritis, and Parkinson's disease or poor vision were less likely to be able to open and obtain the tablets in the blister than their male, younger, and non-disease counterparts (Muhlfeld et al., 2012).

Meyer and Schuna (1989) assessed older adults' ability to open packaging for tablet medications and compared two types of containers. The first container had a child-resistant opening mechanism that required the participant to push down and turn the cap (Meyer and Schuna, 1989). The second container was a non-child-resistant "flip cap" (Meyer and Schuna, 1989). The researchers did not find statistically significant differences in participants' ability to open the two containers (Meyer and Schuna, 1989).

Keram and Williams (1988) tested older adults' ability to open 15 different medication containers, including six child-resistant designs, four non-child-resistant designs, three nitro-glycerin patches, and two miscellaneous containers (i.e., blister pack, plastic pocket box), which the authors considered to be child-resistant in their analysis. Adults took longer to open the child-resistant designs than the non-child-resistant designs (Keram and Williams, 1988). In addition, none of the child-resistant designs could be opened by all participants,

while all participants could open the non-child-resistant designs (Keram and Williams, 1988).

Lovegrove et al. (2013) were the only researchers to use structured observation to assess the effect of packaging design among children. They investigated how the inclusion of flow restrictors on bottle openings affected children's ability to empty bottle contents. Each participant attempted to empty the liquid contents of two bottles (Lovegrove et al., 2013). The first was an open bottle without a cap but with a flow restrictor (Lovegrove et al., 2013). One of three different designs of flow restrictors and accompanying bottles were used for this condition (Lovegrove et al., 2013). The second bottle tested served as the control and was either an open bottle without a cap or a bottle with an incompletely closed child-resistant cap (Lovegrove et al., 2013). If the participant failed to empty either bottle in five minutes, the researchers demonstrated how to remove the liquid (Lovegrove et al., 2013). Regardless of whether a demonstration was provided, children were less successful at emptying completely and removing different amounts of test liquid from the flow restrictor bottle compared to the control bottles (Lovegrove et al., 2013). Older children (i.e., aged 54–59 months) were more likely to be able to empty the flow restrictor bottles than younger children (Lovegrove et al., 2013).

3.2. Interrupted time series studies

Interrupted time series studies investigated the effects of policies requiring child-resistant packaging for ethanol-containing mouthwash in 1995 (k = 2) (Massey and Shulman, 2006; Mrvos and Krenzelok, 2007), aspirin-containing products in 1972 (k = 1) (Rodgers, 2002), and oral prescription drugs in 1974 (k = 1) (Rodgers, 1996). Mrvos and Krenzelok (2007) analyzed data from 1985 through 2005 on toxic exposures involving children and the ingestion of ethanol-containing mouthwash. The number of toxic exposures dropped during the year that child-resistant packaging requirements were implemented, but the total number of exposures post-implementation of the requirements was greater than the total number pre-implementation (Mrvos and Krenzelok, 2007). The researchers were unable to determine whether this effect was a result of the increased availability of ethanol-containing mouthwash or the failure of child-resistant packaging requirements (Mrvos and Krenzelok, 2007). However, they found some evidence that health outcomes related to the exposures were less severe after the rule was implemented (Mrvos and Krenzelok, 2007).

In another study assessing the effect of the 1995 rule, Massey and Shulman (2006) analyzed data on the incidence of overingestion of ethanol-containing mouthwash from 1989 through 2003. In contrast to the previous study, the researchers adjusted the number of exposures by the proportion of the US population under six and served by poison control centers (Massey and Shulman, 2006). The incidence of overingestions involving mouthwash decreased after the implementation of the 1995 rule but began to increase in 2002 (Massey and Shulman, 2006).

Rodgers assessed the impact of child-resistant packaging requirements on aspirin-containing products (Rodgers, 2002) and oral prescription drugs (Rodgers, 1996). In both studies, he used multivariate regression models to estimate the effect of the requirements on the child mortality rate, while taking into account potential confounding variables (Rodgers, 1996;

Rodgers, 2002). Both studies included a large number of time points before and after the intervention. The study on aspirin-containing products included data from 1958 through 1990 (Rodgers, 2002), while the study on oral prescription drugs included data from 1964 through 1992 (Rodgers, 1996). Both studies found statistically significant declines in child mortality as a result of the packaging requirements (Rodgers, 1996; Rodgers, 2002).

4. Discussion

We sought to summarize the literature on the effects of special packaging on health and behavioral outcomes. Studies have generally found that products with child-resistant designs have been more difficult to access than those with non-child-resistant designs. Moreover, child-resistant packaging requirements for oral prescription and aspirin-containing products have been associated with reductions in child mortality. Although only a small number of studies have been conducted and a small number of packaging designs have been assessed, it is reasonable to infer that child-resistant packaging has had a positive effect in reducing toxicant exposures in children and associated mortality. If applied to tobacco products, child-resistant packaging would likely reduce tobacco-related ingestions.

It is worth noting that child-resistant designs were not only difficult for children to access but also older adults. With the Child Nicotine Poisoning Prevention Act, liquid nicotine containers in the U.S. will need to satisfy the child-resistant requirements and pass the “ease of adult opening” tests outlined in section 1700.15 of the Poison Prevention Packaging Act (114th Congress, 2015; Code of Federal Regulations, 1973). “Ease of adult opening” tests are intended to ensure that adults aged 50 to 70 can successfully access the product as outlined in section 1700.20 of the Poison Prevention Packaging Act (Code of Federal Regulations, 1973). Including such tests in child-resistant regulation could indirectly prevent pediatric ingestions of tobacco products. Significant proportions of pediatric poisonings have been linked to the ingestion of grandparents’ medications, and improper storage of medication has been cited as a potential factor (McFee and Caraccio, 2006; Jacobson et al., 1989). Older adults who struggle to open child-resistant containers may leave these containers open or transfer the contents to non-child-resistant packages (e.g., plastic bags), which could increase the likelihood of pediatric poisoning. Tobacco use, including e-cigarette use, is lower among the geriatric population than other age groups (King et al., 2015; U.S. Department of Health and Human Services, 2014). However, policymakers proposing child-resistant regulations may still want to consider including “ease of adult” tests in addition to child-resistant tests for tobacco products.

This review has identified several areas for future research. First, research on the ability of children to open special packaging would be informative as they are vulnerable to poisonings due to tobacco product ingestion, particularly e-liquids and electronic cigarette cartridges. Second, from a methodological standpoint, researchers should consider randomizing the order of stimuli in these studies, using probability samples, assessing and reporting on the psychometric properties of measures, and providing detailed descriptions of the packaging designs being compared. Third, studies assessing packaging types as varied as those that house tobacco products would be useful. Research studies should also consider evaluating a range of tobacco product formulations. For example, Lovegrove et al. (2013)

tested flow restrictors and bottle designs that were being used for liquid medicines in the United States at the time of the study. Their results may not generalize to all flow restrictor or bottle types or to bottles with different contents (e.g., non-liquid or different viscosity) (Lovegrove et al., 2013). Fourth, as jurisdictions begin to implement child-resistant packaging requirements for e-cigarette liquids and components, opportunities to conduct natural experiments exist. In addition to analyzing data prior to and after the implementation of such requirements, such as the interrupted time series studies included in the review, researchers could consider analyzing data from a control community that has not implemented such requirements. Such a design would be an improvement over existing designs since it could help researchers assess the impact of historical factors that could be biasing study results. Fifth, research suggests that the size and shape of the container (Keram and Williams, 1988), material of the cap (Done et al., 1971), and force required to open the container (Page, 1981) could influence the effectiveness of special packaging. Future studies could manipulate these factors and evaluate their independent and combined impacts on participants' opening ability. Lastly, although we aimed to investigate tamper-resistant packaging in addition to child-resistant packaging, we did not locate any articles on this topic. Tamper-resistant packaging may be a promising area of research associated with tobacco products.

Strengths of this study include our comprehensive search of the literature and our independent approach to screening articles for eligibility and coding data. Limitations are that we may have missed potentially informative articles as a result of our eligibility criteria. Since we excluded descriptive studies, studies reporting the pattern of poisoning ingestions over time without including packaging type or regulation as an independent variable were excluded. Though outside the scope of our review, descriptive studies like these and review articles may yield potentially useful information to policymakers. Also, as noted previously, a number of studies were excluded due to low external validity or insufficient data to assess external validity. Despite excluding them from this review, we reviewed their results post-hoc and found them to be generally in line with our study findings.

5. Conclusion

To our knowledge, this is the first systematic review to assess the effects of special packaging on health and behavioral outcomes. Although more studies would expand the evidence base, child-resistant packaging holds the expectation to reduce tobacco product poisonings among children under six years. This review supports the growing number of efforts to require child-resistant packaging for e-cigarette products.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

Arrazola RA, Singh T, Corey CG, Husten CG, Neff LJ, Apelberg BJ, Bunnell RE, Choiniere CJ, King BA, Cox S, McAfee T, Caraballo RS. Tobacco use among middle and high school students - United States, 2011–2014. MMWR Morb Mortal Wkly Rep. 2015; 64:381–385. [PubMed: 25879896]

114th Congress. S.142 - Child Nicotine Poisoning Prevention Act of 2015. 2015. http://thomas.loc.gov/cgi-bin/bdquery/z?d114:s142, (Accessed May 29, 2015)

Bear River Board of Health. Electronic smoking device regulation. 2014. http://www.brhd.org/images/BRHD_ecigarette_regulation_Revised_Sept_2014.pdf (Accessed May 29, 2015)

Buettner-Schmidt K, Miller DR, Balasubramanian N. Electronic cigarette refill liquids: child-resistant packaging, nicotine content, and sales to minors. J Pediatr Nurs. 2016

Centers for Disease Control and Prevention. Injury prevention & control: data & statistics. Web-Based Injury Statistics Query and Reporting System (WISQARS). 2013. http://www.cdc.gov/injury/wisqars/index.html, (Accessed May 29, 2015)

Chatham-Stephens K, Law R, Taylor E, Melstrom P, Bunnell R, Wang B, Apelberg B, Schier JG. Notes from the field: calls to poison centers for exposures to electronic cigarettes—United States, September 2010–February 2014. MMWR Morb Mortal Wkly Rep. 2014; 63:292–293. [PubMed: 24699766]

Chatham-Stephens K, Law R, Taylor E, Kieszak S, Melstrom P, Bunnell R, Wang B, Day H, Apelberg B, Cantrell L, Foster H, Schier JG. Exposure calls to U.S. poison centers involving electronic cigarettes and conventional cigarettes-September 2010–December 2014. J Med Toxicol. 2016

Clukey, K. Case Closed in Fort Plain Liquid Nicotine Death. Times Union; 2015.

Cobb NK, Byron MJ, Abrams DB, Shields PG. Novel nicotine delivery systems and public health: the rise of the “e-cigarette”. Am J Public Health. 2010; 100:2340–2342. [PubMed: 21068414]

Code of Federal Regulations. Part 1700—Poison Prevention Packaging. 1973. https://www.gpo.gov/fdsys/granule/CFR-2012-title16-vol2/CFR-2012-title16-vol2-part1700/content-detail.html, (Accessed May 29, 2015)

Code of Federal Regulations. Part 211, Subpart G, Sec 211.132–Tamper-evident packaging requirements for over-the-counter (OTC) human drug products. 2016. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=211.132, (Accessed December 8, 2016)

Committee to Review the IRIS Process. Board on Environmental Studies and Toxicology, Division on Earth and Life Studies, National Research Council. Review of EPA’s Integrated Risk Information System (IRIS) Process. 2014

Connolly GN, Richter P, Aleguas A Jr, Pechacek TF, Stanfill SB, Alpert HR. Unintentional child poisonings through ingestion of conventional and novel tobacco products. Pediatrics. 2010; 125:896–899. [PubMed: 20403932]

Deeks JJ, Dinnes J, D’Amico R, Sowden AJ, Sakarovitch C, Song F, Petticrew M, Altman DG. Evaluating non-randomised intervention studies. Health Technol Assess. 2003; 7:iii–x. 1–173.

Done AK, Jung AL, Wood MC, Klauber MR. Evaluations of safety packaging for the protection of children. Pediatrics. 1971; 48:613–628. [PubMed: 5114749]

Durmowicz EL. The impact of electronic cigarettes on the paediatric population. Tob Control. 2014; 23(Suppl 2):ii41–46. [PubMed: 24732163]

European Parliament and the Council of the European Union. Directive 2014/40/EU of the European Parliament and of the Council. 2014. http://ec.europa.eu/health/tobacco/docs/dir_201440_en.pdf (Accessed May 29, 2015)

Forrester MB. Pediatric exposures to electronic cigarettes reported to Texas poison centers. J Emerg Med. 2015; 49:136–142. [PubMed: 25802158]

Frey LT, Tilburg WC. Child-resistant packaging for e-liquid: a review of US state legislation. Am J Public Health. 2016; 106:266–268. [PubMed: 26691114]

Institute of Medicine. Committee on Standards for Systematic Reviews of Comparative Effectiveness Research. In: Eden, J.Levit, L.Berg, AO., Morton, SC., editors. Finding What Works in Health Care: Standards for Systematic Reviews. 2011.

Jacobson BJ, Rock AR, Cohn MS, Litovitz T. Accidental ingestions of oral prescription drugs: a multicenter survey. Am J Public Health. 1989; 79:853–856. [PubMed: 2660604]

Kamboj A, Spiller HA, Casavant MJ, Chounthirath T, Smith. Pediatric exposure to e-cigarettes, nicotine, and tobacco products in the United States. Pediatrics. 2016:137. [PubMed: 27543009]

Keram S, Williams ME. Quantifying the ease or difficulty older persons experience in opening medication containers. J Am Geriatr Soc. 1988; 36:198–201. [PubMed: 3339227]

King BA, Patel R, Nguyen KH, Dube SR. Trends in awareness and use of electronic cigarettes among US adults, 2010–2013. Nicotine Tob Res. 2015; 17:219–227. [PubMed: 25239961]

Kline, RB. Principles and Practice of Structural Equation Modeling. Guilford Press; New York: 2011.

Lisko JG, Tran H, Stanfill SB, Blount BC, Watson CH. Chemical composition and evaluation of nicotine, tobacco alkaloids, pH, and selected flavors in e-cigarette cartridges and refill solutions. Nicotine Tob Res. 2015; 17:1270–1278. [PubMed: 25636907]

Lovegrove MC, Hon S, Geller RJ, Rose KO, Hampton LM, Bradley J, Budnitz DS. Efficacy of flow restrictors in limiting access of liquid medications by young children. J Pediatr. 2013; 163:1134–1139, e1131. [PubMed: 23896185]

Massey CC, Shulman JD. Acute ethanol toxicity from ingesting mouthwash in children younger than age 6, 1989–2003. Pediatr Dent. 2006; 28:405–409. [PubMed: 17036704]

McFee RB, Caraccio TR. “Hang up your pocketbook” — an easy intervention for the granny syndrome: grandparents as a risk factor in unintentional pediatric exposures to pharmaceuticals. J Am Osteopath Assoc. 2006; 106:405–411. [PubMed: 16912339]

Meyer ME, Schuna AA. Assessment of geriatric patients’ functional ability to take medication. DICP. 1989; 23:171–174. [PubMed: 2728508]

Mrvos R, Krenzelok EP. Child-resistant closures for mouthwash: do they make a difference? Pediatr Emerg Care. 2007; 23:713–715. [PubMed: 18090103]

Muhlfeld L, Langguth P, Hausler H, Hagels H. Influence of blister package design on usability among older adults. Int J Clin Pharm. 2012; 34:553–560. [PubMed: 22572904]

National Cancer Institute. Division of Cancer Control & Population Sciences, Smokeless Tobacco and Public Health: A Global Perspective. 2014. http://cancercontrol.cancer.gov/brp/tcrb/global-perspective/index.html, (Accessed August 23, 2016)

National Toxicology Program Office of Health Assessment and Translation. OHAT Risk of Bias Rating Tool for Human and Animal Studies. 2015. http://ntp.niehs.nih.gov/ntp/ohat/pubs/riskofbiastool_508.pdf (Accessed May 29, 2015)

Nikitin D, Timberlake DS, Williams RS. Is The E-Liquid Industry Regulating Itself? A Look at E-Liquid Internet Vendors in the United States. Nicotine Tob Res. 2016

Ordonez JE, Kleinschmidt KC, Forrester MB. Electronic cigarette exposures reported to Texas poison centers. Nicotine Tob Res. 2015; 17:209–211. [PubMed: 25344956]

Page M. An ergonomics evaluation of a reclosable pharmaceutical container with special reference to the elderly. Ergonomics. 1981; 24:847–862. [PubMed: 7338214]

Pepper JK, Brewer NT. Electronic nicotine delivery system (electronic cigarette) awareness, use, reactions and beliefs: a systematic review. Tob Control. 2014; 23:375–384. [PubMed: 24259045]

Popular E-Liquid. Popular E-Cig Liquid, E-Juice Online, Shop Vape Juice. 2016. http://vapingzone.com/product-list.php?asc_action=Paginator_SetRowsPerPage&pgname=Catalog_ProdsList_110&rows=24 (Accessed December 8, 2016)

Rodgers GB. The safety effects of child-resistant packaging for oral prescription drugs. Two decades of experience. JAMA. 1996; 275:1661–1665. [PubMed: 8637140]

Rodgers GB. The effectiveness of child-resistant packaging for aspirin. Arch Pediatr Adolesc Med. 2002; 156:929–933. [PubMed: 12197802]

Rosetta, L. New Smokeless Tobacco Products in Test Markets. The Salt Lake Tribune; 2009.

Sanderson S, Tatt ID, Higgins JP. Tools for assessing quality and susceptibility to bias in observational studies in epidemiology: a systematic review and annotated bibliography. Int J Epidemiol. 2007; 36:666–676. [PubMed: 17470488]

TobaccoProducts.Org. Camel Snus - Tobacco Products. 2010. http://www.tobaccoproducts.org/index.php/Camel_Snus (Accessed May 29, 2015)

Turner L, Boutron I, Hrobjartsson A, Altman DG, Moher D. The evolution of assessing bias in Cochrane systematic reviews of interventions: celebrating methodological contributions of the Cochrane Collaboration. Syst Rev. 2013; 2:79. [PubMed: 24059942]

U.S. Department of Health, Services, Human. Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health. The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General. 2014

U.S. Department of Health and Human Services. Food and Drug Administration, Nicotine exposure warnings and child-resistant packaging for liquid nicotine, nicotine containing e-liquid(s), and other tobacco products; request for comments. 2015. http://www.fda.gov/downloads/TobaccoProducts/Labeling/RulesRegulationsGuidance/UCM453226.pdf, (Accessed June 2, 2016)

Vakkalanka JP, Hardison LS Jr, Holstege CP. Epidemiological trends in electronic cigarette exposures reported to U.S. poison centers. Clin Toxicol (Phila). 2014; 52:542–548. [PubMed: 24792781]

West S, King V, Carey TS, Lohr KN, McKoy N, Sutton SF, Lux L. Systems to rate the strength of scientific evidence. Evid Rep Technol Assess (Summ). 2002:1–11.

Whiting P, Rutjes AW, Dinnes J, Reitsma J, Bossuyt PM, Kleijnen J. Development and validation of methods for assessing the quality of diagnostic accuracy studies. Health Technol Assess. 2004; 8:iii, 1–234.

Wilson, D. Flavored Tobacco Pellets Are Denounced as a Lure to Young Users. 2010. http://www.nytimes.com/2010/04/19/business/19smoke.html?_r=0 (Accessed May 29, 2015)

Zaza S, Wright-De Aguero LK, Briss PA, Truman BI, Hopkins DP, Hennessy MH, Sosin DM, Anderson L, Carande-Kulis VG, Teutsch SM, Pappaioanou M. Data collection instrument and procedure for systematic reviews in the Guide to Community Preventive Services. Task Force on Community Preventive Services. Am J Prev Med. 2000; 18:44–74. [PubMed: 10806979]

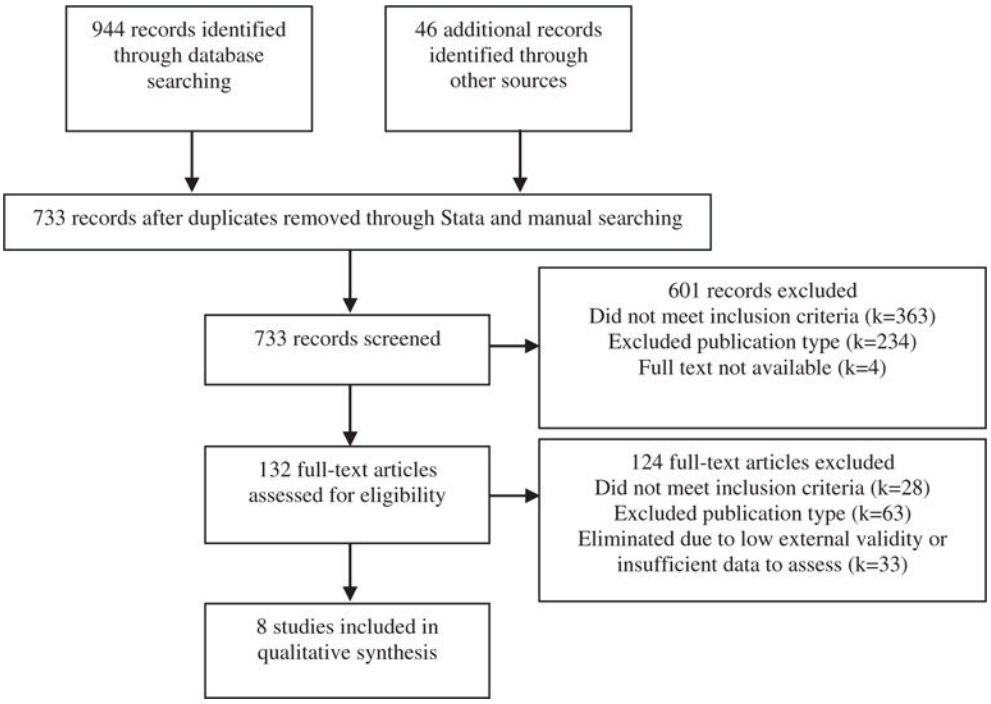

Fig. 1.
Flow diagram of literature search and article identification.