

**The Female Overactive Bladder in our Beverage-Centered Society:
An Evolutionary Perspective**

by

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Abstract

Over recent decades, chronic disease has trended upwards, associated with the mismatch between our modern nutritional environment and our paleolithic genome. The beverage industry has exploded in sync with chronic conditions, including bladder symptomatology. This dissertation uses the logic and paradigm of evolutionary medicine to examine the modern beverage culture as a cause of the current high overactive bladder prevalence rates (17-31%, age dependent). A natural experiment exemplar concludes the dissertation with proof of concept that societal-wide influences to hyper-hydrate by drinking beyond thirst influences non-pathological changes to bladder state. The study is a secondary analysis with main outcome measure as void frequency. In this natural experiment, the preventative treatment group is considered to be 40 women who at 8 months postpartum are not breastfeeding and hence not receiving same degree of societal messaging to hyper-hydrate, as compared to 52 breastfeeding women. The preventative treatment group (non-breastfeeding women) show significantly lower daily beverage intake (62.6 oz) than the breastfeeding group (77.6 oz), $p = 0.01$. Results show a strong trend towards a significantly lower average number of daily voids in the preventative treatment group who have less societal messaging compared to the control group with high societal messaging (6.3 voids/day versus 7.2 voids/day respectively), $p = .04$. This natural experiment

provides first evidence-based proof of concept for the argument that in terms of evolutionary perspective, the new (50 years) cultural milieu of the beverage driven society may be driving the contemporaneous increase in bladder symptoms, and that its prevalence may lessen without conscious individual effort if societal messages to hyper-hydrate (drink beyond thirst) decrease. The dissertation concludes with recommendation for more research to test the theoretical construct that non-pathological but bothersome and costly symptoms of overactive bladder occur when our evolutionarily designed bladder is exposed to the modern beverage driven society.

Chapter 1 Introduction

Overactive Bladder (OAB) is defined as “urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, *in the absence of urinary tract infection or other obvious pathology*” (Haylen et al., 2010, p. 6). Using the logic and paradigm of evolutionary medicine, specifically the interaction over time of our post-industrial beverage-centered environment with our hunter-gatherer genome, this dissertation explores “drinking beyond thirst” as a logical etiology for explaining a portion of the current prominence of the chronic condition of OAB. This dissertation does not address the complex of neurogenic conditions that explain a different portion of the current prominence of OAB. (These are noted in Appendix A.) Rather it does make transparent a simple but ubiquitous cause for OAB, which if addressed, could potentially reduce the astounding total national cost of OAB estimated to reach \$82.6 billion dollars per year by 2020.

Chapter 3 documents the history of the “beverage explosion” in modern society, tracking data that reveal the speed of this explosion over the last several decades. Beverage intake, both type and amount, and dosing of beverage ingredients associated with bladder symptomatology have doubled or more in recent decades. Over the past fifteen years, the number of new beverages on the market in any one-year total more than all the beverages that were available 50 years ago (Popkin, 2010). Looked at in a different way, if you compare the percentage of new food and beverages products in each of the past 6 years, in every one of those years the highest

category for percentage of new products is beverages. This raw data is shown in Table 1 (source Mintel GNPD), and portrayed in simplified form by bar chart in Figure 1.

*Table 1 New Food and Beverage Product Introductions, by Product Type, 2011-16**

Product type	2011	2012	2013	2014	2015	2016
New products (number)	20,432	20,252	20,881	19,536	17,143	21,435
Beverages	19.9	20.7	22.2	21.6	22.4	18.5
Snacks	11.5	13.2	11.2	13.2	14.1	14.8
Bakery foods	12.5	11.8	10.3	11.6	11.6	12.6
Sauces, dressings, and condiments	10.1	8.6	10.0	7.6	9.0	9.0
Candy and gum	9.3	9.1	7.4	7.5	7.2	8.7
Dairy	6.7	6.7	7.0	8.2	7.2	7.2
Processed fish, meat, and egg products	5.6	5.5	5.9	6.2	5.8	6.3
Meals and entrees	6.3	6.6	6.3	5.9	4.9	5.6
Fruit and vegetables	2.4	2.6	3.4	3.4	2.6	3.2
Desserts and ice cream	3.9	4.1	4.1	3.2	4.1	3.2
Side dishes	3.3	3.3	3.4	3.3	2.8	3.1
Breakfast cereals	2.5	2.3	2.4	2.7	3.1	2.8
Sweet and savory spreads	3.5	2.9	2.6	2.3	2.5	2.7
Soup	1.3	1.1	1.8	1.5	1.2	1.2
Baby food	0.7	1.1	1.6	1.5	1.0	0.7
Sweeteners and sugar	0.4	0.5	0.3	0.3	0.5	0.3

*Percent of total. Source: Mintel GNPD.

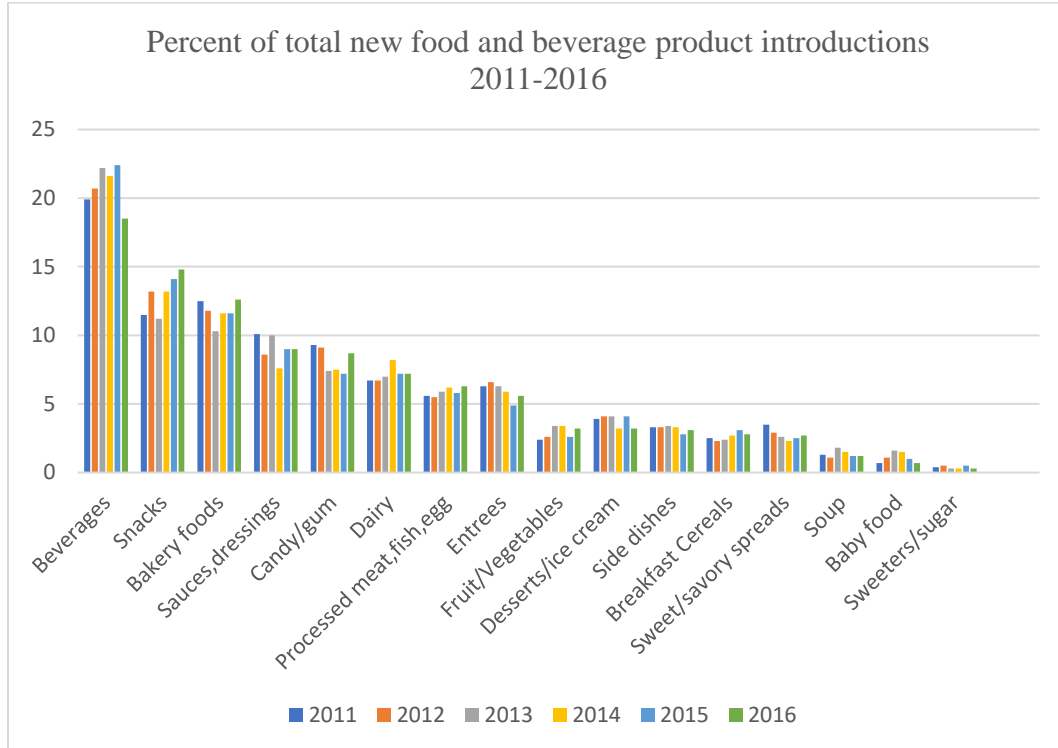


Figure 1 New Food and Beverage Product Introductions, by Product Type, 2011-2016*

*Percent of total. Source: Mintel GNPD

As a matter of common observation as well as evidenced by data reviewed within this dissertation, western culture is saturated with coffee-shops and beverages manufactured to perk you up, deliver vitamins or energy, and “hydrate” you in conveniently packaged bottles, refillable travel mugs, and super-sized jugs. The health and beauty media remind us that 64 oz. of liquid a day is the rule and if you feel thirsty, it is “too late,” you are already dehydrated. Yet analysis generated for this dissertation (Chapter 7) suggests that a reliance on societal influences to drink more than thirst cues may have unintended consequences on the bladder.

A discussion of evolutionary medicine in Chapter 3 highlights the mismatch of current norms for beverage intake with the body’s evolved physiology for excreting reasonable amounts of unneeded fluid in urine. Through the evolutionary lens, arguments made in Chapter 3

emphasize that the label “overactive bladder” can be misleading, implying that something is wrong with the bladder when it is responding appropriately in relation to increased hydration. Rather than applying evolutionary theory to understanding human health and disease, our current medical model places the emphasis on pathology (body gone wrong) and the clinical focus on management of symptoms (treat with drugs) when, in the case of the mismatch of the evolutionarily evolved bladder against a beverage-driven society, a different question is more appropriate. Are we habitually applying medical treatment (e.g. prescribing anticholinergics or Botox to “shut down” the bladder) to treat bladder urgency/frequency symptoms (called OAB) rather than exposing an unappreciated and unacknowledged issue – a society-influenced condition of drinking more than our bodies need, that is, drinking beyond thirst?

Focusing on the “drinking beyond thirst” condition within an evolutionary medicine framework reveals a potential reality that the bladder is an organ forced to cope with a mismatch between our evolutionary biology and the rapid change in our modern beverage intake environment rather than a chronic bladder disease. If this is true, prevention rather than treatment becomes the focus, through resolving the mismatch of modern societal influence to drinking beyond thirst against our genomic physiology bladder capability to manage. Is the impetus to drink 64 ounces minimally per day (8 - 8 oz. glasses = 8 x 8 rule) based in social context rather than true hydration need? (History tracked in more detail in Chapter 6.) As in Hans Christian Andersen’s story, *The Emperor’s New Clothes* (Andersen, 1972), where a small voice in the crowd cries out the obvious “but he has no clothes,” the dissertation questions if the common belief in the 8X8 hydration rule, marking it as a societal messaging, marketing, and other pervasive pressures to drink fooling us into thinking that drinking beyond thirst implying “more is always better” is based on physiologic fact, when it is not.

Chapters 1 and 4 discuss the overactive bladder as an example of a chronic disease that in certain of its forms might be attributed to a mismatch between our nutritional (beverage) environment and our evolutionarily derived genome that codes for bladder development and lifetime function. The overactive bladder is shown to be a newly identified, loosely defined state of bladder urgency/frequency, which roughly corresponds in recognition as a disorder occurring post beverage revolution. Problems with its definition, attempts to define its prevalence, and gaps in the current state of knowledge about risk and protective factors for overactive bladder are reviewed.

The body of literature on relationship of OAB with beverage intake is highlighted in Chapter 5. The connection of beverage intake (type and amount) to overactive bladder is logical, even intuitive, but yields surprisingly scant data for support. This is highlighted in a 2017 systematic review demonstrating both support for but also conflicting evidence for carbonated and caffeinated beverages and total fluid intake as affecting OAB (Robinson, et al, 2017).

As concluded in this systematic review, there is a lack of evidence linking beverage intake and OAB. In addition, specificity of “cause” is unknown, with both volume and ingredient factors of beverage intake intertwined. Do women with some unknown propensity for OAB seek “drinking beyond thirst” at higher rates? Is there a mediating precursor variable for “drinking beyond thirst” that affects the symptoms of OAB?

Fundamentally, this dissertation raises the question of coherence. Given that any empirical study is imbedded in the context of current thought (or scientific theory), the examination of OAB as “appearing” during the rapid rise in beverage intake in the USA offers an evolutionary medicine context. From a deep dive into these formerly disparate bodies of literature (OAB as one body, the rise of the beverage culture in the other) the investigator was

sensitized to possibilities for studying the relationship between these two areas, using an exemplar study arising from a natural history design. This dissertation takes root in critiquing certain biases, such as a “drinking beyond thirst” culture, that may have created a loss of sensitivity and awareness of how to maintain physiologic equilibrium regarding women’s bladders. These bladders are genetically and physiologically unchanged from times when access to high volume intake and great variety of beverages were much more restricted. One might conjure up the conflicting images of a Paleolithic woman’s clay container for water, held in the palm, against today’s version, a 32-oz water jug with drinking spout (Figure 2).



Figure 2 Paleolithic Clay Cup estimated 4-5 oz. Versus Modern 32 oz. Water Bottle

Managing beverage intake as a treatment for OAB (“just drink to thirst”) will fail our OAB patients if there is not societal recognition that drinking to thirst is bladder-friendly whereas “drinking beyond thirst” is not. One might ask, if OAB truly does have its roots (for many who suffer from it) in the interaction between type and quantity of beverage intake, then surely people would have discovered for themselves these simple factors and would modify their

overactive intake and/or beverage type/ingredient or at least understand these factors as a cause of their overactive bladder. For example, within the context of social alcoholic drinking, jokes abound related to the well-accepted “frequency/urgency” issues resulting from alcohol ingestion. However, outside of the commonly shared wisdom of “alcohol makes me pee,” we have no strong evidence regarding overall volume/ingredient type of fluid as a risk factor for a woman diagnosed with OAB. Non-beverage factors associated with a woman’s experiencing “makes me pee,” do have an evidence based, such as prescribed diuretics, but these factors are outside of the scope of this dissertation. And second, even if patients with OAB do believe that stopping or modifying drinking beyond thirst behavior will reduce OAB symptoms, the act of doing so is far more difficult than one might initially think.

As with the parallel chronic and highly prevalent issue of obesity, dietary habits are notoriously difficult to change. When our genomic bodies, adapted for a hunter-gatherer environment (with varying availability of nutrient and water sources) are shifted (in an evolutionarily-speaking fast manner) to our current environment of over-abundance, immense variety, and social/marketing encouragement, the body is ill equipped to manage these influences. Study after study fails to tease apart modern-day beverage issues of multiplicity of dubious ingredients and volume of intake patterns in relation to physiological needs for nutrition and hydration. This was pointed out in a 2017 systematic review (Robinson, et al, 2017).

Clearly, a dissertation cannot fully address or solve these enormous gaps in the literature, though it can illuminate them. A prospective clinical trial of any impact would require enormous resources and length of time, which in part likely explains the lack of data to date. However, consider a natural experiment wherein the modern societal messages at a broad level are reversed, such that *a state of lesser intensity* of the expectations to “drinking beyond thirst”

occurs for a certain group of people – as if mimicking societal wide primary or secondary prevention for OAB? And what if the group of people subjected to this *state of lesser intensity* of the societal messaging to “drinking beyond thirst” occurs “as if random,” which is the defining characteristic of natural experiments. The opportunity for a natural experiment of this sort was identified for this dissertation.

What is a Natural Experiment?

Dunning (2012) offers a comprehensive guide to the increasingly popular methodology of natural experiments. In his seminal work, Natural Experiments in the Social Sciences. A Design Based Approach, he describes natural experiments as “suddenly everywhere” and argues their legitimate use for strengthening causal claims. The advantages he articulates for their use are precise model specification and an emphasis on strong design over complex statistical analysis. Or, as Dunn notes (pg. xvii),

Research that depends on *ex post* statistical adjustment (such as cross-country regressions) has recently come under fire; there has been a commensurate shift of focus toward design-based research—in which control over confounding variables comes primarily from research design, rather than model-based statistical adjustment. The current enthusiasm for natural experiments reflects this renewed emphasis on design-based research.

A natural experiment, “as if randomized” and accompanying simple analytic format, provides one of the strongest experimental designs. Driven by theoretical constructs, it represents the needed cohesion for linking risk and protective factors to outcomes. Quoting from Dunning (pg. 2),

Researchers often ask questions about cause and effect. Yet, those questions are challenging to answer in the observational world—the one that scholars find occurring around them. Confounding variables associated both with possible causes and with possible effects pose major obstacles. Randomized controlled experiments offer one possible solution, because randomization limits confounding. However, many causes of interest to social scientists are difficult to manipulate experimentally. Thus stems the potential importance of natural experiments—in which social and political processes, or clever research-design innovations, create situations that approximate true experiments. Here, we find observational settings in which causes are randomly, or as good as randomly, assigned among some set of units, such as individuals, towns, districts, or even countries. Simple comparisons across units exposed to the presence or absence of a cause can then provide credible evidence for causal inferences from observational data, which is one reason why researchers from such varied disciplines increasingly use them to explore causal relationships.

Dunning goes on to explain that natural experiments are “not so much planned as discovered” (pg. 3). “As if randomized” is positioned as aspiration (pg. 323), “which may be achieved to greater or lesser degrees in practice.” But “when as if randomized is plausible, the analysis may be simpler and more transparent and the underlying models more credible” (pg. 325). Finally, Dunning emphasizes that:

substantive knowledge plays a strong role in discovering natural experiments and validating the claim that assignment is as good as random, in generating

model-validation CPOs [causal-process observations] that may contribute to formulating credible quantitative models, and in shaping interpretation of effects in a way that highlights and reinforces the relevance of the study. In sum, successful natural experiments depend on such substantive knowledge. It is an illusion to believe that mere technique is sufficient to design good natural experiments, just as it is an insufficient basis for regression analysis (Freedman 2009, 2010a, pg. 325-6).

and

Evaluating natural experiments and making recommendations for conducting them, should rely on deep knowledge of the subject matter and the context of research ... this component is critical (page 325).

In the natural experiment evaluated for this dissertation, developing deep knowledge of the subject matter involved linking a wide body of literature reflecting the constructs of the mismatch of evolution with the modern woman's body, in particular the functional expectations of the bladder.

In Chapter 6, the natural experiment is designed to test the hypothesis that lowering the *intensity* of societal messaging (prevention treatment group: lesser intensity of messaging) results in lower beverage intake and decrease in void frequency (control group: intensity of messaging stays high). This exemplar natural experiment is positioned within the postpartum breastfeeding time period, a life course event that is arguably one of the most applicable in terms of applying an evolutionary medicine framework to a situation representing arguably an extreme social messaging to "drink beyond thirst" for the sake of the baby as well as the mother. Paralleling "you're eating for two" in pregnancy this dissertation presumes lactating mothers receive similar

high intensity societal messaging about drinking: “you’re drinking for two.” Keeping the terminology parallel, we use the phrase “drink beyond thirst_{for2}” for breastfeeding versus “drink beyond thirst” for non-breastfeeding women at the 8 months postpartum time point.

The message to “drink beyond thirst_{for2}” does not necessarily originate within the medical community but rather from aspects in our society. However, the medical community is embedded within society, and strong societal messages are all around us. These messages come, for instance in informal support groups, friends and family, blogs, non-medical websites, and even medical websites, which purport the “drink beyond thirst” habit as a hydrate for health culture that we are all entrenched in (as documented later in this dissertation). There is genuine belief (logical belief) that there is maternal fluid lost in breastfeeding, so it seems logical that an increased fluid intake is needed to “keep up milk production.”

Following this logic, if “drinking beyond thirst_{for2}” is needed to maintain breastfeeding it should result in stable void frequency (reflecting stable state of hydration). But, when framed through the evolutionary medicine perspective, where the female body has long ago adapted to the breastfeeding state as a physiological norm, then “drinking beyond thirst_{for2}” within the context of a beverage driven society may be a risk factor for OAB because unneeded fluid results in greater urine volume with accompanying urge to void more. In other words, “drinking beyond thirst_{for2}” exceeds “drinking beyond thirst” to such a degree that one might consider women who only receive “drinking beyond thirst” messages as recipients of a treatment of primary prevention of the OAB tipping point during the high-risk time period of postpartum.

In the natural experiment exemplar study reported in Chapter 7, the untreated group of postpartum women are considered to be the “drink beyond thirst_{for2}” group due to their ongoing exposure to high intensity societal messages to drink beyond thirst. The treatment group is

considered the postpartum women not breastfeeding. That is, they have been treated because *intensity* of “drink beyond thirst_{for2}” is reduced to “drink beyond thirst.”

Consistent with evolutionary medicine theory (and one well-conducted study reviewed in Chapter 5), breastfeeding women are unlikely to require additional fluid intake much beyond their usual intake in the non-breastfeeding state. Data, mostly from animal studies, to support this speculation is presented in Chapter 6. In Chapter 7, findings from this dissertation’s natural experiment exemplar study indicate that a primary or secondary prevention strategy of reduced intensity of the social messaging to drink beyond thirst rather than drink to thirst results in lower consumption of on average 2 less servings of beverage intake per day (15oz less; $p = .01$) and trends towards lower void frequency (6.3, range 5.3-7.8 vs 7.2, range 6.0 – 9.3, $p = .07$). Although difference in voids by only 1 per day may on the surface seem inconsequential, it does represent a (roughly 15% change). This is important to note in terms of the frequency defining by the International Continence Society as the “complaint that micturition occurs more frequently than previously deemed normal by the women” (Haylen et al, 2010).

Assuming same goal of static hydration regardless of breast-feeding status, then logically there should not be a change in void frequency between the two conditions of breast-feeding and non-breasting (see more in Chapter 6). While it may be unlikely that women consciously perceive a one void difference per day in frequency, the data presented in chapter 7 is documented by daily diary, not recall. Taken along with a documented diary intake of a difference by 2 servings per day of beverages, this represents proof of concept that it is the beverage difference that is driving the void difference, not a difference by physiologic condition of breastfeeding or not breastfeeding. This logic chain and evidence base for proof of concept for the larger theoretical questions in this dissertation is detailed in Chapters 6 & 7.

The cohesion of this theory of hyper-hydration due to societal influence is supported by the dual findings that in the context of the postpartum post-vaginal birth time period of one year, within the woman situated within our beverage driven society, a beverage increase with breastfeeding brings on a risk for bladder void frequency increase, close to that seen in OAB. This risk is not necessary for maintaining a state of hydration homogeneous with the non-breastfeeding state. With a theoretical assertion of “drinking beyond thirst” as a risk factor of OAB, this study shows that reduction in intensity of the risk factor results in an intake/output pattern further away from a state of OAB symptomatology. We speculate that the chronic state of OAB may be similarly based, at least for some women, in chronic exposure to the modern beverage-driven society long term, and when effects of an aging bladder/urethra make the situation much less tenable.

Results of this exemplar natural experiment study lead us to the consideration of prevention. Prevention can reduce the burden of chronic disease by reducing exposure to risk factors; the prevention framework should include primary, secondary or tertiary approaches. Briefly, primary prevention operates prior to the onset of disease: for example, preventing young people from becoming addicted to smoking as a deterrence against lung cancer, or as argued in this dissertation, preventing OAB symptoms by reducing exposure to high intensity social messaging for unnecessarily high beverage intake.

This dissertation addresses the need to determine whether primary prevention at a societal rather than individual level regarding our beverage intake intensity is warranted. Trying to overcome pervasive and habitual beverage-in-hand customs is difficult, and beverage intake crosses over into other chronic diseases such as obesity, diabetes, etc. where the relationships are better documented (Davy, Zoellner, Waters, Bailey, Hill, 2015; Popkin, 2006, 2009, 2010, 2011).

Overall, this dissertation questions the logic of our current beverage-driven society as it relates to bladder health by using an evolutionary medicine lens as the theoretical framework and providing a natural experiment design to address issues of studying OAB during a key time period in a woman's life, within the societal context of the modern beverage environment. Overactive bladder is a chronic disease, with epic proportion incidence and prevalence (chapter 2) and enormous cost in both dollars and quality of life.

Chapter 2 **Overactive Bladder Definition**

Overactive Bladder (OAB) is currently viewed as a collection of symptoms and not one disease process, which can create confusion for both clinician and patient alike. Prior to the 1980's, "unstable detrusor" and "detrusor hyperreflexia" were favored terms for OAB. "Urge-frequency syndrome" and "irritable bladder" have also been used to describe the symptoms of OAB (Dmochowski & Newman, 2007). The term "overactive bladder" was first used clinically in the 1990's, coined by Abrams and Wein (1997, 1999) but it was only in 2002 that the International Incontinence Society formalized the clinical diagnosis of "overactive bladder syndrome" as "urgency, with or without urgency incontinence, usually with frequency and nocturia" (Abrams et al., 2010; Lee, et al, 2013). The International Continence Society (ICS) currently defines OAB as "urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, *in the absence of urinary tract infection or other obvious pathology*" (Haylen et al., 2010, p. 6). Frequency is defined by the International Continence Society as the "complaint that micturition occurs more frequently than previously deemed normal by the women" (Haylen et al, 2010). Clinically, it has been accepted that 8 voids during daytime is considered normal, based on a 1988 study of asymptomatic Swedish women (Larsson & Victor, 1988). American studies have used frequency cut offs as low as 8 and as high as 10 voids daily to indicate OAB (Fitzgerald, Stablein, Brubaker, 2002; Hashim & Abrams, 2006) indicating a need for more studies to establish "normal" voiding patterns in both asymptomatic women and aging women. It seems common sense that in these studies, there is a

need for correction for fluid volume intake and even season of the year or climate. Intuitively, frequency of urination is related to total fluid intake and total voided volume. Without correcting for fluid intake, an established mean frequency variable is nonsensical. The International Continence Society has been unable to clearly define a numerical set point for frequency, based on research data. Ultimately, there is no current true objective measure of OAB.

It is important to differentiate OAB from stress incontinence. The defining symptom of OAB is subjective urinary urge and this may or may not result in urine leakage (wet or dry OAB). With stress incontinence, the complaint is “the involuntary leakage on effort or exertion, or on sneezing or coughing”; there is no sensation of urinary urgency (Luber, 2004). Anecdotally, however, women with stress incontinence who have intrinsic sphincter deficiency (a weak and open urethra) may also have urgency as the urine dips into the widening of the urethra at the urethrovesical junction. Hence, urgency from this age-related condition, can lead to development of a pattern of frequency related to the effort of maintaining bladder control, lost under the slightest provocation. The woman’s goal in this case is to maintain bladder volume at a level so low that large volume stress-type leakage does not occur. In these cases, increased frequency should not be defined as OAB, rather stress incontinence known as urethral sphincter deficiency. The inadvertent result of this failure to capture this nuanced category is a hidden subset of patients sometimes diagnosed with OAB but who might also be subsumed under the category of stress incontinence (Payne, 1998). In addition, other conditions such as painful bladder syndrome can mimic OAB symptoms. (Some of these alternative explanations for and associations with OAB are discussed briefly in Appendix A, but these patient populations are not the main focus of this dissertation).

Scope of the OAB Problem

Partly due to the elusive definition of OAB, the true prevalence is unknown, and may be underestimated. Attempts at measuring urgency are highly subjective and fraught with issues (for more detail, see Appendix B). For complex reasons, such as shame, patients may never seek medical help and therefore remain unreported. In addition, because OAB is a more recently identified condition, its precise definitions, prevalence, and natural history are evolving in relation to other urinary disorders, such as stress incontinence and detrusor instability. Until recently, epidemiologic surveys commonly investigated incontinence *together* with urgency and frequency, yet failed to capture urgency and frequency if the study subject was *not* incontinent.

OAB, with or without incontinence, is a prevalent and serious health problem worldwide for both men and women (Stewart, et al, 2003; Reynolds, Fowke, Dmochowski, 2016). The National Overactive Bladder Evaluation (NOBLE) survey assessed a sample of 5204 adults (>18 years), representative of the US population by sex, age, and geographical parameters, and found an overall OAB prevalence of 16.0% in men and 16.9% in women, increasing with age to about 31% in both sexes (Stewart, et al, 2003).

An indirect indicator of increasing OAB prevalence over time is that prior to 1980, there were no disposable incontinence products on the market. Kimberly Clark was the first company to become involved in producing incontinence products, introducing Depend incontinence briefs (adult diapers) in 1980 and Poise incontinence pads for women in 1990 (Kimberly-Clark, 2017). Before the availability of commercial products, women (and men) used menstrual pads or devised their own pads to protect against leakage. Women continue to use menstrual pads in place of or along with incontinence pads, as they are sufficient for slight/mild incontinence and are less expensive (Subak, Van Den Eeden, Thom, Creasman, Brown, 2007). Did the marketing

of incontinence products occur due to an increase in OAB symptoms/ urinary leakage events in the population, a decrease in personal discomfort in facing the issue, a desire to “cash in” on a long standing or evolving health issue, or a combination of these reasons? There is now an abundance of incontinence products in supermarket aisles, marketed to men and women.

It is unclear then if OAB symptoms have increased in recent decades, have been clinically differentiated from other lower urinary tract symptoms such as stress incontinence, or have become more visible due to decreased stigma, spurring discussion between patient and doctor. What is clear however, is that the frequency of research (journal articles) reported using the term “overactive bladder” increased beginning in the late 1990’s (Figure 3), and this timeframe is additionally substantiated in usage frequency in published books (Figure 4).

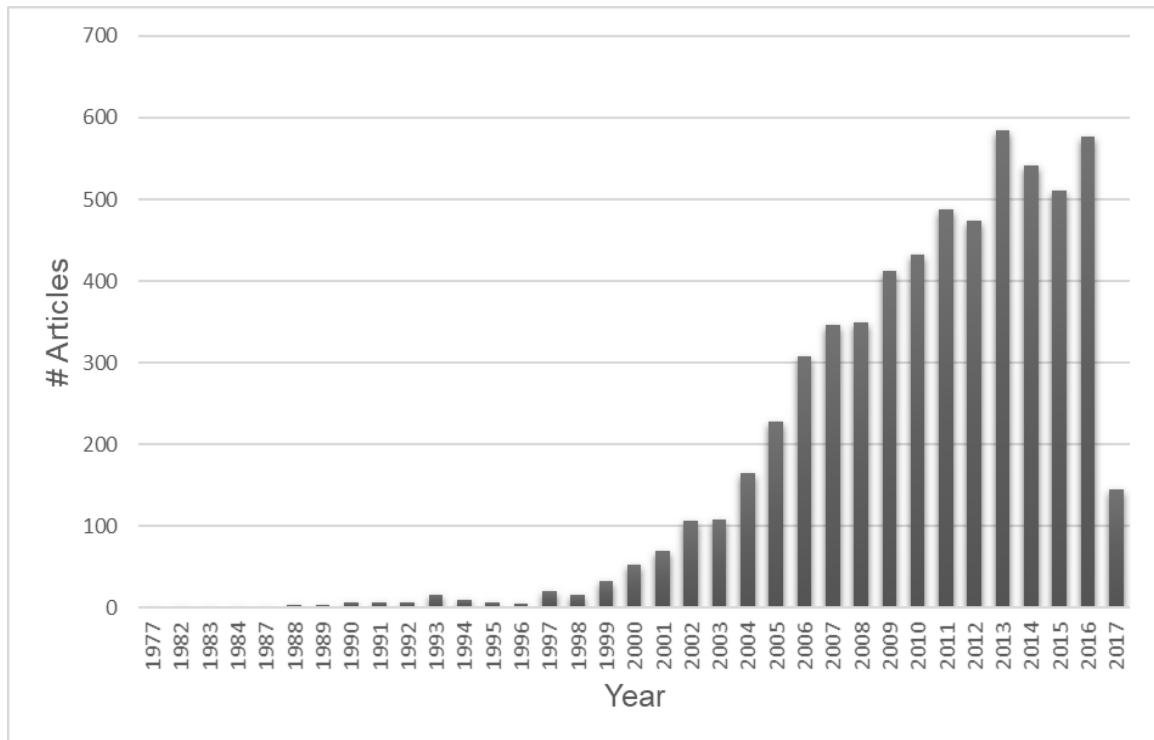


Figure 3 Frequency of Journal Articles Using "Overactive Bladder" in a PubMed Search, 1970-2017

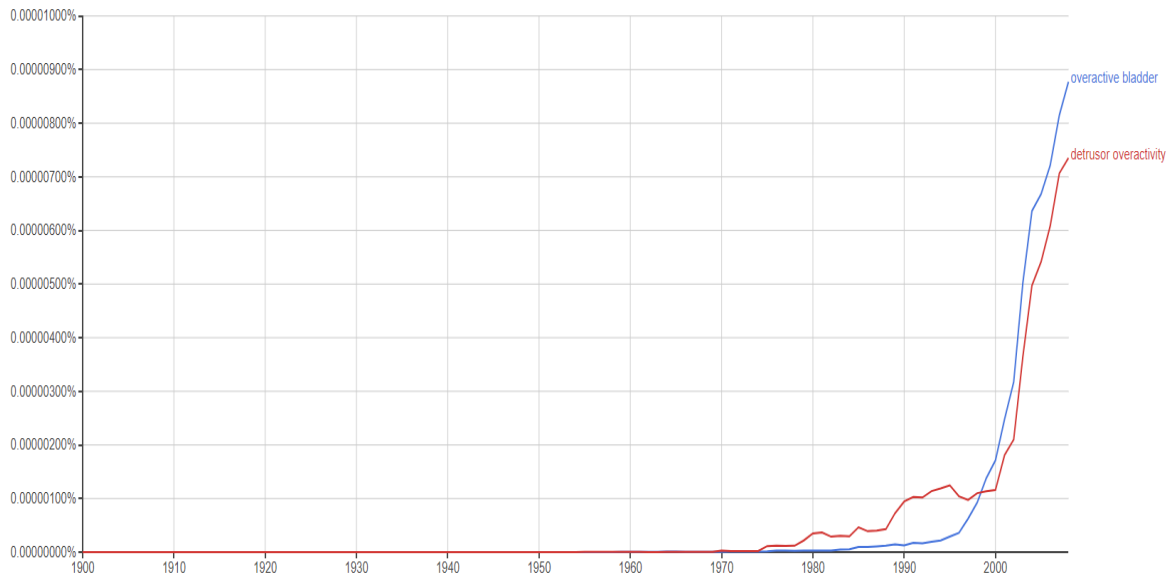


Figure 4 Frequency of Number of Books Published on "Overactive Bladder" and "Detrusor Overactivity" 1900-2017, as Constructed by Google Books Ngram Viewer*

*Ngram viewer is an online search engine that charts frequencies of any set of comma-delimited search strings using a yearly count of n -grams found in sources printed between 1500 and 2008. As an adjustment for more books having been published during some years, the data is normalized, as a relative level, by the number of books published in each year.

The Cost of OAB

OAB takes a significant toll both on the quality of life and the finances of the individual. Ganz, et al (2010) most comprehensively assessed the direct total annual costs in 2007 of OAB (with urinary incontinence) for adults (≥ 25 years) to be \$65.9 billion. Direct costs included personal care (e.g. incontinence pads, laundry, and diapers), medications, and doctor visits, and did not include lost work or productivity of the patient. OAB also has a pervasive impact on the quality of life of an individual. Patients monitor proximity to a bathroom, restrict their fluid intake, wear incontinence pads, and generally are aware of their bladder state at most times. Sleep may be negatively impacted due to nocturia, and isolation and depression are experienced more often as individuals curtail their daily activities and social events (Gentili, Weiner, Kuchibhatil, & Edinger, 1997; Zorn, Montgomery, Pieper, Gray, & Steers, 1999). Negative effects are experienced in social, recreational, professional, and sexual arenas as well as personal

relationships with family members (Coyne et al., 2007; Coyne et al., 2004; Coyne et al., 2008; Dmochowski & Newman, 2007; Irwin, Milsom, Kopp, Abrams, & Cardozo, 2006; Wyman, Burgio, & Newman, 2009).

Given the difficulties with the definition of OAB, the differential diagnosing of OAB, and the compounding individual and familial cost OAB poses, it is clearly important to address the current rising trend of OAB symptoms systematically.

Chapter 3 **Evolutionary Medicine and Chronic Disease**

Evolutionary medicine is a field of research that examines and seeks to understand human health and disease within the principles of evolutionary theory. In evolutionary medicine, adaptation to the environment through epigenetic and physiological changes is a focus in considering human health and disease. Three levels of consideration are holistically applied when understanding chronic disease from an evolutionary perspective. The classic medical history of symptoms is initially gathered. Second, the developmental history is considered, including information from conception onward. Finally, ancestral history is added, which in the broadest context is the evolutionary history of mankind. Considering health and disease in the context of these levels lends a focus towards not only direct therapy but also for clinical prevention (Gluckman, Beedle, Hanson, 2009). In essence, “proximate” considerations for disease are complemented with “ultimate,” or evolutionary concerns (Nesse, Stearns, 2008; Nesse, 2011).

Evolutionary selection operates to foster reproductive fitness. This means that the chronic diseases associated with aging in our modern society fall outside the age parameters for reproductive fitness. Lifespan and aging health are not evolutionary concerns. Reproduction occurs early in our life course, passing on genes that are adaptive for survival early in the lifespan. Traits that are expressed after reproduction in the life course are not selected against and may then contribute to chronic disease and the aging process (Mace, 2013). There is no

“higher purpose” imbedded within the evolution of the human genotype/phenotype. Human traits have evolved as environmental adaptations (Gluckman, Beedle, Hanson, 2009).

Disease then, in the context of evolution, is not in any way selected for as evolutionary adaptation to the environment. However, many symptoms of disease, such as inflammation, fatigue, fever, pain, gastrointestinal distress, and respiratory problems are evolutionary adaptations. These adaptations are useful physiological defenses which have evolved for survival reasons, yet they can result in disease states within organ systems (Nesse, Williams, 1996; Ruhli, van Schaik, Henneberg, 2016).

Evolutionary Medicine and Beverage Intake

Our current genome is basically unchanged from that of the hunter-gatherer; 99% of mankind’s existence has been spent consuming a forager’s diet (Gluckman, Beedle, Hanson, 2009). The Paleolithic era (35,000-20,000 B.P.) was the last time period our genome existed within a bio-environmentally matched environment (Eaton, Konner, Shostak, 1988). Our diet has changed significantly from the hunter-gatherer diet due to the agricultural revolution (5,000-11,000 B.P., depending on location) and more recently, due to the Industrial Revolution (1760-1840). The agricultural revolution transitioned cultures from the hunter-gatherer lifestyle to a lifestyle of settlement and domestication of plants and animals. This change limited the diet of hunter-gatherers, who had previously consumed a range of tubers, seeds, fruits, and lean meats, into a more restricted and less optimal diet. The major adaptation to beverages during this time period was the ability to digest lactose in some populations, which evolved in Northern Europe within the dairy farming environment (Bersaglieri, Sabeti, Patterson, et al., 2004) and in Africa due to animal domestication (Tashkoff, Reed, Ranciaro, et al, 2007).

Recent evolutionary history introduced animal milk, production of fermented wine and beer (between 10,000-4000 BCE), distillation of other alcohols (8th century), fruit juices, and coffee (15th century) and teas (~1st Century CE) (Standage, 2006). Most recently, the Industrial Revolution moved civilization toward more dependence on manufactured food, which increased the production, availability, and consumption of fats, sugars, and refined grains. These foods and beverages have become increasingly processed and modified, with additives for shelf stability, convenience, and taste appeal. We find ourselves now with a wide selection and abundance of nutrient-poor, calorie-rich foods and beverages.

Until approximately 10,000 years ago, (and most of our evolutionary history), we drank only water and breast milk. Breast milk provided protein, carbohydrates, fat, and water, formulated at the perfect ratio for the infant and toddler throughout development until weaning, when water contributed zero calories or nutrients to the diet. At weaning, the ability to digest milk was lost. It was 5,000-10,000 BP (before present) when the enzyme lactase persisted beyond toddlerhood in segments of the world population, allowing adults to digest milk products (Wolf, Bray, & Popkin, 2008) (Figure 5).

Remarkably Short History for New Beverages:

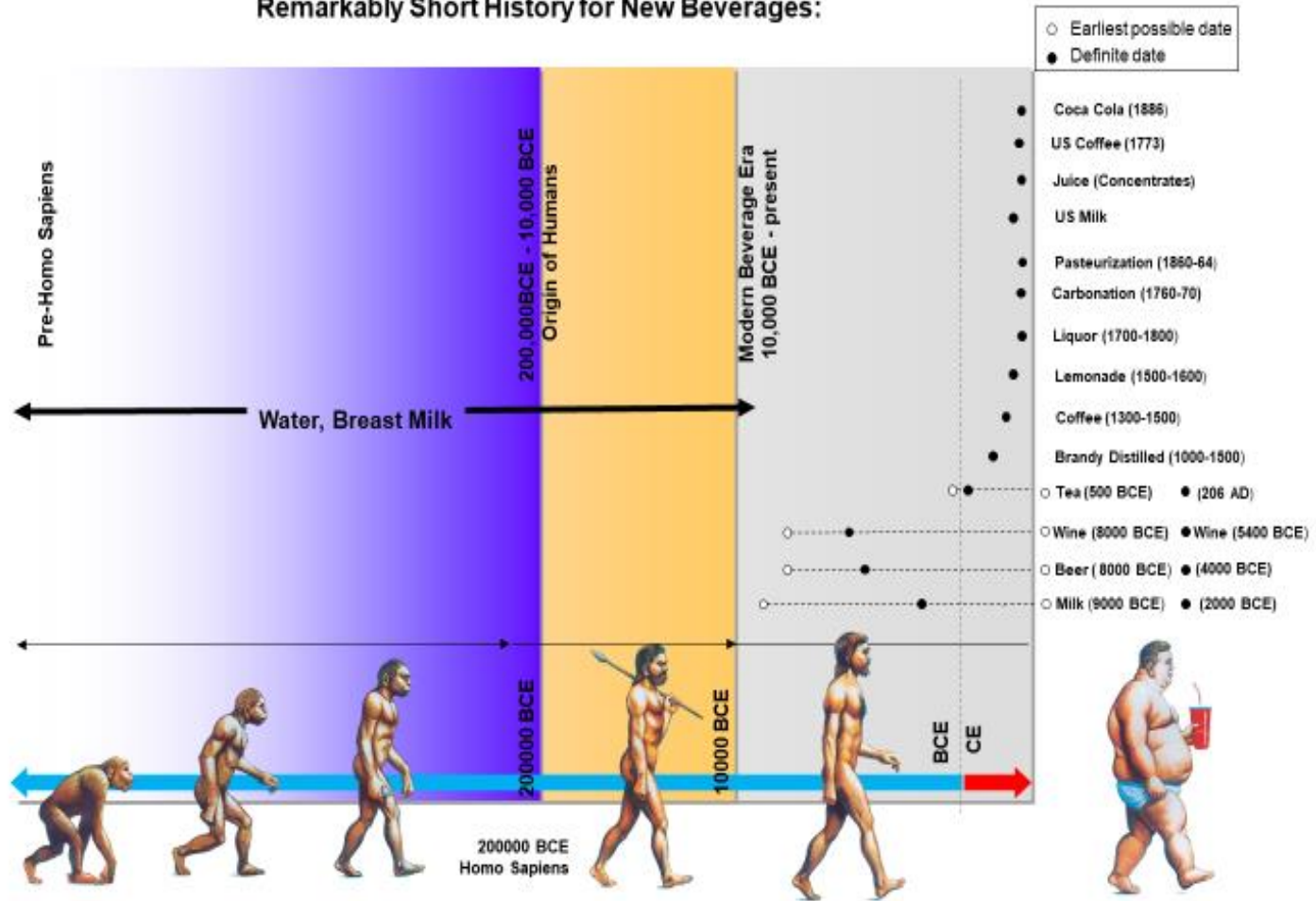


Figure 5 History of Beverages*

*Adapted from Popkin, B. (2009)

Until 2015, carbonated soft drink consumption involved 37% of all beverage sales and soft drinks were the most popular beverage choice in the United States. Recently, nutritional concerns have caused a decline in soft drink sales, including diet soft drinks, and it is anticipated that this trend will continue (Del Buono, 2016). The largest consumer of diet beverages is the adult aged 40-59 (Popkin, 2010), and tends to be female, Caucasian, and have a higher income (Fakhouri, Kit, Ogden, 2012). Carbonated sodas, especially caffeinated diet sodas, are particularly associated with the OAB symptom of urgency (Dallosso, et al, 2003; Maserejian et al., 2013). But, as soft drink sales have gone down, bottled water sales have gone up (See Appendix A).

The theoretical implications of evolutionary medicine connect the development of the modern obesogenic environment (diet, lifestyle, technology, thrifty genes) to a mismatch with our hunter-gatherer genome (Figure 6). The resulting adaptations/symptoms are linked to increased susceptibility for “affluent” chronic diseases such as obesity, hypertension, cardiovascular disease, and cancer (Luckock, Martin, Yates, & Veyses, 2014). Chronic disease is rare in cultures with a more traditional nutritional environment. Although a comparison between modern foraging cultures and our ancient origins is only an approximation, it is notable that obesity and type II diabetes typically are the first chronic diseases to appear in economically transitioning societies (Eaton, Konner, Shostak, 1988). Industrialized, western culture has a higher prevalence of diabetes (3.0-10.0 %), for example, than hunter-gatherers and more simple horticulturists and agriculturists (0.9-2.0%) (Hamman, 1983). Immigration from third-world countries to western culture results in increased diet related chronic disease such as obesity and type II diabetes, (Popkin 2004; Satia, 2010).

Hunter-Gatherer Genome, Nutritional Environment & Chronic Disease

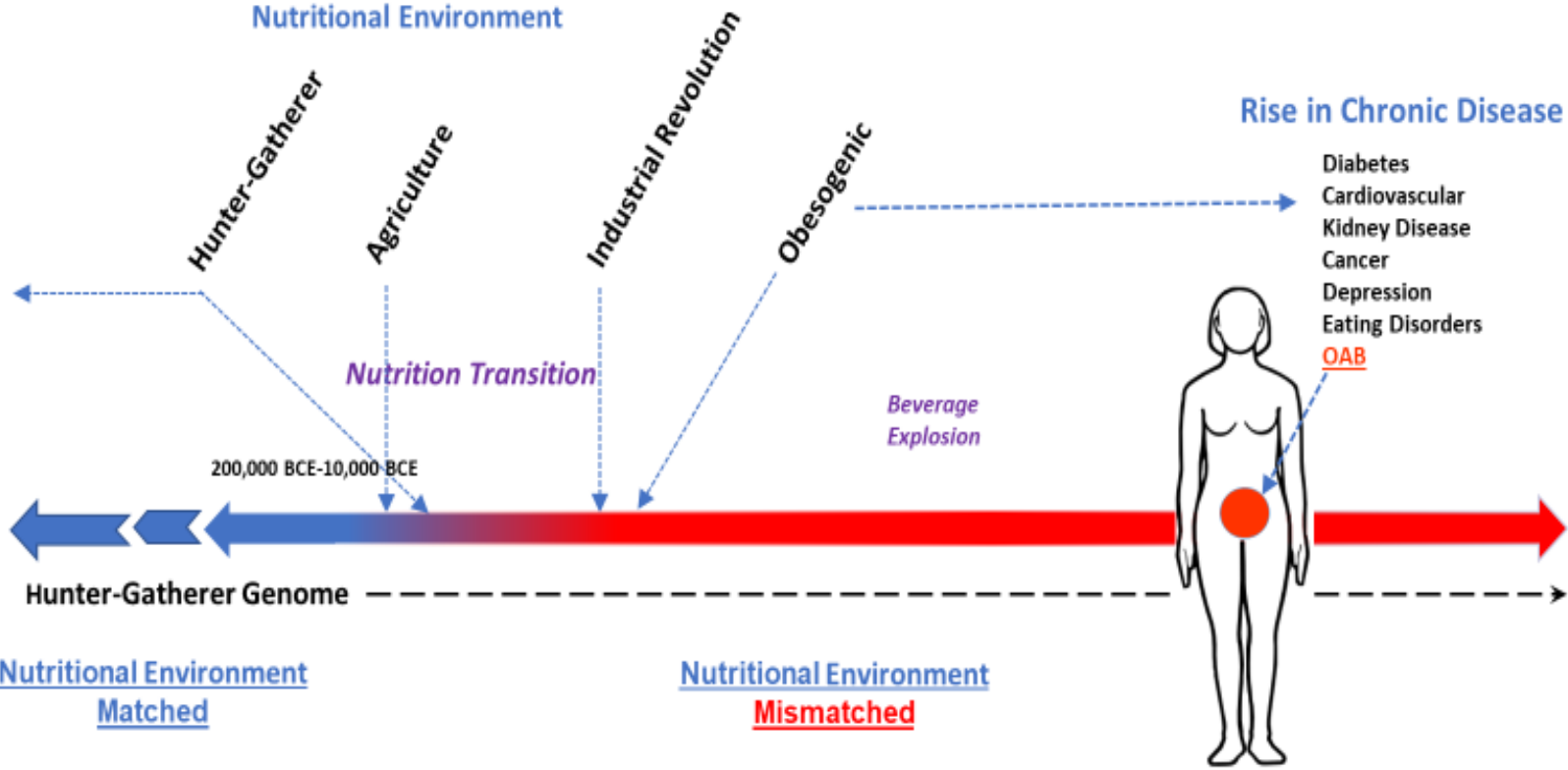


Figure 6 Mismatch Between Modern Nutritional Environment and Hunter-Gatherer Genome with Chronic Disease Outcome

Humans are, after all, animals. During the last century, bears were fed carbonated, sugar sweetened beverages at wildlife parks, for the amusement of tourists who found it completely out of character for a “wild animal.” The thought of pouring a carbonated soda or power drink into the water bowl of a thirsty family dog feels unacceptable and unhealthy. As a society, however, we feel no dissonance in drinking these beverages ourselves routinely, sometimes in high volume. Like a bear given soda in the artificial environment of a circus, we are now given a manufactured experience of beverages that appeal to our taste, pleasure, urge for excitement and sensory alteration. We use beverages for comfort and to aid social connections. Arguably, we have been primed to do so beginning even with one of the most popular television advertisements ever made, sung on a hilltop by a multicultural group of young people (Figure 7). The song became a hit record in the US and UK, promoting a positive message of love and hope, centered on the drinking of Coca Cola.

Fundamentally, however, we remain “wild animals” whose biological needs for fluids are satisfied by water: the water in the foods we eat and mother’s milk until we are weaned. It is not clear what the cost of a lifetime of these other beverages, with additives and metabolites, are on the human body. The bladder may be negatively affected by established and enduring exposure.

Over the last 50 years, the beverage intake habits of Western Society have dramatically changed. The proportion of water and milk in the daily beverage diet has decreased, intake of

I'd Like to Buy the World a Coke
1972 lyrics

I'd like to buy the world a home
And furnish it with love
Grow apple trees and honey bees
And snow-white turtle doves
(Chorus)
I'd like to teach the world to sing
In perfect harmony
***I'd like to buy the world a Coke
And keep it company***
That's the real thing
(Chorus)
(Chorus 2)
What the world wants today
Is the real thing
What the world wants today
Is the real thing

Written by Billy Davis, William M. Backer,
originally written by Roger Greenaway,
Roger Cook.

*Figure 7 "I'd like to buy the world a coke"
1972*

sugar sweetened beverages and caffeinated drinks has increased, and associated with these trends, calorie intake and BMI have risen (Vartanian, Schwartz, Brownell, 2007; Malik, Schulze, Hu, 2006; Malik, Popkin, Bray, et al., 2010). With increased variety and volume of beverages, the intake of beverage ingredients such as regular and artificial sweeteners, caffeine, and other chemicals have also risen. Starbucks, one of the most popular coffee houses, began in 1971 with one store in Seattle, Washington. By 1990, there were 84 stores in the United States, and by 2015 there were 22,519 global Starbucks stores (Starbucks Company Timeline, no author). On the other hand, the number of drinking fountains supplying free city water has diminished, both in public spaces (Gleick, 2010) and in schools (Popkin, 2009), replaced by vending machines and bottled water.

Not only beverage type has changed, but beverage size has evolved. Overall portion sizes of both beverage and food began to increase in the 1970s, with a 5% increase during that decade. In the 1980s, portions increased by 20-35% and by the late 1990s, portion size had increased by 63% from the pre-1970 portion sizes (Young & Nestle, 2002). As an example, a 64-oz. “Double Gulp” from 7-Eleven contains almost 800 kcal and is 10 times the size of the original Coca-Cola’s sold at the turn of last century. Starting in the late 1880s, a Coca-Cola bottle contained 6 ½ oz. until 1955, when 10 and 12 oz. bottles were introduced (Coca-Cola Company, no author).

Between 1977 and 2001, energy intake from sugar-sweetened beverages increased by 135% in all age groups (Nielsen & Popkin, 2004). There are several additives used to sweeten beverages: high-fructose corn syrup, corn syrup, sucrose, fructose, dextrose, honey, lactose, brown sugar, corn sweetener, corn syrup, maltose, malt syrup, and molasses. Sugar-sweetened beverages include: regular (non-diet) soft drinks, sports drinks, energy drinks, fruit drinks, sweetened waters, vitamin drinks, and sweetened coffee and tea beverages (U.S. Department of

Agriculture, 2015). Although intake of tea and coffee has remained stable, more of these beverages are now being consumed as high calorie, sweetened beverages at coffee shops. Between 2011-2014, 63% of children and 49% of adults drank at least one sugar sweetened beverage per day (Rosinger, Herrick, Gahche, Park, 2017). “Diet” or artificially sweetened beverages have also dramatically increased, from only about 3% of adults consuming diet beverages in 1965 to at least 20% of adults today. Diet drinks are either free of calories or are low calorie versions of sugar sweetened beverages, and do not include fruit drinks or unsweetened coffee and tea beverages. They do include carbonated water beverages (Fakhouri, Kit, & Ogden, 2012).

Mismatch Between Nutritional Environment and Genome

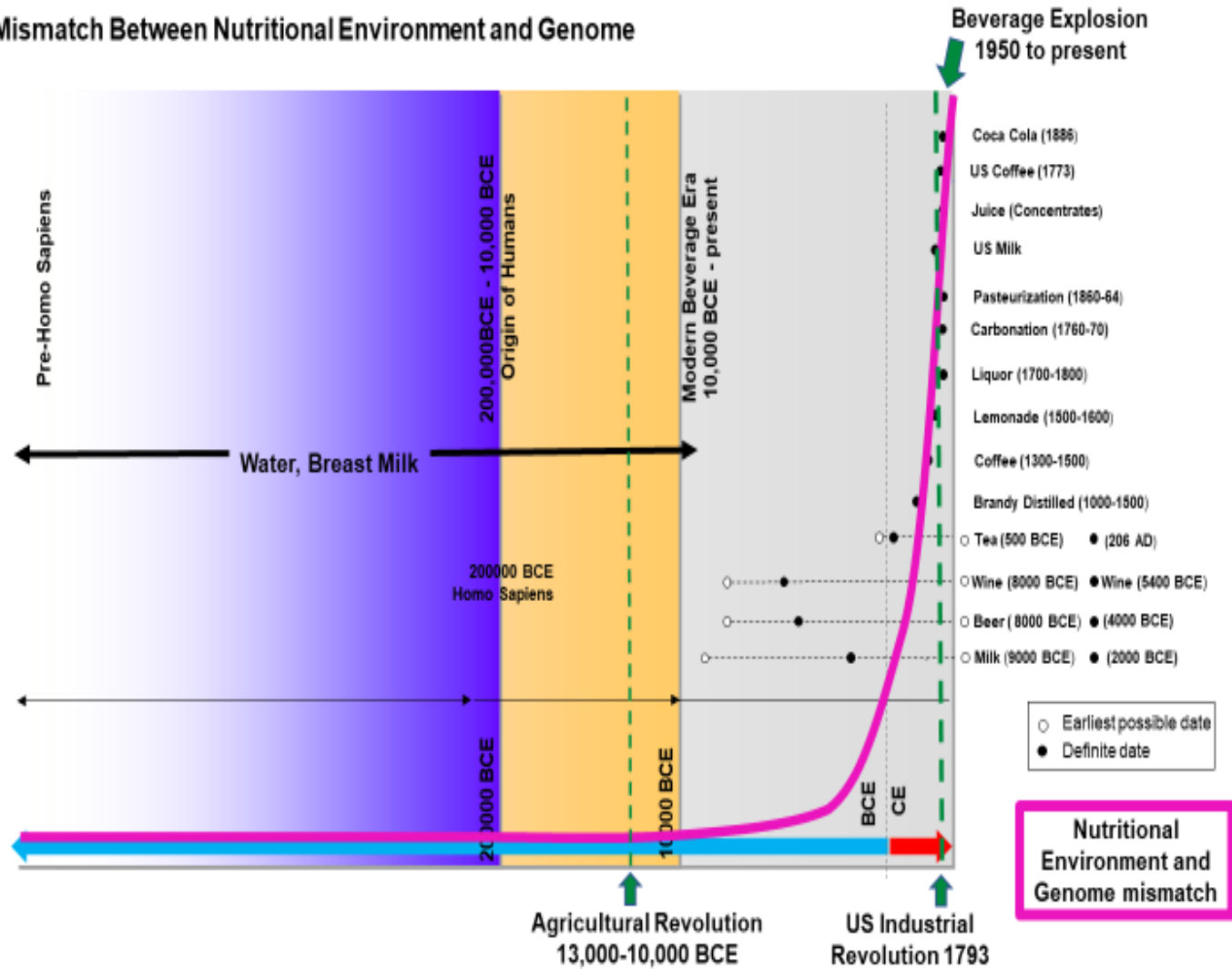


Figure 8 Mismatch Between Nutritional Environment and Genome

In recent history, as our nutritional environment has rapidly changed (including the beverage explosion), the incidence of chronic disease has trended upwards, partly as a function of our aging population and partly because of modern lifestyle choices, complicating issues of health care assessment, diagnosis, and treatment. Chronic disease, in this discussion, refers to any condition or syndrome that results in a decrease in optimal functioning over time. In 2012, roughly half of all adults in the USA had one or more chronic disease conditions such as obesity, cancer, heart disease, type 2 diabetes, or arthritis (Ward, Schiller, Goodman, 2014), with the cost of chronic disease health care taking 86% of total health care costs (Gerteis, et al, 2014). Overactive bladder is a condition within this overarching problem facing us in today's modern world (Figure 8).

Chapter 4 **The Overactive Bladder: Measurement**

It is important to remember that OAB is a presentation of symptoms without evident pathology of the bladder. The term OAB has become a catch-all umbrella term, but implies in its definition an origin and cause of frequent voiding that is attributed to sources outside of the bladder itself. More data is needed to differentiate in what manner the “non-pathological” bladder presents as the actual problem in terms of its anatomy (including other urinary structures), and physiology. If urgency/frequency symptoms are to be defined as pathologic, and OAB is currently defined as “non-pathological” bladder, then where is the pathology?

Various theories exist to explain the bladder symptoms of OAB. In this dissertation, the theoretical explanation posed is that our modern beverage environment, dramatic in the variety and emphasis on beverage intake, is mismatched with the evolutionarily-evolved bladder capacity to such an extent that the mismatch reveals itself as void frequency. The “normal” bladder responds to neuromuscular messaging and empties at a physiologically determined capacity that is at odds with the volume of urine produced in the hyper-hydrated woman. A variety of alternative theories have also been posed. None of these are well substantiated. Regardless, a brief mention is in order here, and details are more fully provided in Appendix A.

Neurogenic theories and myogenic theories (covered in Appendix A), each suggest bladder pathology, and for this reason fall outside of a strict definition of OAB. The role of caffeine in triggering a pathological activation of the detrusor muscle has also been explored, and like other theories, provides mixed evidence geared to a developed bladder pathology. Ghelin, a

hormone of the digestive system, is implicated in the development of obesity, which itself is strongly associated with bladder symptoms (Lawrence, Lukacz, Liu, Nager, & Luber, 2007; Auwad et al., 2008; Subak, Richter, & Hunskaar, 2009). Interestingly, ghrelin receptors are also found in the urinary tract and bladder of rats (Rizk & Fahim, 2008; Suzuki, Simpson, Minnion, Shillito, & Bloom, 2010; Chancellor, Oefelein, Vasavada, 2010).

Gaps in the OAB literature include a lack of acknowledgement of the obvious, in terms of hyper-hydration (as noted in the Chapter 1 introduction referencing *The Emperor's New Clothes*), and include difficulty with the objective measurement of OAB. Measurement of OAB is currently dependent on subjective "urgency" sensation. Since 2000 there has been poor consistency in the research literature on instruments to measure urgency. Das, Buckley, and Williams (2013) systematically reviewed 11 years of research literature for OAB methodology and found that out of 216 instruments used to assess OAB, only 13 were reported more than 10 times. Out of these 216 instruments, only 58 were named (not just described), and accompanied by psychometric properties. In addition, many instruments were adapted/modified and/or unnamed. The authors believe, and it seems likely, that the high modification and adaptation rate could be related to the methodological difficulty in defining and capturing the concept of "urgency," requiring researchers to modify instruments to capture their unique parameters of interest. There were also "duplicate" instruments that contribute significantly to the overall number of 216, in that measures differed only in slight wording of scales or which number was used to anchor a 4-point scale.

The 13 instruments most identified within the OAB literature are the American Urological Association Symptom Score; Urinary Sensation Scale; Urogenital Distress Inventory; International Prostate Symptom Score; Bristol Female Lower Urinary Tract Symptoms

Questionnaire; King's Health Questionnaire, O'Leary-Sant Interstitial Cystitis Symptom Index and Problem Index; Pain Urgency Frequency Questionnaire; Overactive Bladder Questionnaire; Urgency Perception Scale; Indevus Urgency Severity Scale; verbal ordinal scales given with cystometry testing; and urgency event records within frequency charts and bladder diaries (Das, Buckley, and Williams, 2013).

Because urgency is a subjective phenomenon in OAB, the formulation of an accepted definition of "urgency" is both problematic and essential. The International Incontinence Society has consistently defined urgency as 'a sudden, compelling desire to pass urine (or to void), which is difficult to defer,' (Abrams et al., 2003; Haylen, et al., 2010, pg. 6) yet there is a debate as to whether urgency is a sensation felt along a continuum of increasing discomfort versus an all or nothing experience (Coyne, Harding, Jumadilova, & Weiss, 2012). In addition, measurement of urgency has resulted in the modifying and adaptation of instruments to suit varying definitions of the variable, supporting the lack of consensus on a definition of the variable.

Hence, measurement and evaluation of OAB has been an ongoing challenge, both in the clinical and research setting, and mainly due to the subjective nature of the variable of urgency that is definitional the hallmark of OAB, yet a subjective phenomenon and difficult to standardize. And, as mentioned earlier, OAB is a cluster of symptoms, not one defined disease process. With no objective measures of urgency, defined as "difficult to defer," clinicians and researchers often add an additional outcome measure that is easier to quantify: void frequency, to supplement the strictly subjective self-report of urgency. Hence, measure of void frequency per diary is nearly always hand in hand with a measure of urgency in studies on OAB. The "bother" of OAB to women pragmatically, is needing to be near bathrooms to act on the sensation of

“difficult to defer”; it is not the sensation in and of itself. Urgency is not pain (if pain accompanies, then patients are given a diagnosis of “painful bladder syndrome”).

From the woman’s perspective, “frequency” is when a woman considers her daytime urinations to happen more often than she desires or more often than previously considered normal for herself. Conventionally, 8 daytime voids have been clinically and methodologically considered the upper limit of “normal” when defining frequency, however individuals differ in what is “normal” for them (Homma, 2007). Frequency that is experienced at night is termed “nocturia” and defined as one or more voids during the night (Haylen et al., 2010). Frequency is commonly measured by voiding diary (Wyman, Choi, Harkins, Wilson, & Fanti, 1988).

Chapter 5 **Beverage Modification**

Most fluid modification programs for OAB are based on anecdotal reports from women who have reported decreased symptoms from individually selective fluid modifications. Increasing or reducing fluids (for example reducing fluids at night and avoiding potentially irritating or diuretic fluids) are often suggested in clinical settings, despite the lack of research on beverages and compounds within them.

“Potentially irritating” fluids have been variously defined, but for the purposes of this paper include coffee, tea, chocolate, colas, and alcohol as well as acidic fruit juices and beverages with artificial sweeteners. There is acceptance among health professionals and the lay public that certain fluids are bladder irritants. Currently it is unknown whether individuals with bladder symptoms are disadvantaged by insufficient or inappropriate counseling on differing fluid types or by being referred for more invasive and costly therapies that neglect a potential underlying and reversible cause of urge incontinence and overactive bladder. Even the most commonly consumed “potentially irritating” ingredient, caffeine, has scant and mixed data. See Appendix A for details of the literature on caffeine. The remainder list of potentially “irritating beverages” to the bladder essentially has no backing in evidence. Though a needed area of investigation, we focus here instead on beverage intake volume as the most likely driver of the OAB symptom of void frequency.

Total beverage intake volume

Physiologically, beverages provide about 80% of the daily need for hydration, with water content in foods making up the balance of the daily content (Food and Nutrition Board of the

Institute of Medicine, 2004). The common adage to drink eight-8-ounce glasses of water a day has unclear and unfounded historical/scientific roots (Valtin, 2002) and has been difficult to understand regarding what constitutes water (pure water vs beverages that contain water vs. the water in food), whether the daily 64 ounces is meant for an average sedentary individual, or if there must be compensation for body type, gender, weight, activity, etc. The traditional understanding by lay person and medical community alike has been to hydrate with at least 64 ounces of fluid per day, omitting “diuretic” beverages such as coffee and tea. Currently, the recommended intake of fluid has been changed to “drink to thirst” (Hew-Butler et al, 2015), however the medical community, media, and general population is lagging in knowledge.

A prospective, observational crossover study found that decreasing overall fluid intake significantly improved OAB symptoms (voiding frequency, $p=0.003$, urgency weeks 1&2, $p=0.006$, $p=0.042$, and incontinence episodes, $p=0.006$) in 30 women with idiopathic detrusor overactivity. Interestingly, decreasing caffeine intake made no significant improvement in symptoms when replacing caffeine-containing beverages with non-caffeinated drinks (Swithinbank, Hashim, Abrams, 2005). Miller, Garcia, Becker Hortsch, Guo, and Schimpf (2016) attempted a study design which asked women to reduce intake of potentially irritating substances (containing caffeine, artificial sweetener, citric acid, and alcohol) while retaining total beverage intake. Although the subjects were unable to completely eliminate potentially irritating substances from their diet, they did experience symptom relief from potentially irritating beverages reduction, although not in proportion to elimination. As the authors noted however, the OAB relief could not be linked to the reduced potentially irritating beverages intake, the reduced total daily beverage intake, the increase in attention to bladder habits, or a combination

of those factors. As well stated by expert urogynecologist and co-author of the report (M. Schimpf, personal communication, December 9, 2107):

Part of the problem I hear from patients is that they don't want to decrease their irritants (they will almost threaten me physically if I "take away" their coffee) or don't believe me that those are important. That societal messaging (and addiction?) is so powerful it often trumps my advice. We saw that in our study, and it's SO true in real life. Think of all the people who'd never even consent to being in a study that asked them to reduce irritants!

What influences overall fluid intake?

People drink beverages for numerous reasons, only one of them being thirst. Nutritional research supports beverage intake as a unique and important dimension in food intake. Beverage intake can be separate from food intake and experienced in different contexts from eating, with the beverage intake episodes "important parts of their daily routines" (Bisogni et al, 2007, p 226).

Beverages have become a focal point of cultural interaction, with coffee houses serving as social hubs, side tables at conferences and business meetings filled with water bottles and beverages of all varieties, and individuals toting bottled water and various beverages with them in disposable or reusable containers.

It is important to consider the increase in beverage consumption and associated ingredients and health consequences within the broader framework of evolutionary medicine. The patient with OAB is faced not just with the advice to modify the quantity of fluid she drinks during the day; she is asked to avoid beverages thought to be irritating, all while immersed in a culture that is focused on sugar-sweetened, artificially sweetened, stimulating, vitamin-laced,

diet -focused and hydrating/oral pleasure. Miller, et al. (2016) found that in a study focusing on beverage elimination, specifically potentially irritating beverages, and bladder symptoms, study participants had a difficult time voluntarily reducing their intake of these potentially irritating beverages. Even when the eliminated beverages were replaced with alternative, non-potentially irritating beverages, the subjects were unable to completely avoid or omit these potentially irritating beverages. This inability to avoid potentially irritating beverages focuses attention on the beverage environment and the subjective experience of beverage intake.

Beverages serve unique purposes in our society. They are mediators in social connections, as in “getting together for coffee at the local coffee shop.” Beverages anchor workplace meetings, with coffee, tea, water bottles and soda provided on conference side tables. Individually based fluid modification programs do tend to help with OAB symptoms, but they are difficult to maintain for the long term, given the emphasis on beverages in our society.

Currently, OAB cannot be fully resolved in treating the patient at the individual level. Clinicians offer educational, behavioral, pharmaceutical, and surgical options for treatment, but patient compliance and relief is variable and pharmaceutical side effects remain ongoing. If prevention, rather than treatment becomes the focus for OAB, then correct societal messaging about beverage intake may be one of the strongest pieces in the puzzle in relieving OAB symptoms. Perhaps then, another way to approach treatment for OAB is a preventative approach.

Chapter 6 **Background to a Natural Experiment: How Societal Mores Affect Beverage Intake with Implications for the Bladder**

An experiment was designed to address part of the question of what “drinking to physiologic need/hydration” means within a population of postpartum women. Nutritional quality, including beverage intake, is an important societal and medical focus for pregnant and lactating mothers. This research examines how beverage intake in postpartum women (amount and type) relates to voiding pattern and bladder functioning. If the postpartum period with breastfeeding is a transition point within the life course perspective, motivated nutritional choices can impact both the health of the mother and the new child. Bladder health or dysfunction, if related to beverage intake over time (type and amount), is a possible outcome of beverage/nutritional transitions. The overactive bladder is an obvious choice for examination considering breastfeeding woman within our beverage-centered society.

Women and Beverages

Life course perspective frames food choice within historical, social, and temporal contexts. Women often have a complex relationship to nutritional choices, mediated by such variables as societal expectations for feminine beauty, individual phenotype, and developmental aspects such as self-identity, which partly forms within the relationship with the mother. A life course perspective partners easily with the evolutionary medicine framework, as both examine health within the context of history. In the life course perspective, individual biological variables interact with life history factors (prenatal through old age) such as environmental, social, and behavioral influences, in examining the complex origins of health problems (Devine, 2005). It is

not the purpose of this paper to address the complexities of how women choose beverages, however, further research is needed to understand what drives the consumption of beverages for women, from a cognitive, behavioral, and cultural perspective. For example, it is important to understand the anecdotal trend of women and diet coke consumption (reviewed in more detail in appendix A).

Breastfeeding Women and Beverages

The nutrition and health of women and children are interwoven before, during, and after childbearing. Pregnancy is often the first time a mother considers her nutritional intake and health status as affecting more than herself. After childbirth, a woman's identity in relation to nutrition affects not only herself, but her family, often determining the type and quality of nutrition available in the household. In addition, variables such as socioeconomic status, knowledge level, ethnicity, and the historical context of societal diet contribute to nutritional choices. Overall, the period of pregnancy and childbirth is a transitional point in the life of a women and for some women, nutritional choices change (Devine, 2005).

Fluid management has a longstanding tradition in the clinical education and care of postpartum/breastfeeding women. Postpartum women are advised, both clinically and culturally, to increase their fluid intake while breastfeeding to facilitate both milk production and to prevent dehydration. The presumed need for an increase in fluid intake/volume does not take into consideration the impact on the bladder, as it is often assumed that the additional intake will equal the output of breastmilk.

Avoiding dehydration has been a focus in our culture over the past decades, with the common adage to drink eight, 8-oz. glasses of water a day serving as a minimum hydration rule. This 8 x 8 hydration rule first appeared in dietary guidelines in 1945 by the Food and Nutrition

board of the National Academy of Sciences, as a footnote recommending 1 mL of water for each kilocalorie for the average male, requiring 2,500 kilocalories per day. This translated to 2,500 mL of fluid per day (84.5 oz.). This recommendation included fluid intake from both food and beverages (Valtan, 2002; Tsindos, 2012). A public misconception over this unsubstantiated fluid intake claim has further complicated this matter by assuming that some beverages, such as caffeinated drinks and alcohol did not count toward the daily total, as these drinks were perceived to be diuretics (caffeine is a mild diuretic and alcohol is indeed a diuretic). In addition, the inclusion of fluid intake from food is frequently forgotten. The 8 x 8 hydration rule has persisted until recently, despite lack of scientific evidence to support this advice. The current advice is to “drink to thirst” (Hew-Butler et al, 2015), although the 8 x 8 rule is slow to leave clinical advice and is still deeply imbedded in societal messaging.

There has been, and currently is, a lack of data on beverage intake (both type and amount) for women, including lactating women. There is confusion regarding what “hydrate for health” means for a lactating woman, or for any individual. Again, one of the sources of confusion comes from lack of education on including fluid intake within foods as part of the daily fluid balance.

The World Health Organization recommends breastfeeding up to the first 6 months. Breast milk is naturally formulated to provide infants with the required energy, nutrients, protein, and water (WHO, 2002). Unfortunately, 25-35% of women stop breastfeeding early due to a subjective perception of insufficient breastmilk supply (Blyth, et al.,2002; Kirkland, Fein, 2003; Millar, McLean, 2005; O’Brien, Fallon, Brodribb, Hegney, 2007; Sheehan, Krueger, Watt, Sword, Bridle, 2001) with 33% stopping by 8 weeks postpartum (Millar, McLean, 2005; Sheehan, Krueger, Watt, Sword, Bridle, 2001).

Little empirical data exists on the recommended fluid intake of lactating mothers, however most advice is based on the theory that the pregnancy weight gain of the mother and demands of milk production together result in an increased demand for water to support the physiology of lactation. The American Congress of Obstetricians and Gynecologists (ACOG) advises breastfeeding women to drink “plenty of fluids” and limit caffeine to 200mg per day, and to avoid breastfeeding for 2 hours if alcohol is consumed (ACOG, 2013). The EFSA Panel on Dietetic Products, Nutrition, and Allergies (2010) recommends an increase of 300 mL per day for pregnant women. To compensate for loss of water through lactation, their recommendation for breastfeeding women is to increase fluid intake by 600-700mL per day. More importantly, an additional 500 calories per day are optimal for the required energy needed to lactate (ACOG, 2016).

In clinical settings, popular pregnancy handbooks for the layperson, and the internet, and discussion between new mothers, there is a wide range of advice for lactating mothers to “adequately hydrate” to support milk production. Methodological differences in calculating median water intake for lactating women result in a range of advice for total water intake per day (including water, beverages, and the water in food). Europe (EFSA, 2010) advises 2700 mL/d, Australia and New Zealand (NHMRC, 2006) advise 3500 mL/d, USA & Canada (IoM, 2004) recommend 3800 mL/d, and the World Health Organization (WHO, 2003) globally recommends 5500mL/d. Advice then for lactating women ranges from one 8 oz. glass of water per breastfeed, plus additional water to thirst (NHMRC, 2006, ACOG, 2013), up to an astonishing additional 20 plus cups (5500 mL/d total beverage and food) per day (WHO, 2003).

The number one reason that women stop breastfeeding early is due to perceived lack of milk supply, this is 25%-35% of lactating mothers (Blyth, et al.,2002; Kirkland, Fein, 2003;

Millar, McLean, 2005; O'Brien, Fallon, Brodribb, Hegney, 2007; Sheehan, Krueger, Watt, Sword, Bridle, 2001). In an attempt to increase milk production, many women increase their fluid intake. However, there is no evidence to that links an increase in fluid intake to increased milk supply nor do restricted fluids have an effect (Dearlove, Dearlove, 1981; Dusdieker et al., 1985; Dusdieker et al., 1990; Horowitz et al, 1980; Prentice, 1984). High fluid intake with lactation has also been associated with negative symptoms such as nausea, depression, and diuresis (Anderson, 2006) and may decrease milk supply (Illingworth, 1953), although further research is needed to investigate this association. In regard to the study presented in this dissertation, there is no evidence in the literature that women decide not to breastfeed based on a perceived or personal decision to drink more fluid. If breastfeeding women supplement with extra fluids to avoid perceived inadequate milk supply, are they at risk of decreasing their milk supply as a result, and are they in fact overhydrating?

Within the evolutionary framework, it would make sense that the physiology of breastfeeding would be hardy in mammals. To promote survival in both harsh and fortunate environmental conditions, the ability to breastfeed would likely be protected from restricted water availability. Animal studies support this theory, with physiological adaptations such as an increase in glomerular filtration rate, the reabsorption of salt and water in the proximal convoluted tubule, and an increase in renal plasma flow in response to restricted fluid intake, all resulting in normal lactation rate (Alamer, 2009; Peng, Somes, Rozeboom, 2007). In a human study, extra fluid vs. restricted fluid intake showed no difference in milk production for 21 lactating women (Horowitz, Higgins, Graham, Berriman, Harding, 1980) and most human studies show no change in lactation even if the mother has several children, is slightly undernourished, extremely physically active, or losing weight (Brown, Akhtar, Robertson, Ahmed, 1986; Dewey,

Lovelady, Nommsen, McCrory, Lonnerdal, 1994; McCrory, 2000; Winkvist, Jalil, Habicht, Rasmussen, 1994; McCrory, 2001; Rasmussen, 1992).

Breastfeeding women and OAB

No one has explored fluid intake and OAB symptoms in breastfeeding. Health professionals and the lay public accept certain fluids as bladder irritants that breastfeeding women should avoid: caffeine, alcohol, and beverages with artificial sweeteners (ACOG, 2016; Murkoff & Mazel, 2014). Potentially irritating beverages intake or management have not been explored as variables in the treatment of OAB and postpartum women. Is a postpartum mother able, in our beverage-driven society, to avoid potentially irritating beverages, and is it realistic to expect her to do this? If postpartum women can limit potentially irritating beverages as instructed, they are in effect being given an intervention for OAB. We would then expect to see breastfeeding women experience less OAB symptomatology than their non-breastfeeding counterparts in relation to potentially irritating beverages intake.

Theoretical Model: Breastfeeding women, beverage intake, and OAB

The theoretical model used in this paper addresses the effect of beverage volume, mediated by beverage type and obesity, over time, on overactive bladder symptoms (Figure 9).

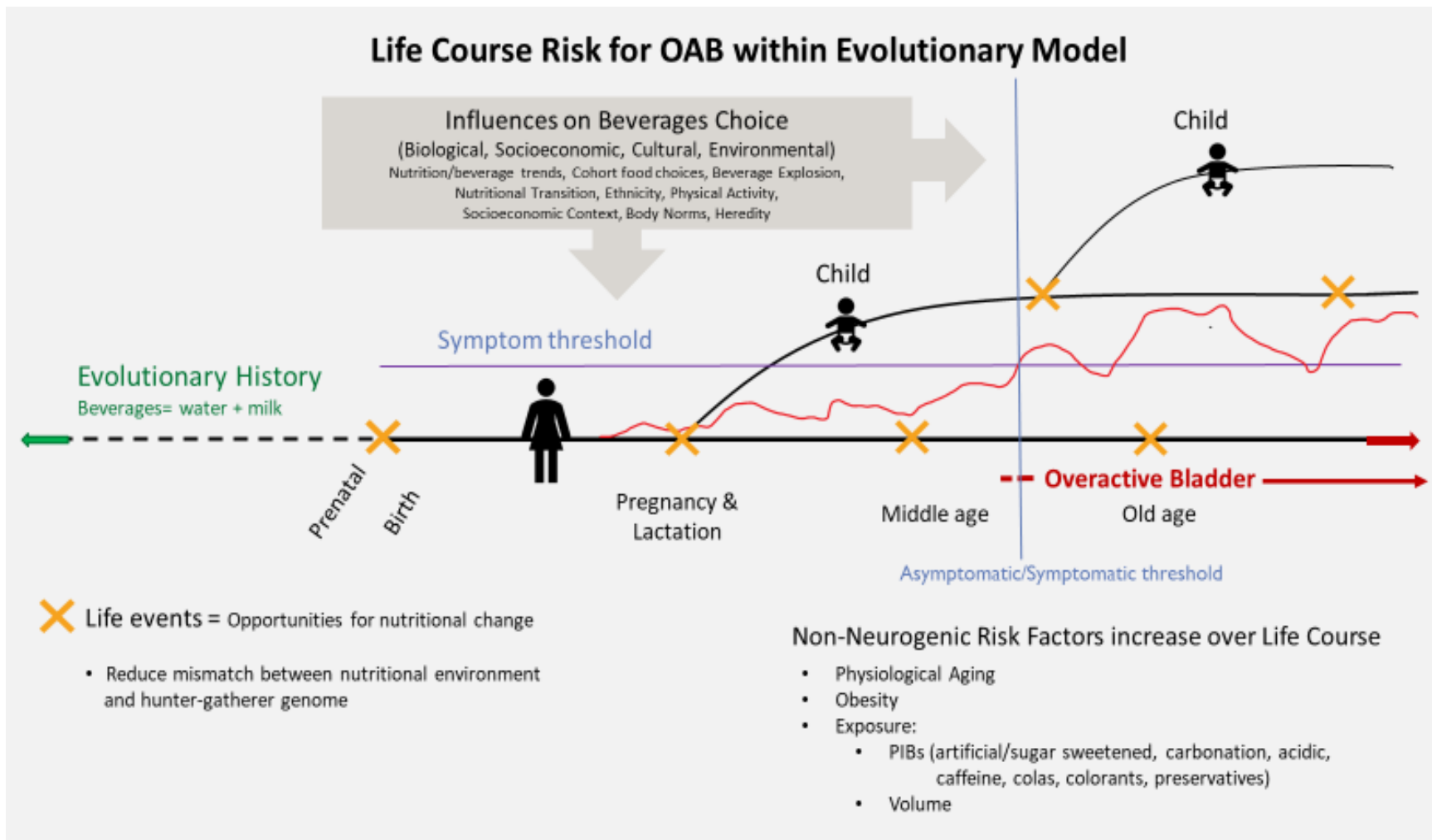


Figure 9 Breastfeeding Women, Beverage Intake, and OAB Within the Evolutionary Medicine Framework

This framework rests on the evolutionary foundation of our modern bodies and physiology remaining essentially the same as our hunter-gatherer forbearers. If drinking to thirst (mainly water) during our lifetime is what our bodies are “designed” to do, regardless of the status of pregnancy or breastfeeding in a female, then our current beverage environment is not matched to our bodies.

There are biological, socioeconomic, cultural, and environmental influences on our choice, amount, and frequency of beverage intake (Figure 9). Over the recent evolutionary past, and certainly since the beverage explosion, nutrition and beverage trends, cultural influences, reduction in physical activity, and other influences have affected the choices available for beverage intake. Added as risk factors for the development of chronic disease related to beverage intake are the aging of the population, increasing incidence of obesity, exposure to ingredients associated with overactive bladder symptoms (artificial and sugar-sweetened, carbonation, acidity, caffeine, colorants, preservatives) and the emphasis on hydrating the body adequately for health (type of beverage and volume) (Figures 9 and 10).

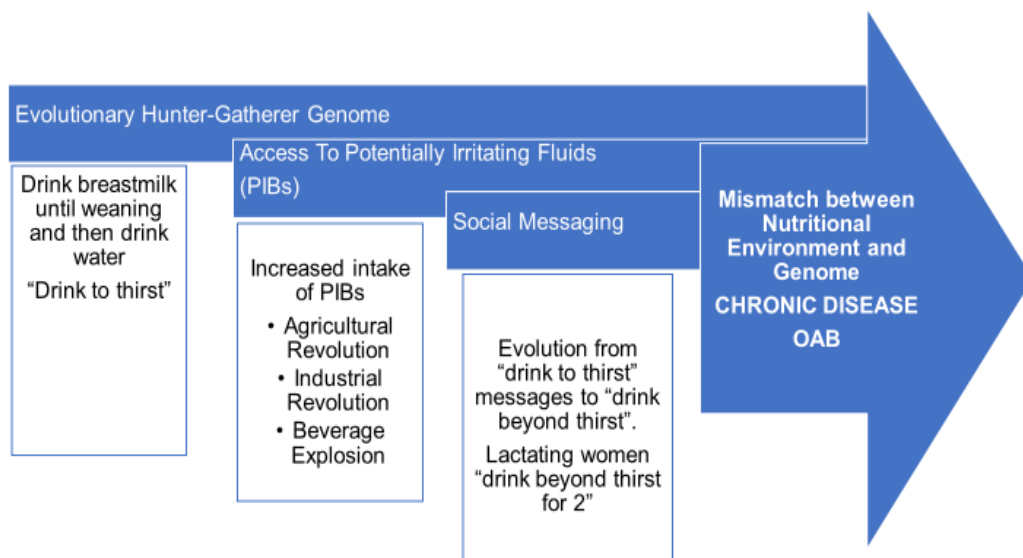


Figure 10 Variables Associated with OAB Development

At time frames in a woman's life (life course theory), there are opportunities to reevaluate nutrition intake, alter current patterns, or remain unchanged. If our genomic bodies are designed to drink mainly water after weaning, life events such as pregnancy, breastfeeding, middle age and old age are opportunities to alter beverage intake to more closely resemble our hunter-gatherer diet and potentially reduce the mismatch between our current nutritional environment and our physiology. If the beverage environment is mismatched, depending on continuing beverage intake (type of beverage and volume), there is a theoretical point where the asymptomatic and symptomatic threshold is crossed, resulting in overactive bladder symptomology.

Expectations

Within an evolutionary perspective, it would be expected that breastfeeding mothers would increase their beverage intake at an amount that would compensate for the fluid lost in breastfeeding and the physiological need for milk production. An indirect measure of hydration is number of voids, so additional intake volume by breastfeeding women would be anticipated to be at an amount that would maintain the same number of daytime voids as non-breastfeeding.

At the birth of a first baby, there is no reason to believe that women who choose to breastfeed have different physiologic bladder capacity than non-breastfeeding women, prior to making the choice to breastfeed or not. We assume in this natural experiment design that differing bladder capacities among the subjects are randomly distributed between those who choose to breastfeed and those who choose not to breastfeed, at the time of breastfeeding choice.

Because lactating women are assumed to be motivated to decrease potentially irritating beverages intake, especially caffeine and alcohol, we would also expect to see a decrease in

potentially irritating beverages intake of breastfeeding mothers in comparison to non-breastfeeding mothers.

In Chapter 7, we justify conducting a natural experiment to answer these questions.

Chapter 7 **Designing and Conducting a Natural Experiment on Bladder Symptoms as it Pertains to the Postpartum year**

As discussed in chapter 1, natural experiments are driven by theoretical constructs and are strong experimental designs when researching questions that are “discovered” in the observational world and are not amenable to intervention and manipulation (Dunning, 2012). In this natural experiment, the environmental influence and milieu of the beverage explosion provides a setting for observing the effect of our beverage culture on the “as if randomized” population of breastfeeding and non-breastfeeding women in relation to bladder symptoms. The beverage-driven culture that our society experiences is indeed “enhanced” during the life course time of lactation, with the emphasis to hydrate for the health of the mother and infant for breastfeeding success.

In the previous chapters, OAB was discussed as a non-pathological bladder state characterized by a subjectively felt sense of urgency, with consequent action of toileting. In a beverage-driven society, unsuited to an evolutionarily evolved need for less fluid intake, it is logical to hypothesize that certain presentations of OAB are the direct result of this mismatch between our unchanged bladder and the environment of our societal beverage messages. The rapid rise in beverage type and volume made available, coupled with aggressive marketing over the past 50 years is concomitant to the introduction and rise of the term “overactive bladder” and the explosion of literature that describes efforts to treat the bladder. Surprisingly, there are scant data to know whether the socially ubiquitous messaging and cultural norming of high beverage intake is at the root cause of at least a portion of the current OAB prevalence.

We speculated, in Chapter 6 that in the USA culture (and perhaps in industrialized societies worldwide) lactating women are particularly subjected to subtle or direct messaging to drink beyond thirst_{for2}, without an evidence base for clear determination of how much more they should drink to accommodate for the process of breastfeeding. In the USA beverage-driven society, drinking beyond thirst_{for2} during lactation is without consideration of whether over-hydration may be a women's usual state when not lactating. (Like over-eating, is it then necessary for the lactating woman to still consume more?).

Worded differently, does an absence of lactation remove situation-specific social messaging to push fluids, and by doing so, shift the bladder towards a lesser state of OAB?

When framed in this way, it becomes apparent that there is potential for a natural experiment design to test the effect of removing (creating absence) the beverage-driven societal messaging as preventative treatment for the “non-pathological” condition of OAB. This chapter presents such a study design: one that demonstrates proof of concept that when heightened expectations to drink (more than a body requires) are removed, less frequent voiding occurs, without any seemingly conscious intent at the individual level to void less. We conduct this experiment by collecting data on beverage intake and void frequency (outcome) in women at approximately 8 months postpartum. In this natural experiment design, breastfeeding is considered the beverage-driven societal heightened messaging of “drink beyond thirst_{for2}” condition and non-breastfeeding is considered the “drink beyond thirst” condition but without the even more heightened messaging to “drink beyond thirst_{for2}”. Thus, one might call the “drink beyond thirst” condition a preventative approach for OAB risk as compared to the “drink beyond thirst_{for2}” condition.

In a natural experiment design (which is an observational study), we hypothesized that the “drink beyond thirst” group will show significantly less urination frequency compared to the “drink beyond thirst_{for2}” group. In this natural experiment with intent to treat postpartum women, the preventative treatment condition is “drink beyond thirst,” represented by those who are not breastfeeding, whereas the control condition is “drink beyond thirst_{for2},” represented by those who are breastfeeding.

The intent of this research design is to serve as an exemplar proof of concept study developed to investigate how social messaging affects bladder symptoms that have been over recent years labeled as the overactive bladder.

In this natural study, the conceptual framework of evolutionary medicine is focused on the beverage intake of women within the context of the childbirthing year. In a population of lactating primipara women, with roughly 50% breastfeeding at 8 months and 50% having stopped, approximately ½ of the study population weren’t exposed to the society message (social, medical, and media) of “drinking beyond thirst_{for2}” during lactation. This natural experiment allows for conservative testing of the degree to which the beverage-driven society influences outcomes such as bladder symptoms.

Materials and Methods

Study design.

This is an observational, natural experiment study.

Study sample and data collection.

The data gathering process used an existing dataset from the Evaluating Maternal Recovery from Labor and Delivery (EMRLD) study, a longitudinal, cohort study which recruited participants from January 14, 2004 to April 1, 2012 (University of Michigan Institutional Review

Board HUM00051193). The parent EMRLD study’s main aim was to evaluate risks for and outcomes of childbirth-related levator ani (Kegel muscle) injury. Details of the recruitment process for the parent project have been previously published and included generating an enriched sample of 92 primiparas more likely to have incurred levator ani tears with childbirth (Low, et al, 2014), as well as 60 primipara’s at the lowest risk for levator ani tears (Miller, J.M., personal communication, April 2017) and with a first evaluation time point occurring at about 6 weeks after childbirth. The primary outcomes of the parent study are reported in Miller, et al, 2015. The parent study recruitment and dropout numbers are portrayed in Figure 11. The data used in this secondary analysis is from 92 women who filled out voiding diary variables on beverage intake and voiding frequency at the 8 months postpartum data collection.

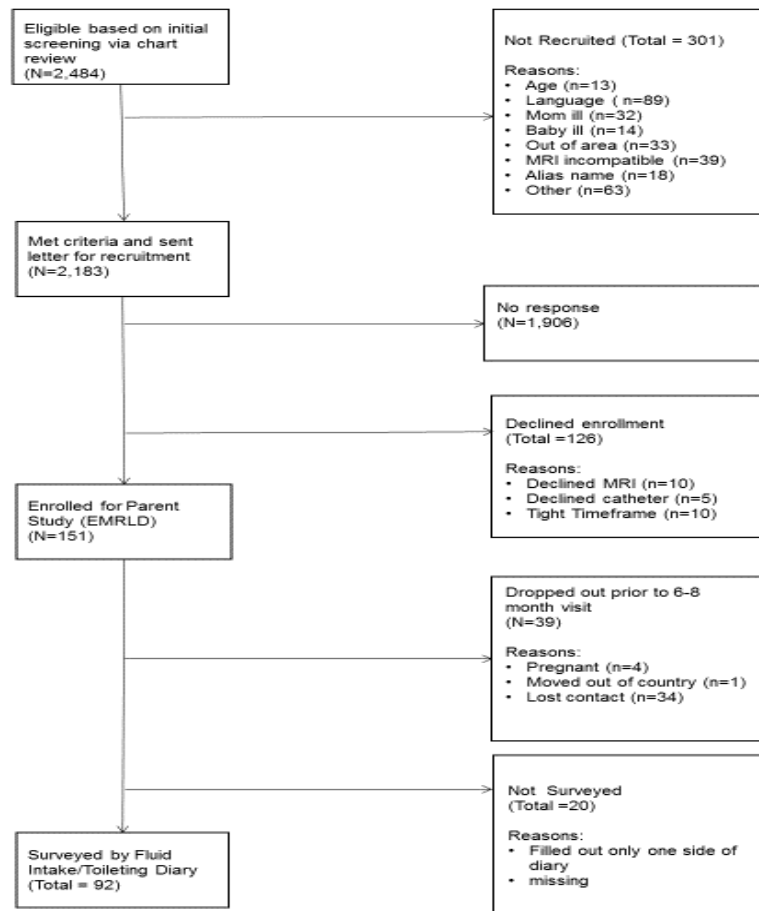


Figure 11 Parent Study Evaluating Maternal Recovery from Labor and Delivery (EMRLD)

Measures.

The beverage/bladder diary (primary outcome) is shown in Appendices A and B. This 3-day diary was completed by each participant. The daily fluid intake was recorded on one side of the diary (Appendix E) and included measures in ounces across 24-hours of type and amount of beverages. Type of beverages were divided into non-potentially bladder irritating beverages and potentially irritating bladder beverages. Non-potentially irritating beverages included water, milk, or non-dairy, soy. The 4 categories of potentially irritating beverages included alcohol, juices, caffeinated and decaffeinated drinks such as tea, soda, coffee, chocolate, and “other.” On the flip side of the diary (Appendix F) toileting pattern was recorded and once per day the study participant was asked to volitionally cough hard on a full bladder and check a box if leakage occurred with the cough. Marks were also recorded for other daily urine leakage episodes, and for number of intentional bladder emptying (voids).

Participants completed a standardized questionnaire form providing demographic information and other self-report items, including whether she was breastfeeding. Questionnaires on bladder symptoms were addressed using the Sandvik Incontinence Severity Scale (2006). The Sandvik Incontinence Severity Scale (2006) asks two questions; How often do you experience urine leakage (0=never, 1=less than once a month, 2=one or several times a month, 3=one or several times a week, 4=every day and/or night)? How much urine do you lose each time (1=drops or little, 2=more)? The Severity Index is obtained by multiplying the score for the first question by the score for the second question and the result is categorized from none (0) to slight (1-2), moderate (3-4) and severe (6-8).

Study procedures.

The beverage/bladder log was mailed to the study participant 2 weeks prior to her “late” postpartum clinical exam appointment. The diary was then collected at the clinical appointment. If the study participant neglected to complete the diary prior to her clinical appointment, she was encouraged to still do the diary and mail it to the study coordinator. Per parent study protocol, additional contact with EMRLD participants occurred at telephone screening early postpartum, in accompanying the participant to two appointments for magnetic resonance imaging of the levator ani muscle, and two study-related clinical exams conducted at 6 weeks and 8 months postpartum. In none of these parent study contacts was there any reference to, nor instruction about beverage intake or breastfeeding.

Statistical methods.

Demographic, birth, and clinical characteristics at 8 months postpartum are displayed using means, standard deviations, and ranges, or median and interquartile ranges for continuous variables and frequencies and percentages for categorical variables. Comparisons by treatment versus control status were made using t-tests and chi-square tests, respectively. Similar comparisons were made between women who completed the beverage diary and those who did not complete the diary and were excluded from the analysis. Incontinence symptoms at 8 months postpartum are shown both as frequencies and percentages of symptom present versus not present and medians and interquartile ranges (IQR) of symptom severity. Comparisons of incontinence symptoms at 8 months postpartum were made using chi-square tests for symptom presence and Wilcoxon two-sample tests for symptom severity.

Finally, average number of daily voids by average total daily beverage intake was plotted using a scatter plot, group by treatment versus control status, and boxplots were used to show the

distribution of daily alcohol intake, daily caffeine intake, daily potentially irritating beverages intake, and total daily beverage intake by treatment versus control status, with p -values from Wilcoxon two-sample tests.

Results

Sample characteristics are portrayed in Table 2. Examining the women who were excluded from analysis, they were on average 3 years younger, less likely to be white race, and more likely to have lower education and lower income. These women were otherwise similar in demographic characteristics and in clinical characteristics.

Body mass index (BMI) differed by group with “drink beyond thirst” lower than “drink beyond thirst_{for2}”, but there was no difference by groups in maximum urethral closure pressure (MUCP) nor status of the levator ani muscle (birth-related tear severity). Both the “drink beyond thirst_{for2}” group and “drink beyond thirst” group showed very low levels of incontinence (Table 3).

Examining the average total daily beverage volume intake across three days, “drink beyond thirst_{for2}” group women showed significantly higher intake volumes compared to “drink beyond thirst” group (median 75.3 with an IQR range of 57-93.7 oz. versus 60 with an IQR range of 43.8-71.7 oz. respectively, $p = 0.002$, Table 3). Neither the 3-day average daily total of potentially irritating beverages intake nor type of potentially irritating beverages differed significantly between controls and preventative treatment women and less than 3% of the entire sample had a diary reflecting potentially irritating beverages intake as “none,” under the definition of potentially irritating beverages used in this analysis.

The total daily potentially irritating beverages volume intake (oz.) (averaged over 3 days) for the “drink beyond thirst_{for2}” group was median 21.3 oz., interquartile range 12.3-32 oz.

compared to 26 oz., interquartile range 14.7-34.7 oz. in the “drink beyond thirst” group (Table 4).

Volume of various potentially irritating beverages, overall potentially irritating beverages, and overall beverage intake by “drinking beyond thirst_{for2}” vs “drinking beyond thirst” are shown graphically in Figure 11.

Table 2 Sample Characteristics by Breastfeeding Status Among n = 92 Women Who Completed Beverage/Bladder Diary at 8 Months Postpartum

Characteristic	Breastfeeding at 6mo pp (n=52)			Not breastfeeding at 6mo pp (n=39)			p-value
	Total N	Mean(SD) or %(N)	Range	Total N	Mean(SD) or %(N)	Range	
Demographics							
Maternal age (years)	52	31.0 (4.9)	23.0 - 46.0	40	29.1 (6.1)	19.0 - 46.0	0.12
Race	52			39			0.59
African-American		5.8% (3)			5.0% (2)		
Asian		1.9% (1)			7.5% (3)		
White		88.5% (46)			80.0% (32)		
Other Race		3.8% (2)			5.0% (2)		
Non-hispanic	52	98.1% (51)		39	97.5% (39)		0.38
BMI (kg/m ²)	50	24.7 (5.2)	17.2 - 42.0	39	27.9 (7.3)	18.2 - 44.7	0.02
Education	52			38			<.01
High school or less		1.9% (1)			10.0% (4)		
Some college		9.6% (5)			32.5% (13)		
College graduate		32.7% (17)			20.0% (8)		
Graduate school		55.8% (29)			32.5% (13)		
Annual Income	51			38			0.02
<\$20,000		3.8% (2)			25.0% (10)		
\$20,000-\$40,999		17.3% (9)			15.0% (6)		
\$50,000-\$60,000		23.1% (12)			12.5% (5)		
>\$60,000		53.8% (28)			42.5% (17)		
Clinical Characteristics at 6m pp which could influence bladder symptoms							
Levator Ani Tear Severity							0.40
No tear		63.5% (33)			62.5% (25)		
I		13.5% (7)			12.5% (5)		
II		7.7% (4)			17.5% (7)		
III		11.5% (6)			5.0% (2)		
BMI (kg/m ²)	50	24.7 (5.2)	17.2 - 42.0	39	27.9 (7.3)	18.2 - 44.7	0.02

The boxplot below demonstrates that the “drink beyond thirst” group (not breastfeeding) had a significantly lower total daily beverage intake compared to the “drink beyond thirst_{for2}” group ($p = 0.003$). Interestingly there was no significant difference between groups in any of the PIBS (Figure 12).

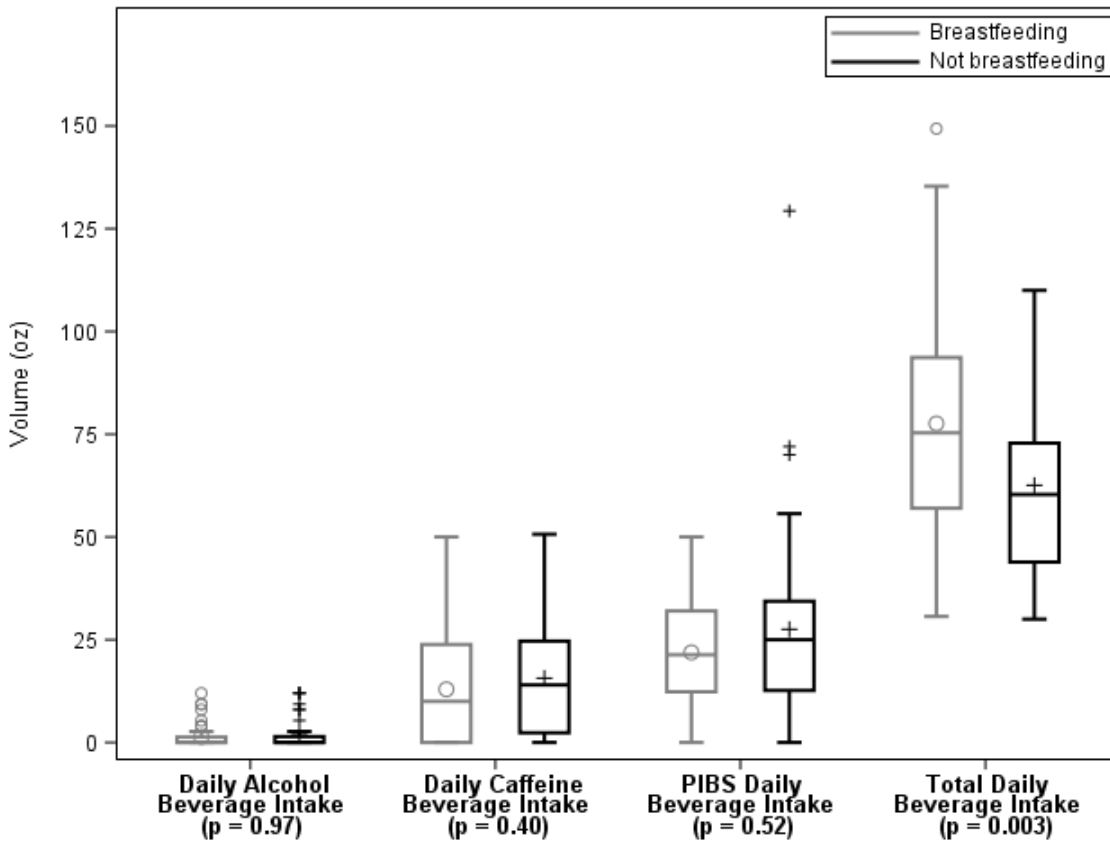


Figure 12 Boxplots of Average Daily Intake by Breastfeeding Status at 8 Months Postpartum*

*Comparisons were made using Wilcoxon Two-Sample tests

Analysis of frequency (daily voids) was significantly lower in the “drink beyond thirst” group (6.3 voids per day) compared to the “drink beyond thirst_{for2}” (7.2 voids per day) group (Table 3).

Table 3 Beverages and Bladder Symptoms at 8 Months Postpartum

Characteristic	Controls (Breastfeeding at 8 mo. pp, n=52)			Preventative Treatment (Not Breastfeeding at 8 mo. pp, n=39)			p-value
	Total N	Median or %(N)	IQR	Total N	Median or %(N)	IQR	
Beverages							
Total daily beverage volume intake (oz.)	52	75.3	57-93.7	39	60	43.8-71.7	0.002
Total daily PIBS volume intake (oz.)	52	21.3	12.3-32	39	26	14.7-34.7	0.43
Number of PIBS types consumed per day	52			39			0.55
None		1.9% (1)			7.7% (3)		
1		25.0% (13)			28.2% (11)		
2		42.3% (22)			33.3% (13)		
3		28.8% (15)			25.6% (10)		
4		1.9% (1)			5.1% (2)		
Bladder Symptoms:							
Average # daily voids (frequency)	50	7.2	6.0 - 9.3	39	6.3	5.3 - 7.7	0.04
Any leakage on 3-day diary	48	28.8% (15)		36	33.3% (13)		0.64
Any leakage on Standing Stress Test	50	7.7% (4)		39	7.7% (3)		0.96
<i>The parent study did not collect intake volume per void</i>							

Discussion

In accordance with evolutionary theory and data in animal studies, the expectation for lactating women would be a very minor increased need for fluid intake to support the physiological processes of lactation. The minor increase would be sufficient to maintain the same hydration level as non-breastfeeding women, and consequently the number of average daily voids would be the same for breastfeeding and non-breastfeeding women. However, in this study, situated within the milieu of the beverage-driven society, the condition of “drink beyond thirst_{for2}” resulted in significantly higher total daily beverage volume intake than “drink beyond thirst.” We can speculate that the women who were breastfeeding were responding to societal messaging to hyper-hydrate to drink beyond thirst for breastfeeding. The significantly lower average daily voids in the non-breastfeeding women may indicate that avoiding drinking beyond thirst to a level of hyper-hydration is a primordial level of prevention from tipping towards symptoms associated with OAB.

Although data from the literature addressing how societal messaging affects the relationship between beverage intake and bladder symptoms such as OAB was absent, there are small studies where teaching was attempted in order to modify beverage intake for either volume and/or bladder irritant ingredients. Miller, Garcia, Becker Hortsch, Guo, & Schimpf (2016) found in a sample of 30 community-dwelling women, that although adherence to study protocol (reduction in potentially irritating beverages intake) in the 3-phase study design was problematic, reduction of both daily potentially irritating beverages and overall daily beverage volume resulted in a reduction of daily voids (Phase 2, 10.5 vs 9.2 voids; $p=0.002$, Phase 3, 10.5 vs. 9.6 voids; $p=0.04$), and a reduction of the OAB symptom of urgency. Other studies concur that when overall fluid intake is reduced, the reduction is associated with a decrease in daily voids and/or a

reduction in OAB urge symptoms (Bryant, Dowell, & Fairbrother, 2002; Swithinbank, et al., 2005).

There is documentation that from 1989 to 2002, there was an increase in average daily beverage intake from 78.9 to 100.1 oz./day (Duffey, Popkin, 2007). Consistent with this trend of increased fluid intake in the last decades, this study reported that both the “drink beyond thirst_{for2}” and “drink beyond thirst” groups reported a higher mean daily beverage intake compared to 68% of an earlier study reported by Miller, Guo, & Becker Rodseth (2011) of 352 community-dwelling women completing a 3-day voiding diary. In that study, cluster analysis of bladder diary variables grouped beverage intake of the participants into: “conventional,” “benchmark,” and “superplus” categories. The “conventional” group (68%) had a mean daily intake of 44.6 ± 12.7 oz./day, the “benchmark” group (25%) had 82.7 ± 18.4 oz./day, and the “superplus” group (7%) had 127.6 ± 30.9 oz./day. Comparing the mean daily intake of this current sample of postpartum women, both the breastfeeding (78.3 ± 27.2 oz./day) and non-breastfeeding women (62.5 ± 27.5 oz./day) had a higher mean daily beverage intake than the “conventional” daily beverage intake (44.6 ± 12.7 oz./day). Miller, et al. (2011) compared 14 years of output data and found an overall 10.1 oz. increase per day of urine voided, which was an indirect measure of a trend towards an increase in fluid intake and output over the last two decades.

In effect, this natural experiment study design supported the presumptions of strong social/marketing messages to drink beverages considered potentially irritating to the bladder, since intake of beverages classified in this way was consistent across both preventative treatment (non-breastfeeding) and control (breastfeeding) women. It seems that messages to decrease potentially irritating beverages intake were not picked up by either group, as only overall volume

of non-potentially irritating beverages differed by group. This consistency in consuming potentially irritating beverages in this postpartum sample, regardless of breastfeeding status, parallels current beverage trends in society. For example, anecdotally, women attempt to “kick their diet coke habit” with websites devoted to information on how to quit diet soda and other potentially irritating beverages. More research is needed to explore “addiction” and potentially irritating beverages intake, whether it is regular or diet soda, caffeine drinks, or others.

Clinically, when women are told to reduce potentially irritating substances they have great difficulty managing this task (Miller, Garcia, Hortsch, Guo, Schimpf, 2016). We cannot effectively manage patients if they cannot successfully follow treatment guidelines, based on clinical evidence. Pharmaceutical companies continue to research new drugs to address the detrusor muscles, clinicians continue to counsel patients to limit fluids at night and to cut down on possible bladder irritants, and patients purchase urinary pads, medications, and continue to drink carbonated beverages and other popular beverages, despite the advice to limit them.

Clinically and practically, we don’t fully know what “drink to hydration” means for breastfeeding women or women in general. There is a need to operationalize this concept in a realistic manner both for clinical purposes and public knowledge so that rather than loose recommendations, evidence-based, targeted recommendations are relied upon. It is not clear whether leaning towards the upper end of hydrating, or hyper-hydrating, can lead to OAB symptomatology. We have seen here that regardless of breastfeeding status, our sample of postpartum women, when viewed at the individual level, experienced increased number of daily voids associated with increased total beverage volume intake per day, though at the extreme ends where OAB levels of void frequency were reached, these were nearly all represented by women in the breastfeeding group – that is, those receiving the highest societal messages to hyper-

hydrate. Instead of being “dehydrated” from breastfeeding, they were instead taking in more than needed and voiding the excess out (Table 3).

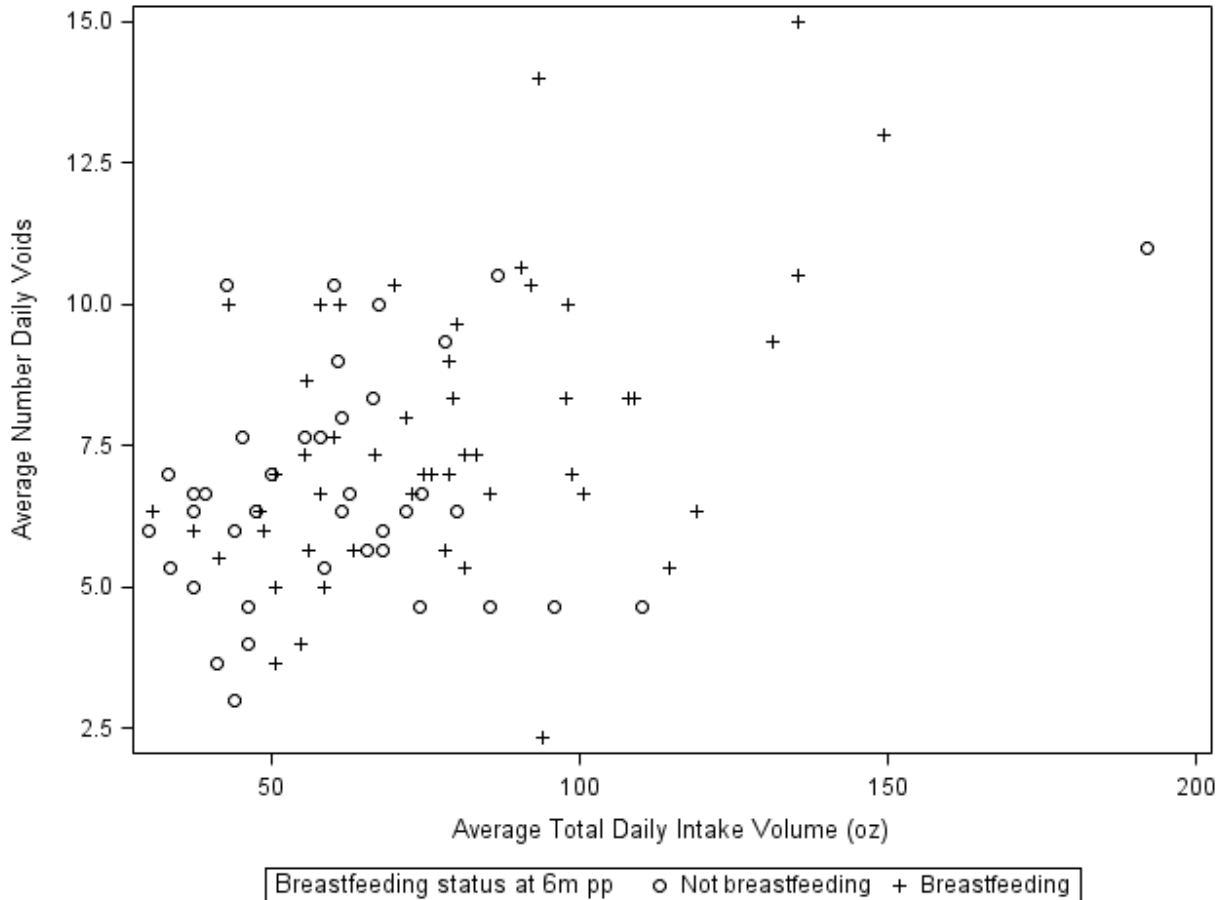


Figure 13 Scatterplot of Drink Beyond Thirst_{or}2 Group (Breastfeeding) and Drink Beyond Thirst Group (Not Breastfeeding), Showing That Instead of Drinking Just Enough to Equilibrate for Body Hydration Needs, a Significant Number of Breastfeeding Women are Drinking Beyond to the Degree that Void Frequency is Increased

The implications of this proof of concept that societal messages are impacting behavior around beverage intake is very important. As volume of beverage intake has increased in recent decades, it is important that we determine how beverage volume and potentially irritating beverages contribute to OAB symptoms, as women have difficulty moderating their intake when they are asked to do so at the individual level, when living within the current beverage driven society of the United States (Miller, Garcia, Hortsch, Guo, Schimpf, 2016). Complex nutritional

and societal changes, including increased potentially irritating beverages intake (in particular sugar sweetened beverages), are associated with obesity and increase in chronic disease in the United States (Popkin, 2004, 2006, Popkin & Nielsen, 2003; Popkin & Gordon-Larsen, 2010).

Pregnancy and postpartum are significant life course transitions in both the life of the mother and infant. The focus on nutrition for the mother includes advice to limit intake of empty calories, focusing on healthy nutrients in food and overall healthy hydration. When a pregnant mother drinks a potentially irritating beverage, she exposes herself and her growing baby to unknown effects of potentially irritating beverages metabolites. When potentially irritating beverages intake continues through the mother's life, the children are more likely to have a higher intake of potentially irritating beverages (Johnson, Sharkey, Dean, McIntosh, Kubena, 2011). We can accept that drinking more fluid leads to more voids, but we must understand how a lifetime of drinking potentially irritating beverages and high-volume intake in general may affect our health.

Does this study meet natural experiment criteria?

It is crucial to establish “as if random” treatment assignment in a natural experiment. To prevent confounding factors affecting outcome variables, assignment to a treatment or control group must be independent from group variables and the group members cannot self-select into the treatment or control group. There also cannot be manipulation from the researcher towards assigning treatment or control populations.

In this study, the preventative treatment variable is lack of heightening of the lifetime exposure to the milieu of our beverage-driven society. Regardless of control or treatment group assignment, each group was initially exposed to intake messaging in the beverage-driven society. There is no capacity for a subject to self-select into preventative treatment (drink beyond thirst

group) or drink beyond thirst_{for2} group based on any knowledge of the preventative treatment variable that reflects emphasis on our beverage culture. Similarly, researchers cannot affect assignment into control or treatment group based on knowledge of the treatment.

Within the control and preventative treatment groups, assignment into the two groups was based on breastfeeding status as a first-time mother. The assumption is made that subjects made the decision to breastfeed or not independently from any influence from our beverage culture, also independent of perceived or actual bladder health. Breastfeeding status was defined at the 8-month clinic visit. There were no incentives in this natural experiment design for subjects to belong to either group.

From an empirical stance, to support the “as if random” assertion, assignment to drink beyond thirst_{for2} group or drink beyond thirst was independent and to our knowledge uncontaminated by interaction of one participant with another in terms of the presumed intervention or outcomes. It is assumed that fluid intake, both baseline and postnatal had no bearing on decision to breastfeed, nor did void frequency. In addition, measured pre-treatment characteristics in the two populations were independent from the outcomes. There is no reason to suspect that the bladders of the drink beyond thirst_{for2} or drink beyond thirst groups were in any way different prior to assignment into either group.

Limitations of the present study

This study was a secondary analysis of data in which measures of urgency as a stand-alone variable were unavailable. Urgency, as a measure, was imbedded within scales of incontinence. As a result, the sentinel OAB symptom of “urgency,” with or without incontinence, could not be adequately evaluated in this secondary analysis of postpartum women, few of whom were experiencing incontinence.

The instructions for the 3-day beverage/bladder diary was communicated imprecisely, resulting in potentially conservative results (see Appendices A & B). It is not clear if women interpreted the instructions as recording daytime intake and voiding versus daily (24 hour) intake and voiding. A major limitation is that none of the study women were asked to document voided volume.

The conceptual model and data lack incorporation of solid food intake, which may include potential bladder irritants, for example caffeine and artificial sweeteners. Nutritional research supports beverage intake as a unique and important dimension of overall food intake. Beverage intake episodes can be separated from food intake and occur in different contexts from eating, as “important parts of their daily routines” (Bisogni et al, 2007, p 226). There seems to be nothing in the literature about fructose or artificial sweeteners in food as relating to OAB. Despite this overall limitation in the data, since potentially irritating beverages intake showed no difference between breastfeeding and non-breastfeeding women, it is reasonable to expect that ingredients in foods, such as caffeine, would also not differ between them.

The literature at this point provides little as a starting point for teasing out artificial sweeteners in food vs beverages, caffeine in food vs beverages, and fructose in food vs beverages. The same is true for environmental irritants (other than smoking, which is a risk for OAB and a cancer risk). Smoking and OAB symptoms are closely tied but usually difficult to look at apart from caffeine consumption, which go hand-in-hand in studies. These limitations are important to note, but overall are beyond the scope of a dissertation to address.

Measurement of beverage intake by diary alone has all the usual limitations of self-report, but with a natural experiment study design, these limitations are assumed to be equivalent in each group.

An additional area to highlight as a barrier to answering research questions on relationship of beverage intake to bladder function is its reliance on diary data, which is dense data gathered across multiple days and within multiple day time points (Appendix E & F) requiring extensive and costly analysis. This degree of labor intensity and human interpretation by both subjects and investigators interacting with the hand-written diary entries may be a reason why so little data is available in the literature.

This study sample was not a representative sample of the population in that it was a secondary analysis of data from women recruited for the Evaluating Maternal Recovery from Labor and Delivery (EMRLD) longitudinal cohort study, which recruited participants from January 14, 2004 to April 1, 2012. EMRLD is an institutional review board-approved (University of Michigan Institutional Review Board HUM00051193) study on primiparous women with history of childbirth and a focus on levator ani (LA) tear and/or difficult childbirth delivery. In addition, the sample was underrepresented by minorities (84.8% white), was more likely to be highly educated (46% with a graduate school education), and financially secure (49% with annual income over \$60K). In addition, the cohort design was compromised in that the two groups were significantly different in the areas of level of education and annual income (Table 3), but consistent with these differences in the lactation literature. Obviously, this dissertation's two study groups would differ by hormonal status, since inclusion criteria was based on half the sample lactating. There is no reason to suspect, however, that beverage intake and bladder function would differ between these two groups.

Generalizability is also not relevant to women outside of the postpartum year, nor necessarily to women who have pronounced OAB. Additional study is warranted, perhaps in other natural experiments.

The limitations of natural studies lie in the inability to directly control and manipulate an intervention. This may affect the ability to test for replication and reliability, but importantly, natural studies allow research where, for practical (and ethical) reasons, the independent variable cannot be manipulated.

Despite these limitations, this is the first data-based look at the relationship of beverages, potentially irritating beverages, and void frequency as these pertain to women in the postpartum period. This proof of concept study could be repeated and validated within a larger population of primiparas or other natural experiments. A natural experiment by definition is observational. It is not so much that it has occurred in nature, rather it is that an existing set of circumstances that equate to random allocation to treatment or control has happened organically, without investigator intervention and without participant choice. It is “as if random.” Once you have been attuned to a natural experiment, you begin to see the possibilities of their existence in numerous natural situations. Some of these are noted in the next chapter in the section: Future Directions for Research.

Chapter 8 Synthesis

The medical paradigm evaluates and focuses on the bladder as the organ to “fix” in relation to OAB symptoms. OAB becomes a set of symptoms caused by a “diseased organ.” If one expands out from a purely medical model of OAB, and appreciates OAB symptoms as outcomes of the hunter-gatherer body compensating for a radically fast transition in the beverage diet of our evolutionary history, a different focus is brought to causes and treatments for OAB. Are we physiologically capable of managing a lifetime load of sugar, additives, supersize servings, micronutrients, and metabolites without consequence to our bladder function? Is the bladder vulnerable to a lifetime load from these substances and metabolites which the renal system was never designed to interact with?

Again, the example of feeding a thirsty dog or bear carbonated, sweetened soda comes to mind. We are disturbed at these examples, yet we have been conditioned in our society, via marketing and in other multifaceted ways, to view drinking these beverages ourselves as “normal”. We must shift our focus from the current accepted beverage paradigm to consider the possible consequences of prolonged exposure to these popular, high-calorie or artificially sweetened, artificial ingredient beverages.

No “cure” has been found for OAB. Symptom relief has been dependent on the compliance/engagement of the patient with medications and behavioral change. This process is often a lengthy struggle resulting in management, not cure. Perhaps then our aim should not be to “fix” OAB, but to focus on OAB prevention. An evolutionary medicine, nutritional focus may

help prevent OAB. This preventative approach would entail educating society from an early age and changing our beverage culture into one that drinks water and with a more precise, personalized medical approach to drink only what is required for adequate hydration.

Much time, research, and funding has been poured into an attempt to understand OAB symptomatology. The defining feature of OAB is the subjective feeling of urgency, yet the concept of “urge” remains undefined at a level accepted by the research community. Most fundamentally, the question of cause remains unclear; is OAB related to physiological or structural variables such as detrusor muscle overactivity or urethral insufficiency? Is OAB related to beverage type and volume, mediated by time? If a cultural return to a more closely aligned beverage diet is maintained from an early age, will OAB symptom prevalence be reduced?

Recommendations for Future Research

It remains unclear what our prevention or treatment interventions for OAB should entail, as situated within the beverage driven society. Additional natural experiments are the logical approach to gain more data. These might include:

- Repeat and expand sample size in the experiment highlighted in this dissertation. Data collection procedures should include obtaining void volume to further substantiate differences in urine production by groups.
- Watch for natural experiment possibilities that may arise from situations in which beverage availability and social activity that centers around beverages changes “as if by random,” and compare bladder habits with a control group. For instance, a natural experiment could be pointed out in the Flint water crisis of the mid-2010 decade, with dramatic change in beverage intake patterns occurring. A logical comparative group

would be Detroit residents, since both Flint and Detroit used the same water sources prior to the crisis. Multiple hypotheses about intake/output and possibly bladder symptoms could be potentially addressed from designing a natural experiment from this scenario.

- Similar natural experiments might be found in comparing social messages regarding intake in dry verses humid environments. Does bladder functioning or symptoms differ significantly?
- Cross-cultural settings that compare societies less driven by messages for hyper-hydration to those with those messages could inform, with evidence, about effect on bladder health. For example, Amazonian tribes or other indigenous peoples who keep apart from industrialized society could address our genomic physiology and anatomy. Agricultural and Industrial Revolution time periods could be addressed with such populations as the Congo, where access to clean drinking water is variable and access to PIBs is very limited. Various religious populations could address access to modern day beverage intake while limiting or omitting PIBs. To look at the effects of the beverage explosion on our genome, the population of Ann Arbor would be suitable as well as addressing further research on a subgroup of lactating women.

Additional research questions that follow on the framework introduced in this dissertation include:

- We need to explore what drives the consumption of total beverage intake and potentially irritating beverages, from a cognitive, behavioral, cultural, and evolutionary medicine framework. Within a personalized medicine approach, how can optimal intake volume for an individual be addressed, with neither over-hydrating or under-hydrating in consideration of today's environments?

- What drives potentially irritating beverages (PIBs) intake and what interferes with PIBs reduction?
- Within a life course perspective, what influences and defines women in relation to beverage choice? How do life course transitions interact with beverage intake? What sources are women turning to for information at the various life course transitions, such as the rapid (overnight) transition to breastfeeding?
- What epigenetic factors are associated with beverage intake and OAB?
- Is there a threshold (both time and volume) for exposure to PIBs and onset/degree of OAB symptoms?
- Is a reduction in PIBs intake from an early age protective against OAB?

In summary, we have much to learn about the true effects of the beverage driven society as it influences rising prevalence of overactive bladder. Keeping vigilance for natural experiments that hone in on the larger circumstances at play may offer the most efficient means of building the needed evidence base.

Appendices

Appendix A

Pathophysiological Theories of the Overactive Bladder

Neurogenic Theory

Research on the overactive bladder has focused mainly on bladder storage symptoms. That is, can the bladder “hold” without negative symptoms. Bladder storage symptoms, on the one hand, are the focus of neurologically-driven bladder research. Neurogenic research addresses central nervous system injuries, neuropathies, and diseases which alter inhibitory neural impulses of the bladder. Increased afferent impulses from the bladder lead to a rise in voiding reflexes (de Groat, 1997). In addition, although chronic disease such as Type I and Type II Diabetes, kidney disease, obesity, and metabolic syndrome also involve OAB symptoms, these diseases and conditions are not directly addressed in this paper.

Detrusor Muscle Instability

Myogenic theories focus on the function of the smooth muscle fibers of the bladder, more specifically, the detrusor muscle fibers. Most of the research on OAB has focused on the bladder (detrusor muscle) and/or the effects of substances on it. This layer of bladder muscle is arranged in circular, longitudinal, and spiral muscle bundles and is thought to involuntarily contract due to hypersensitivity in the muscle cells, with structural changes between cells leading to changes in cell communication. A contraction that begins in any portion of the (hypersensitive) bladder muscle can spread and propagate a full, coordinated bladder contraction (Brading, 1997, 2006). This hypersensitivity or “instability” of the detrusor cells in the bladder with OAB was supported by a study where bladder wall specimens with confirmed detrusor instability and control bladder

wall specimens without detrusor instability were exposed to electrical stimulation, potassium, and a cholinomimetic drug, carbachol. The bladder samples with detrusor instability were abnormal in areas of denervation, high sensitivity to potassium, and their tendency to “couple” cells electrically, which altered the stability of the contractions (Mills, Drake, Brading, McCoy, Noble, 2000). Dysfunction of the detrusor muscle was again supported by Drake, Mills, & Gillespie’s (2001) model of bladder function, with muscarinic stimulation ultimately leading to detrusor muscle overactivity. Brading’s (2006) exposure of the detrusor muscle of the bladder to cholinergic stimulants resulted in increased activity (excitability transmission in the smooth muscle cells) with “micromotions” stimulating afferent receptors in the smooth muscle and leading to the subjective sense of urgency.

Subjective Hyperawareness/Afferent Output

The increased sense of urgency, or the subjective awareness of bladder dynamics due to the mechanism of increased afferent output has been considered (McCarthy, et al, 2009; Morrison, 1999). As the walls of the bladder stretch and fill, an increase in afferent signaling to the spinal cord increases the release of acetylcholine from the urothelium, which in turn increases the sensitivity of the detrusor muscle to neurotransmitters. The proposed result is a hypersensitivity of the detrusor muscles, increased afferent signaling and “micromotions” of the detrusor muscles and the resulting subjective sense of urgency.

Factors Influencing Development of OAB

We do not know risk and protective factors; including whether environmental factors contribute to OAB. Despite decades of research, changing interventions, and evolution of terminology, we are no closer to definitively establishing the causative factors that surround OAB symptomology or successfully resolving symptoms for patients on a long-term basis.

Again, this may in part be to lack of clear definition of a problem that may exist outside of the bladder (overactive intake, for instance). Or it may be due to the difficulty of measuring “urgency” as anything other than void frequency, again as a symptom though not a stand-alone diagnostic definitive. Regardless, several factors have been studied as potentially contributory and these are further explored here.

Beverage ingredients potentially influencing OAB.

Caffeine.

Physicians have routinely given patients advice to avoid potentially irritating substances in fluids. Caffeine has long been one of the ingredients most often cited as a bladder stimulant and irritant. However, research has found that caffeine has had varying impact on the overactive bladder.

Caffeine: Animal studies.

High dose caffeine (150 mg/kg) has produced overactivity in mouse detrusor cells with increased urinary frequency and decreased volume per void, however the doses of caffeine used with the mice were equal to 15- 20 times the daily human intake of a heavy caffeine imbiber. When the caffeine doses were lowered to the equivalent of the average daily human intake (10 mg/kg), researchers found evidence of detrusor overactivity with elevated bladder pressures, increased nonvoiding bladder contractions, a reduction of bladder capacity, and firing of afferent bladder nerves when compared to mice with no caffeine ingestion. Interestingly, there was no increase in frequency or volume of void which was seen in the high caffeine mice (Kershen, Mann-Gow, Yared, Stromberg, & Zvara, 2012). Caffeine also stimulated smooth muscle contraction in studies of isolated animal and human detrusor muscle specimens via an increase in cytoplasmic free Ca²⁺ concentrations (Suguita, Tokutomi, M., Tokutomi, Y., Terasaki, & Nishi,

1998; Lee, Wein, & Levin, 1992). Low concentrations of caffeine induced transient muscle contractions, but higher doses inhibited smooth muscle contractions due to a decrease in cytosolic free Ca²⁺ stores following absorption of intracellular Ca²⁺ from sarcoplasmic reticular storage sites and a decrease in the sensitivity of the smooth muscle to Ca²⁺ (Lee, Wein, & Levin, 1992).

Caffeine: Human studies.

High dietary caffeine intake has been associated with detrusor instability symptoms in a case control study of 131 women with OAB symptoms on cystometry, compared to 128 controls with the mean caffeine intake of women with detrusor instability (484 ± 123 mg/day) significantly higher ($p= 0.002$) than that of the controls (194 ± 84 mg/day (Arya, Myers, and Jackson, 2000). However, equivalency of the two groups was altered by nonreporting of total fluid intake, including non-caffeinated beverages and no baseline bladder capacity.

A prospective study of 49 men and women found urgency and frequency increased ($p<0.05$) with caffeinated coffee vs no increase with decaffeinated coffee. Only subjects with previous “low coffee use” had a significant increase in bladder symptoms compared to those with previous “frequent coffee use”, suggesting that human physiology adapts to caffeine use. The study design did not control for differential decrease in overall beverage intake by caffeinated versus decaffeinated beverages, which left the contribution of total beverage volume on the bladder unknown (Staack, Distelberg, Schlaifer, Sabate, 2017).

A prospective cohort study of 65,000 women found higher caffeine intake (≥ 4 cups coffee, ≥ 10 cups /cans caffeinated tea or soda per day) was associated with a “modestly increased risk” of “frequent urgency incontinence” ($p =0.05$) (Jura, Townsend, Curhan, Resnick,

& Grodstein, 2011). However, the subjects were limited to women who already experienced urinary incontinence, which limits the generalizability of the findings.

Dallosso, McGrother, Mathews, Donaldson, & Leicestershire (2003) found an association between caffeinated, carbonated beverages and 1-year incidence of OAB and stress urinary incontinence in a prospective cohort study of 6424 women. However, when caffeine was controlled for, carbonated beverages continued to be associated with OAB incidence (Odds Ratio [CI 95%] 1 drink/week = 0.96, 2-6 drinks/week = 1.44, \geq daily = 1.70, $p = 0.0002$) and caffeine fell out of any significant association with OAB. Carbonated beverages often include sugar, artificial sweeteners, preservatives (citric acid) and coloring agents, and these components were not assessed in this model.

An association between high caffeine intake (≥ 204 mg/day) and general urinary incontinence (adjusted for total beverage intake) was found in a large survey of US women, 2005-2008. However, high caffeine intake was not associated with type of incontinence (urge or stress, or mixed) (Gleason, et al., 2013). Because this study used self-report data and included food intake, type of caffeine (beverage vs food) was unknown.

Caffeine is frequently classified as not only an irritating agent, but also as a diuretic. Maughan & Griffin (2003) review of the literature on caffeine's diuretic effects between 1966 and 2002 found that most of the limited studies on caffeine-containing beverages during that time period employed experimental models using caffeine itself rather than beverages such as coffee or tea. Although studies were careful to restrict consumption of caffeine-containing beverages prior to experimental caffeine ingestion, this manipulation of caffeine consumption did not follow the lifestyle routines of the general public, thus restricting the applicability of results. The numbers of subjects in the studies were generally low and focused mainly on healthy

males of college-age, thus limiting any generalizability of the effects of age or gender. In addition, standardization of caffeine doses was lacking and both decaffeinated coffee (which has trace caffeine content and may have other active components) and water were used as controls, making comparisons between studies difficult. In sum, Maughan & Griffin (2003) “tentatively” proposed three general conclusions from the eleven articles reviewed: 1) “Large doses of caffeine (above 250 mg) have an acute diuretic action; 2) Single caffeine doses at the levels found in commonly consumed beverages have little or no diuretic action; (and) 3) Regular caffeine users become habituated to the effects of caffeine, diminishing its actions” (p. 416). Although research is incomplete, there appears to be evidence to support caffeine as a mild diuretic agent when used on a regular basis at average doses; chronic intake promotes tolerance.

Is it caffeine or co-occurring factors?

Given the conflicting research evidence, the contribution of caffeine in OAB etiology is unclear. Most studies do indicate an association however, supporting the routine current clinical advice to women that they limit caffeine consumption to treat OAB symptoms.

The data is too scant to definitively know if caffeine is a major culprit in the equation of if and how beverages are associated with OAB. It may be that drinkers of caffeinated beverages have a higher volume of intake overall (Valtin, 2002), or that they use more artificial sweeteners, adding them to their favorite caffeinated drink. Artificial sweeteners have been viewed as bladder irritants (Shorter, Lesser, Moldwin, Kushner, 2007). It is possible that women with urgency and frequency process caffeine differently than those free of symptoms. Support for this latter theory was provided by Creighton & Stanton (1990) looking at 20 women with detrusor instability and 10 controls, administered a standardized drink of caffeine (200 mg of caffeine citrate). Only the group of women symptomatic of detrusor muscle instability experienced a rise

in detrusor pressure with bladder filling following ingestion of the caffeine. Further research is needed to tease out the effects of beverage components and their metabolites, both caffeine and others commonly consumed within an individual woman's daily life.

Carbonated beverages, preservatives, ascorbic and citric acid, artificial sweeteners, and other ingredients.

Carbonated beverages are complex fluids composed of colorants, preservatives (e.g. citric acid), sugars (sucrose, and high fructose corn syrup used extensively in the USA), caffeine, carbonation, and other additives. Carbonated sodas, especially caffeinated diet cola sodas, are associated with lower urinary tract symptoms in women, with increased intake over 5 years resulting in increased urgency and voiding symptoms (Maserejian, et al 2013). Carbonated soft drinks have also been found to be independently associated with onset of OAB symptomatology within the following 12 months (Dallosso, McGrother, Matthews, Donaldson, Leicestershire MRC Incontinence Study group, 2003).

It may be that additives such as caffeine, sugar, colorants, preservatives, and artificial sweeteners are associated with urgency through their interaction with the detrusor muscle. Both preservatives (Dasgupta, Elliott, & Tincello, 2009) and artificial sweeteners (Dasgupta, Elliott, Doshani, & Tincello, 2006) have been investigated in relation to carbonated soft drinks and overactive bladder symptoms. Using methodology similar to the caffeine studies with isolated animal detrusor specimens (Lee, Wein, & Levin, 1993; Sugita, Tokutomi, Tokutomi, Terasaki, & Nishi, 1998) ascorbic acid and citric acid were found to augment bladder muscle contraction via a hypothesized enhanced Ca²⁺ influx. The researchers also postulated that although the stimulating effects of the two preservatives on bladder contraction were small and non-dose dependent, the combination of these additives with other soft drink additives may have an

enhancing effect. Three artificial sweeteners (acesulfame K, aspartame, and sodium saccharin) were also evaluated with isolated animal detrusor specimens. These artificial sweeteners were found to stimulate the contractile response of bladder muscle and significantly enhance bladder muscle contractions via hypothesized L-type Ca²⁺ channels. In addition, ascorbic acid increased the release of presynaptic neurotransmitter (Dasgupta, Elliott, Doshani, & Tincello, 2006; Dasgupta, Elliott, & Tincello, 2009). Of course, animal detrusor specimens may or may not interact with these additives in the same way human detrusor cells do.

A small but interesting study of 20 asymptomatic subjects in a four-way crossover study compared the effect of carbonated water, Classic Coke, Diet Coke, and caffeine free Coke on bladder symptoms. Diet Coke and caffeine free Coke were significantly associated with increased frequency with Diet Coke in comparison to carbonated water and also significantly associated with increased urgency. Classic coke was associated with a small, nonsignificant increase in urgency in comparison to carbonated water (Cartwright, Srikrishna, Cardozo, Gonzalez, 2007). It would be important to repeat this study with a larger population.

In the United States, beverages such as soft drinks, coffee drinks, energy drinks, and juices, are commonly sweetened with fructose. Not only does sugar consumption contribute directly to obesity, a suggested risk factor for overactive bladder (Wyman, Burgio, & Newman, 2009; Milne, 2008), but fructose itself has been implicated as a possible contributor to bladder dysfunction associated with metabolic syndrome. Tong & Cheng (2007) looked at rats fed a fructose diet, in comparison to their controls. The fructose fed rats developed metabolic syndrome and its associated syndromes. In addition, the urinary tract was affected, with the bladder of fructose fed rats 45% heavier than the control rats. Unstable bladder contractions were noted in 5 out of the 8 fructose fed rats, suggesting detrusor instability, whereas none of the

control rats experienced this ($p \leq 0.01$). Up regulation/increase of M2,3-muscarinic receptors was also found in the detrusor muscle and urothelium of fructose fed rats, increasing the potential for excitability of the detrusor muscle. Implications for diet, obesity, metabolic syndrome, and OAB are clear for humans.

Consumption of sugar solutions in animals has also been found to significantly increase consumed volume (Kizhner & Werman, 2002), presumably due to taste preference, lending hypothetical evidence for increased volume with habitually consuming potentially irritating beverages. Soft drink consumption is currently the most popular beverage choice in the United States (Wolf et al., 2008) and beverages sweetened with high fructose corn syrup account for 80% of the added sugars in the US diet (Popkin & Nielsen, 2003). Sugar and artificial sweeteners are also associated with increased appetite and obesity, with artificial sweeteners resulting in higher overall increased weight compared to sugar sweeteners (Black, Leiter, Anderson, 1993; Lavin, French, Read, 1997; King, Appleton, Rogers, Blundell, 1999, Ma, et. al, 2016, Woodward-Lopez, Kao, Ritchi, 2010, Yang, 2010).

As noted above in Chapter 3, and repeated here up until 2015, carbonated soft drink consumption involved 37% of all beverage sales and soft drinks were the most popular beverage choice in the United States. Recently, nutritional concerns have caused a decline in soft drink sales, including diet soft drinks, and it is anticipated that this trend will continue (Del Buono, 2016). The largest consumer of diet beverages is the adult aged 40-59 (Popkin, 2010), and tends to be female, Caucasian, and have a higher income (Fakhouri, Kit, Ogden, 2012). Carbonated sodas, especially caffeinated diet sodas, are particularly associated with the OAB symptom of urgency (Dallosso, et al, 2003; Maserejian et al., 2013). But, as soft drink beverage intake has decreased, bottled water sales have risen, and have recently surpassed soda in annual

consumption (MarketWatch, Nov. 26, 2017) (Figure 14).

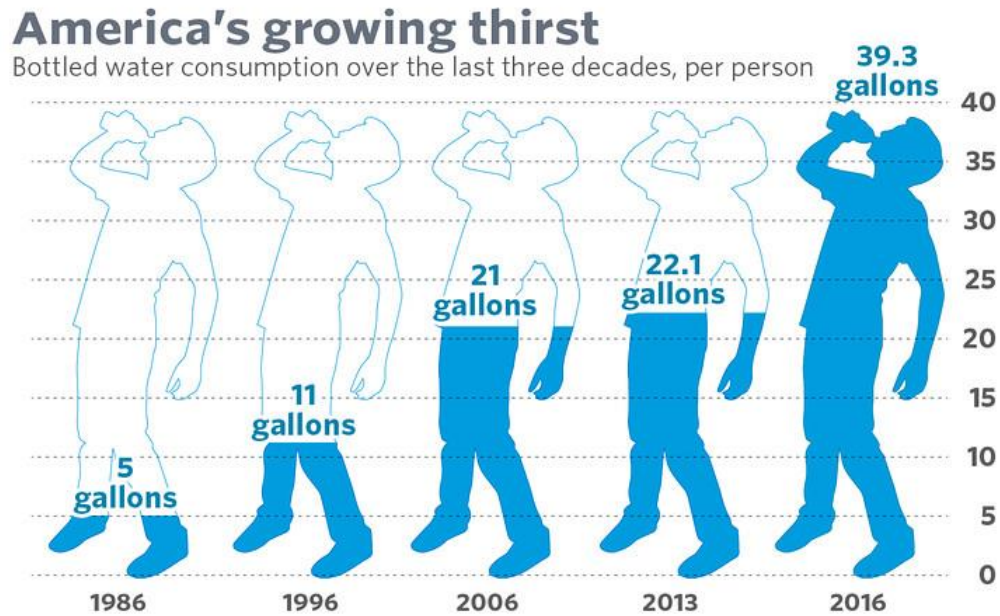


Figure 14 Increase in Bottled Water Consumption, 1986-2016 (Fottrell, Marketwatch, Nov. 26, 2017)

Obesity

Obesity is strongly associated with a variety of bladder symptoms in the urogynecologic research literature. Obesity is associated with stress urinary incontinence (SUI) (Auwad et al., 2008; Lawrence, Lukacz, Liu, Nager, & Lubner, 2007; Subak, Richter, & Hunskaar, 2009) and has also been found to be an independent risk factor for OAB in women (Hunskaar, 2008). The positive correlation between body mass index (BMI) and intra-abdominal pressure suggests that increased weight in the body induces stress to the bladder via increased intra-abdominal pressure (Auwad et al., 2008; Lawrence, Lukacz, Liu, Nager, Lubner, 2007; Subak, Richter, Hunskaar, 2009). Whereas the pathophysiology of SUI and obesity is more mechanical in nature, the literature supports more chemical and inflammatory mediators of obesity and OAB.

Body mass index, or BMI, is a measurement of the percentage of fat and muscle mass in the human body. Mass (in kg) is divided by height (in m) squared. The result is an index of

obesity. BMI fails however to measure the distribution of obesity in the human body and the waist-hip ratio has been advanced as a measure of “central” obesity, or abdominal obesity. The waist-hip ratio has been associated with SUI not with OAB or Mixed Urinary Symptoms, which suggests that there is something other than mechanical pathophysiology associated with OAB (Townsend, Curhan, Resnick, & Grodstein, 2008).

The lining of the bladder of obese women has been found to experience chronic inflammation due to increases in urinary chemokines (Tyagi et al., 2015) and adipocyte-induced inflammation associated with leakage of macrophages into adipose tissue (Neels & Olefsky, 2006). In addition, ghrelin, a 28-amino acid peptide, appetite-stimulating gut hormone, recently studied in relation to appetite and weight loss, has been found to have receptors in tissues other than the gut, including the anal canal, urethra, and urinary bladder of rats (Chancellor, Oefelein, & Vasavada, 2010; Rizk & Fahim, 2008; Suzuki, Simpson, Minnion, Shillito, & Bloom, 2010). The importance of ghrelin has also been established in the aging of support structures of the pelvic floor in animal models (Rizk & Fahim, 2008) and was found to inhibit in vitro contractile response of rat detrusor muscle, with lean rat muscle strips having a more pronounced relaxant effect than the obese rat muscle strips (Chancellor, Oefelein, & Vasavada, 2010). Obesity is associated with decreased levels of circulating ghrelin, and it is hypothesized that the risk of OAB and SUI rises as levels of ghrelin lower, negatively influencing the function of the urethra and the stability of detrusor contractibility (Chancellor, Oefelein, & Vasavada, 2010; Rizk & Fahim, 2008).

Management of the Overactive Bladder

Traditional management of the OAB has been entirely at the individual treatment level with nearly no prevention emphasis on either the individual or societal messaging level.

Typically, some combination of patient education, behavior modification, medication, or neurostimulation is used when addressing OAB symptoms with a patient. “Success” of treatment is a subjective variable, as clinicians and patients may view this meaning in different ways, especially when looking at OAB symptoms from a long-term perspective. In any case, treatment has been the focus rather than prevention for OAB symptoms, and without a known etiology, the treatments at an individual patient level are trial and error. Hence, the patient experiences OAB as significant burden, the clinician as an ongoing challenge, and the researcher as a compelling enigma.

Shown pictorially in Figure 15, individual treatments have included pharmacological treatment, fluid management programs, weight loss, bladder training regimens, and pelvic floor muscle training (Gormley et al., 2012; Milne, 2008; Vij, Robinson, & Cardozo, 2010; Wyman et al., 2009). Neuromodulation and Botulinum Toxin Type A are also used to treat severe OAB and lastly, surgery is an option (Ismail, Hashim, & Abrams, 2012). For current OAB treatment guidelines, see Appendix G.

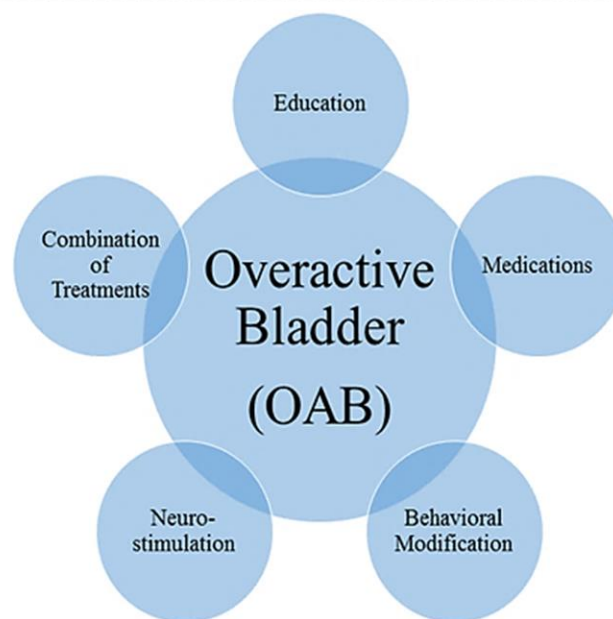


Figure 15 Current Treatment Options for OAB

Pharmacotherapy.

Pharmacotherapy focuses mainly on antimuscarinic agents that compete for the receptor sites in the detrusor muscles, blocking the uptake of the neurotransmitter acetylcholine and subsequent contraction of the detrusor muscle. Beta adrenoceptors are also targeted by newer pharmacotherapy, which relax the detrusor muscle, and decrease contractions (Ismail, Hashim, & Abrams, 2012). Side effects, such as dry mouth, are not uncommon with these medications and women seldom stay on them voluntarily and long-term (Schabert, Bavendam, Goldberg, Trocio, & Brubaker, 2009).

Appendix B

Measurement of OAB

One standard tool used both in the clinic and in research, is the frequency chart. Unfortunately, use of the frequency chart is insufficient in that time and volume of voids are not adequate alone to capture the urgency sensation that defines OAB (De Wachter & Wyndaele, 2003). The addition of a bladder diary incorporates times of beverage intake and voids and incontinence episodes into the micturition chart. Some bladder diaries include the reporting of urgency, the amount of the incontinence per episode, the fluid intake per day, the particular beverage ingested, and time of rising from bed and going to bed each day. The full number of diary variables is rarely incorporated into research findings, however, as the complexity of the data management is a limiting factor. For example, an average bladder diary can yield over 504 variables for one person. Because beverage diaries are rich in data, numerous hypotheses could potentially be addressed, such as the relationship of the timing between beverage intake and voids. In reality, analytical techniques for evaluation are complex, so simplistic averages are reported for daily intake and output without considering the entirety of the data. Even the process of obtaining simple averages is expensive and/or prone to error. Done properly, all bladder diary variables must be double-entered and reduced computationally. Done inexpensively, most investigators quickly hand calculate daily averages and enter these into the database, which prohibits relational analysis by time. In clinical environments using bladder diaries, the clinician can review the diary with the patient and make clinical decisions based on an overall gestalt of the data and the information gleaned from the patient. This approach, however, remains

subjective and not answerable to scientific evaluation. Anecdotally, clinicians tend to favor certain variables of interest in bladder diaries, selectively corresponding to personal theories or popular belief. For example, a focus on total beverages consumed (Clinician A) versus a focus on type of beverages consumed (Clinician B). What is not apparent is how these diaries are used in relation to evidence based practice or if there is any reliability across clinicians in how the material is evaluated and/or utilized. Due to these factors, validity of bladder diaries as clinically diagnostic tools has not been firmly established. As a substitute, simple “recall diary” is often supplemented in clinical settings (Ayra, Myers, Jackson, 2000). This refers to a clinician asking, “on average, how many times do you urinate each day?” and “on average, how much to you drink?”

Appendix C

Prevalence of OAB by Race

OAB also appears to be equally distributed among racial groups. Finkelstein, Glosner, Sanchez, & Uddin (2008) administered an OAB-bother questionnaire for symptoms to a cross-sectional survey of women (in a clinical population). Of the 947 women, 82% of subjects were black, with 19% white and 4% Hispanic. The percentage of women scoring ≥ 8 on the OAB symptom scale was black (35%), white (30%) and Hispanic (36%) indicating a similar incidence of OAB within the racial groups. It would be important to look at this analysis again with an increased subject pool of white and Hispanic subjects.

Secondary data analyses have either found no difference in OAB prevalence among ethnic groups or have indicated that OAB is more prevalent in African American women, with Asian women least likely to report OAB symptomatology. The studies used for analysis, however, have been focused on urinary incontinence symptoms, preventing sufficient attention to OAB evaluation. (Coyne, Margolis, Kopp, et al., 2012; Finkelstein, Glosner, Sanchez, et. al, 2008). A more rigorous cross-sectional survey including ethnic groups and directly addressing the OAB symptom of “urgency “found African American women reported OAB urgency more often (33%) than White or Hispanic women (both White and Hispanic women 29%). Asian women were not included in this study (Coyne, et al., 2013).

Internationally, in western countries, the prevalence of OAB is similar to that in the USA. The prevalence of OAB in Japan was estimated analyzing 4570 questionnaires (self-

administered) to men and women >40 years. Overall prevalence was found to be men (14%) and women (11%), and for both sexes, prevalence increased with age with 40-49 years (5%) rising to ≥ 80 years (37%) (Homma, Yamaguchi, Hayashi, 2005). A study of OAB in Brazil with 848 subjects (aged 15-55) who answered a self-administered questionnaire, found that women had a higher overall prevalence of OAB symptoms than men (23.2% compared to 14%), with no significant differences between age groups. It is notable that the cut off age for subjects was 55, which may have resulted in a failure to capture OAB prevalence in the aging population (Teloken, et al, 2006). In other studies, incidence of OAB increases with age, with women showing increase in prevalence after the mid-40's (Stewart, et al., 2003; Milsom, et al., 2001).

Appendix D

Fluid Intake Log

FLUID INTAKE LOG										
Please record the type and amount of your fluid intake, throughout the day, using the KEY below.										ID# 3 _____
Use hash marks to record how many times you empty your bladder in the box under the time intervals.										6m clinic visit
Day 1	Date:	Day 2	Date:	Day 3	Date:					
Morning 6a-12p	Type/ Amount	Morning 6a-12p	Type/ Amount	Morning 6a-12p	Type/ Amount					
<i>example</i>	W / 8 oz	<i>example</i>	W / 8 oz	<i>example</i>	W / 8 oz					
Afternoon 12p-6p	Type/ Amount	Afternoon 12p-6p	Type/ Amount	Afternoon 12p-6p	Type/ Amount					
Evening 6p-12a	Type/ Amount	Evening 6p-12a	Type/ Amount	Evening 6p-12a	Type/ Amount					
Night 12a-6a	Type/ Amount	Night 12a-6a	Type/ Amount	Night 12a-6a	Type/ Amount					
<u>TYPE of FLUIDS :</u>										
<i>A</i> = alcohol	<i>(including non-alcoholic)</i>			<i>M</i> = milk	<i>(dairy, non-dairy, soy)</i>					
<i>C</i> = caffeine	<i>(tea, soda, coffee, chocolate)</i>			<i>W</i> = water						
<i>DC</i> = decaffe	<i>(tea, soda, coffee, chocolate)</i>			<i>O</i> = other	<i>(soup)</i>					
<i>J</i> = juice										
<u>AMOUNT of FLUIDS:</u>										
<i>oz</i> = ounces	<i>1 measuring cup = 8oz</i>			<i>240 ml = 8oz</i>						

Appendix E

Toileting Log

TOILETING LOG		Each morning, follow the bladder preparation instructions below.					
						ID# 3 _____	
						6m Clinic Visit	
Day 1	Date:	Day 2	Date:	Day 3	Date:		
Please take a moment to intentionally COUGH VERY HARD on a <u>full</u> bladder.		Please take a moment to intentionally COUGH VERY HARD on a <u>full</u> bladder.		Please take a moment to intentionally COUGH VERY HARD on a <u>full</u> bladder			
Did you leak with this cough? Y N		Did you leak with this cough? Y N		Did you leak with this cough? Y N			
Throughout your day, indicate with a hash mark (e.g. IIII) each time you have a leakage episode.		Throughout your day, indicate with a hash mark (e.g. IIII) each time you have a leakage episode.		Throughout your day, indicate with a hash mark (e.g. IIII) each time you have a leakage episode.			
If No leakage on Day 1 check box <input type="checkbox"/>		If No leakage on Day 2 check box <input type="checkbox"/>		If No leakage on Day 3 check box <input type="checkbox"/>			
Comments:		Comments:		Comments:			
How many times did you empty your bladder today while awake: <input type="text"/>		How many times did you empty your bladder today while awake: <input type="text"/>		How many times did you empty your bladder today while awake: <input type="text"/>			
Bladder Preparation Instructions							
Each morning, when you need to go to the bathroom *, intentionally COUGH VERY HARD three times.							
Did you leak with these coughs? Record your answer above. Empty your bladder and proceed with your daily routine.							
*If you do not feel the need to go to the bathroom, drink approximately 8-10 ounces (240-300 ml) of <u>water</u> . Wait anywhere from 15-30 minutes so that you have a full bladder. Now proceed with COUGHING VERY HARD three times.							



Appendix F

Diagnosis and Treatment of Non-Neurogenic Overactive Bladder (OAB) in Adults: American Urological Association/Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction Guideline

Diagnosis:

1. The clinician should engage in a diagnostic process to document symptoms and signs that characterize OAB and exclude other disorders that could be the cause of the patient's symptoms; the minimum requirements for this process are a careful history, physical exam, and urinalysis. Clinical Principle
2. In some patients, additional procedures and measures may be necessary to validate an OAB diagnosis, exclude other disorders and fully inform the treatment plan. At the clinician's discretion, a urine culture and/or post-void residual assessment may be performed and information from bladder diaries and/or symptom questionnaires may be obtained. Clinical Principle
3. Urodynamics, cystoscopy and diagnostic renal and bladder ultrasound should not be used in the initial workup of the uncomplicated patient. Clinical Principle
4. OAB is not a disease; it is a symptom complex that generally is not a life-threatening condition. After assessment has been performed to exclude conditions requiring treatment and counseling, no treatment is an acceptable choice made by some patients and caregivers. Expert Opinion
5. Clinicians should provide education to patients regarding normal lower urinary tract function, what is known about OAB, the benefits vs. risks/burdens of the available treatment alternatives and the fact that acceptable symptom control may require trials of multiple therapeutic options before it is achieved. Clinical Principle

First-Line Treatments:

6. Clinicians should offer behavioral therapies (e.g., bladder training, bladder control strategies, pelvic floor muscle training, fluid management) as first line therapy to all patients with OAB. Standard (Evidence Strength Grade B)

7. Behavioral therapies may be combined with pharmacologic management. Recommendation (Evidence Strength Grade C)

Second-Line Treatments:

8. Clinicians should offer oral anti-muscarinics or oral β 3-adrenoceptor agonists as second-line therapy. Standard (Evidence Strength Grade B)

9. If an immediate release (IR) and an extended release (ER) formulation are available, then ER formulations should preferentially be prescribed over IR formulations because of lower rates of dry mouth. Standard (Evidence Strength Grade B)

10. Transdermal (TDS) oxybutynin (patch [now available to women ages 18 years and older without a prescription] * or gel) may be offered. Recommendation (Evidence Strength Grade C) *Revised June 11, 2013

11. If a patient experiences inadequate symptom control and/or unacceptable adverse drug events with one anti-muscarinic medication, then a dose modification or a different anti-muscarinic medication or a β 3-adrenoceptor agonist may be tried. Clinical Principle

12. Clinicians should not use anti-muscarinics in patients with narrow-angle glaucoma unless approved by the treating ophthalmologist and should use anti-muscarinics with extreme caution in patients with impaired gastric emptying or a history of urinary retention. Clinical Principle

13. Clinicians should manage constipation and dry mouth before abandoning effective anti-muscarinic therapy. Management may include bowel management, fluid management, dose modification or alternative anti-muscarinics. Clinical Principle

14. Clinicians must use caution in prescribing anti-muscarinics in patients who are using other medications with anti-cholinergic properties. Expert Opinion

15. Clinicians should use caution in prescribing anti-muscarinics or β 3-adrenoceptor agonists in the frail OAB patient. Clinical Principle

16. Patients who are refractory to behavioral and pharmacologic therapy should be evaluated by an appropriate specialist if they desire additional therapy. Expert Opinion

Third-line Treatments:

17. Clinicians may offer intradetrusor onabotulinumtoxinA (100U) as third-line treatment in the carefully-selected and thoroughly-counseled patient who has been refractory to first- and second-line OAB treatments. The patient must be able and willing to return for frequent post-void residual evaluation and able

and willing to perform self-catheterization if necessary. Standard Option (Evidence Strength Grade B C)

18. Clinicians may offer peripheral tibial nerve stimulation (PTNS) as third line treatment in a carefully selected patient population. Recommendation (Evidence Strength Grade C)

19. Clinicians may offer sacral neuromodulation (SNS) as third line treatment in a carefully selected patient population characterized by severe refractory OAB symptoms or patients who are not candidates for second-line therapy and are willing to undergo a surgical procedure. Recommendation (Evidence Strength – Grade C)

20. Practitioners and patients should persist with new treatments for an adequate trial in order to determine whether the therapy is efficacious and tolerable. Combination therapeutic approaches should be assembled methodically, with the addition of new therapies occurring only when the relative efficacy of the preceding therapy is known. Therapies that do not demonstrate efficacy after an adequate trial should be ceased. Expert Opinion

Additional Treatments:

21. Indwelling catheters (including transurethral, suprapubic, etc.) are not recommended as a management strategy for OAB because of the adverse risk/benefit balance except as a last resort in selected patients. Expert Opinion

22. In rare cases, augmentation cystoplasty or urinary diversion for severe, refractory, complicated OAB patients may be considered. Expert Opinion

Follow-Up:

23. The clinician should offer follow up with the patient to assess compliance, efficacy, side effects and possible alternative treatments. Expert Opinion

(American Urological Association, 2012; Amended 2014)

Appendix G

The Etiology, Prevention, and Treatment of the Diseases of Civilization

A Darwinian Conceptual Framework

www.Darwinian-Medicine.com

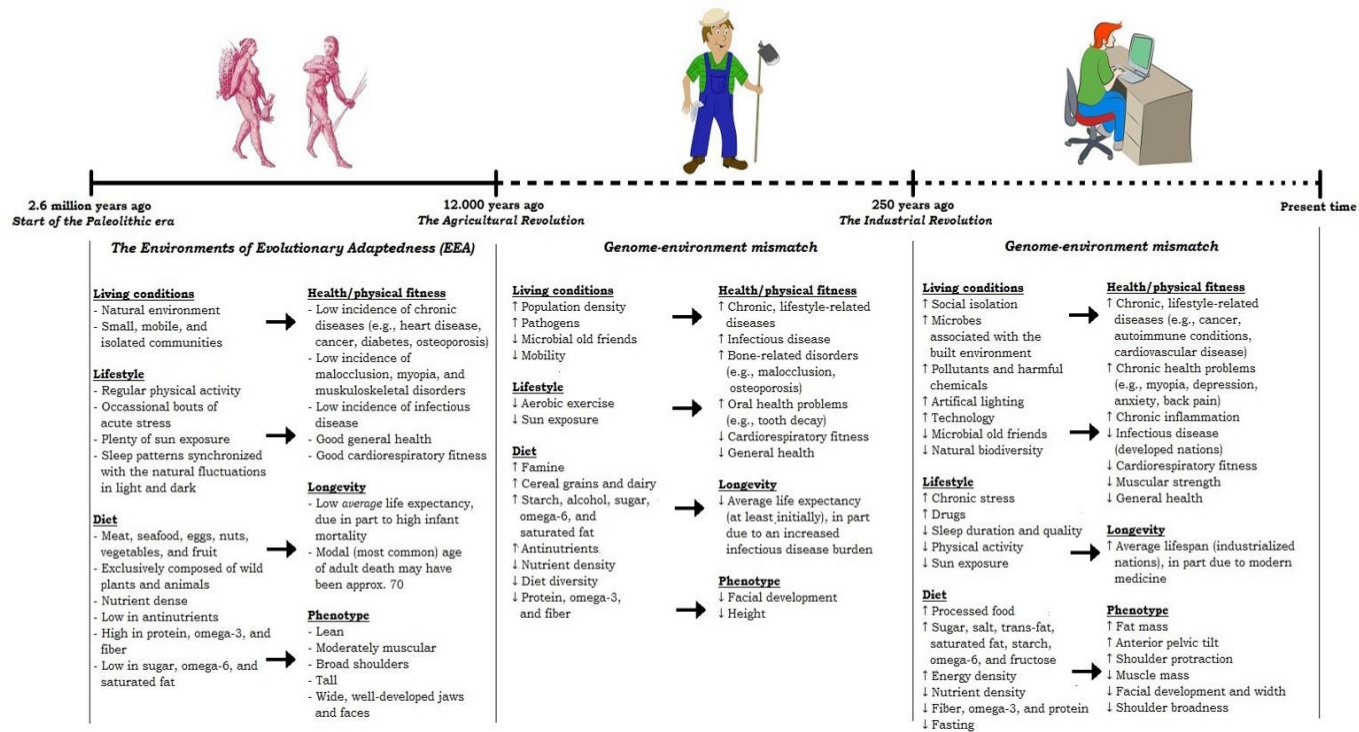


Figure 16 Etiology, Prevention, and Treatment of the Diseases of Civilization

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