VITAMIN AND MINERAL SUPPLEMENT USE BY OLDER ADULTS WITH COMPLEX MEDICATION NEEDS; POTENTIAL FOR ADVERSE DRUG-NUTRIENT INTERACTIONS

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By

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ABSTRACT

Objective: Vitamin and mineral supplements have been increasingly available for decades. The increase in availability of supplements and their use in combination with prescription drugs suggests that the risk of an adverse drug-nutrient interaction has drastically increased. This is especially concerning in populations with greater medication use. The purpose of this study was to assess vitamin and mineral supplement use in older adults with complex medication use to identify supplement use, overuse, and use from multiple sources. A secondary outcome of this study was to assess the potential for adverse drug-nutrient interactions in medically complex patients. **Methods:** A retrospective chart review was completed on 229 medically-complex patients 50 years of age and older who had new assessments of medications completed between January 2014 and January 19th, 2017 at the University of Saskatchewan Medication Assessment Centre. **Results:** Data indicate that 76.9% (n = 176) of patients (mean: 69 years) reported using ≥ 1 vitamin and/or mineral supplement daily. Total product count (oral prescriptions, over-the-counter (OTC) products, dietary supplements) ranged from 1-45 per day, with a mean 9.8 and median of 9. The tolerable upper intake level (UL) for nutrients was exceeded by 39.7% (n = 70) of reported supplement users (n = 176). One case exceeded the UL for 6 different nutrients, from supplemental intake alone. Of reported supplement users, 43.2% consumed supplemental nutrients from more than one source, which was significantly associated ($p < 0.001$) with supplemental nutrient intake at or above the UL. **Conclusions:** Vitamin and mineral supplement use in conjunction with prescription drugs and OTC products was observed in this population, with reported intake of many supplemental nutrients that exceeded the UL.

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LIST OF ABBREVIATIONS

AI	Adequate Intake
CCHS	Canadian Community Health Survey
CCHS-HA	Canadian Community Health Survey-Healthy Aging
DIN	Drug Identification Number
DRI	Dietary Reference Intakes
EAR	Estimated Average Requirement
EMR	Electronic Medical Records
GERD	Gastroesophageal reflux disease
GI	Gastrointestinal
LOAEL	Lowest observed adverse effect level
LTC	Long Term Care
MAC	Medication Assessment Centre
MVM	Multivitamin/mineral
NHP	Natural Health Product
NOAEL	No observed adverse effect level
NVM	Non-vitamin/mineral
OTC	Over-the-counter
PPI	Proton Pump Inhibitor
RDA	Recommended Dietary Allowance
REB	Research Ethics Board
UL	Tolerable Upper-Intake Level
VMS	Vitamin/Mineral Supplement

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CHAPTER 1

INTRODUCTION

1.1 Background

Dietary supplements have been available to consumers for decades. In recent years, consumers have seen an increase in the variety of dietary supplements that are available for purchase and have increased their use of supplements (Health Canada, 2011; Qato, Wilder, Schumm, Gillet, & Alexander, 2016). The increase in available supplements and in use of dietary supplements in combination with prescription drugs suggests that the risk of an adverse drug-nutrient interaction has drastically increased (Health Canada, 2011). This is especially concerning in populations with a higher complexity of medication usage, such as adults over the age of 50 years with morbidities. Previous Canadian nutrition research for this age group has focused on individuals in long term care and acute care settings (Ginter et al., 2013; Goorang, Ausman, Houser, & Whiting, 2015; Goorang, Thorpe, Bailod, & Whiting, 2015; Viveky et al., 2012); thus, the gap in literature for this age group is identified as community dwelling adults over the age of 50. Dr. Whiting's group has shown that individuals who take more medications and are at risk of undernutrition may benefit from using vitamin and/or mineral supplements but recognized that alternatively, too much nutrient supplementation can cause adverse drug-nutrient interactions and intake exceeding the Tolerable Upper Intake Level (UL) of some supplements (Ginter et al., 2013; Goorang, Ausman, et al., 2015; Goorang, Thorpe, et al., 2015; Greene-Finestone, Langlois, & Whiting, 2013; Vatanparast, Adolphe, & Whiting, 2010; Viveky et al.,

2012; Whiting, 2009). Further, few studies of medication use in older adults assessed the impact of dietary supplement use on medication functionality and overall nutrition status.

The Medication Assessment Centre (MAC) at the University of Saskatchewan is a unique and evolving clinic that is run by faculty in the College of Pharmacy and Nutrition and offers in-depth medication assessments for patients with complex medication needs. Additionally, the MAC is a teaching clinic where pharmacy students have the opportunity for early counselling exposure. A retrospective chart audit of 173 MAC patients showed an average age of 64.8 years and an average medication use of 13.8 drugs (including supplements and non-prescription products) per person (Jorgenson, Landry, & Lysak, 2016). Currently, to our knowledge, no published research into the specifics of potential adverse dietary supplement-drug interactions exists for this population, which is known to take many types of medications (Jorgenson et al., 2016).

1.2 Rationale

This research project aimed to identify initial data needed to implement nutritional interventions, particularly to ensure the safe usage of vitamin and mineral supplements at the primary care level. Such nutritional interventions would aid in improving health status of older adults, especially those with chronic disease. In addition, this project sought to highlight the positive attributes that a collaborative interdisciplinary approach could bring to a pharmacist-led medication assessment centre, such as the integration of a dietitian into the assessment and counselling of medically-complex patients.

1.3 Study Purpose and Objectives

The purpose of this study was to assess the personal vitamin and mineral supplement use of older adults with complex medication use. Specifically, the three objectives were to: 1) identify use and overuse of vitamin and mineral supplements; 2) learn the extent to which people were consuming supplemental nutrients from multiple sources; 3) investigate the potential for adverse drug-nutrient interactions.

CHAPTER 2

LITERATURE REVIEW

2.1 Nutrition and Aging

According to the United Nations, the population of older adults (> 60 y) has been steadily increasing over time and is expected to rapidly increase over the coming years (United Nations Population Division, 2015). In general, both physical activity and basal metabolic rate decrease with age, lending to a decrease in appetite and total energy intake, which can cause micronutrient deficiencies (Denny, 2008; Kirkpatrick & Tarasuk, 2008). Research also shows that older adults are at a higher risk of undernutrition secondary to a decrease in mobility, poor oral health, and morbidities (Denny, 2008). Physiologically, a decrease in kidney function and other age-related declines are more likely to affect nutrient absorption in older adults (Otten, Pitzi Hellwig, & Meyers, 2006). In order to meet recommended nutrient needs through later years in life, some people require a vitamin and mineral supplement in addition to their dietary intake.

Recent analysis of data from a large population-based survey in Canada found that approximately one third (34%; n = 979,000) of older adults (≥ 65 years) in Canada were classified as being at nutritional risk in 2008/2009 (Ramage-Morin, Gilmour, & Rotermann, 2017). Data from the Canadian Community Health Survey-Healthy Aging (CCHS-HA) that was completed in 2008/2009 was linked with hospital discharge and mortality data to evaluate the estimated nutritional risk, hospitalization, and mortality of older (≥ 65 years) community-

dwelling Canadians (Ramage-Morin et al., 2017). Further, data from this study indicate that nutritional risk in older community-dwelling Canadian adults was independently associated with both hospitalization and mortality (Ramage-Morin et al., 2017). Seniors who were at nutritional risk had a significantly higher rate (31%) of hospitalization when compared to seniors in the same age group who were not considered to be at nutritional risk (24%) (Ramage-Morin et al., 2017). Overall, the results of this survey reinforce the importance of nutritional adequacy in older adults.

As we transition through different life stages, our requirements for various nutrients may increase or decrease due to physiological changes associated with the aging process, as summarized in Table 2.1. For adults 70 years of age and older, the Recommended Dietary Allowance (RDA) for vitamin D increases to 800 IU/day and all adults over the age of 50 years are recommended to take 400 IU/day of supplemental vitamin D as it rarely feasible to obtain sufficient vitamin D intake from food sources alone (Hanley et al., 2010; Health Canada, 2012; Ross, Taylor, Yaktine, & Del Valle, 2011). The key factor in determining an appropriate intake level for vitamin D in those over the age of 50 years is the risk for bone fracture (Ross et al., 2011). Similar to vitamin D, the recommended increase in calcium intake with age is predominately related to fracture risk, which is of concern at an earlier age for woman (over 50 years) compared to men (over 70 years) (Ross et al., 2011). A vitamin B12 supplement or consumption of B12 fortified foods is recommended for adults over the age of 50 years due to a likely decrease in gastric acidity and thus, a decrease in food-bound vitamin B12 absorption (Otten et al., 2006).

Table 2.1: Summary of changes to nutrient requirements* for older adults (> 50 y)

Nutrient	Change
Vitamins	
Vitamin D	Increase (>70 y)
Vitamin B6	Increase
Vitamin B12	Supplement recommended
Minerals	
Calcium	Increase
Chromium	Decrease
Iron	Decrease (Women)
Sodium	Decrease
Chloride	Decrease

*(Otten et al., 2006; Ross et al., 2011)

2.2 Nutritional Supplement Use by Older Adults

'Dietary supplement' is a broad term commonly used and represents a lack of homogeneity in the literature. Scholars define 'dietary supplement' as: all supplements (including vitamin and minerals) or all supplements (excluding vitamins and minerals). This literature review revealed a lack of recent studies investigating vitamin and mineral supplement use in community-dwelling adults over the age of 50. In Canada, vitamin and mineral supplements are considered to be Natural Health Products (NHPs) and are the most commonly used NHPs (Health Canada, 2011).

Detailed dietary supplement use by older adults has been studied in Canadian Long-Term Care (LTC) facilities but less so for older adults living in the community. To this extent, a scoping review of vitamin and mineral supplement use by community-dwelling adults in both Canada and the United States was conducted and the manuscript can be found in Chapter 3.

Overall, few Canadian studies have investigated the use and safety of vitamin and mineral supplements in community-dwelling adults over the age of 50 and the majority of studies focused on the use of certain nutrients in a specific age group while the studies on overall supplement use were mainly limited to national surveys (Ford & Whiting, 2017). The findings of this scoping review suggest that the prevalence of supplement use varied greatly between the national surveys and smaller cohort studies. The differences in supplement use observed between the national surveys and the smaller cohort studies allude to the importance of smaller cohort studies in specific populations, such as medically-complex older adults, to capture data that is likely not apparent in large national surveys (Ford & Whiting, 2017).

Studies have investigated older adults' motivations for vitamin and mineral supplement use but a consensus has yet to be achieved (Bailey, Gahche, Miller, Thomas, & Dwyer, 2013; Marques-Vidal et al., 2009). Nationally representative data in the United States reported that the three most common reasons for dietary supplement use was to "improve overall health", "maintain health", and "bone health" (Bailey et al., 2013). Despite the previously mentioned reasons for dietary supplement use by Bailey et al. (2013), the same study found that more than three quarters of participants reported using dietary supplements as a personal choice while less than a quarter of participants reported using them secondary to a recommendation from their health care provider (Bailey et al., 2013). Dietary supplements are commonly used for a variety of reasons, with one reason being that they are available to consumers without a prescription. For this reason, health care professionals may be unaware of their patients use of supplements unless it is accurately self-reported to the practitioner. Often, people do not think to report the use of dietary supplements since they are not a prescription-based product. Many consumers are not aware that although supplements can be extremely beneficial to some individuals, they can also

put someone at risk if not taken in correct doses or combinations. This phenomenon is likely linked to the common consumer misconception that 'more is better'. In reality, the intake of vitamins and minerals has a U-shaped distribution where both minimal and excess intake of a particular nutrient can put you at an increased risk for either nutrient deficiency or toxicity (Otten et al., 2006).

Factors that positively affect supplement consumption include being healthier (Bailey et al., 2013) and more educated (Marques-Vidal et al., 2009; Rovira et al., 2013; Vatanparast, Adolphe, et al., 2010). Canadian research found that age, sex, household income, education, food security, and chronic conditions were all factors independently associated with dietary supplement use (Vatanparast, Adolphe, et al., 2010). When compared to other age groups, older adults had a greater prevalence of supplement use (Bailey et al., 2013; Marques-Vidal et al., 2009). Data on sex and age groups show that women over the age of 51 had the highest prevalence of supplement use (60%) when compared to other age groups and males (Vatanparast, Adolphe, et al., 2010).

A systematic review on micronutrient intake from diet and supplements in older community-dwelling adults concluded that a substantial limitation in the current literature is the lack of data on supplement dose and frequency of use (ter Borg et al., 2015). Further, the review found that many studies did not distinguish between micronutrient intakes from dietary and supplemental form (ter Borg et al., 2015). This information is important as many supplements can cause toxicity if taken in large doses, as described below (Otten et al., 2006; Ross et al., 2011).

A recent study in the United States looked at 37 958 adults and reported on national trends in their dietary supplement use (Kantor, Rehm, Du, White, & Giovannucci, 2016). Data was nationally representative (NHANES) and supplement use data were collected during in-home interviews that inquired about supplement usage over the past 30 days. For this study, supplements encompassed all dietary supplements, not simply vitamin and mineral supplements. The main findings of this group included that dietary supplement use increased with age and that more women than men reported supplement use. Data from this study indicate that 72% of adults 65 years of age an older reported the use of at least one dietary supplement. This study found that the use of multivitamin/minerals has decreased by approximately 6% since the late 1990's. Interestingly, the data also show that despite the use of vitamin D remaining relatively stable over the years, adults are now taking vitamin D as a single-nutrient supplement as opposed to getting it in a multivitamin product. Regardless of shifting trends in supplement use, the data indicate that overall supplement use in American adults has remained stable since the late 1990's (Kantor et al., 2016).

The Canadian Community Health Survey (CCHS) is a recurring nationally representative survey that includes data collection on nutritional supplements (Statistics Canada, 2013). The most recent survey was completed in 2015 and the data became available for analysis in the summer of 2017, thus there is currently no published results from the latest survey. The previous CCHS was completed in 2004 and provided data on nutritional supplement use (based on the previous 30 days) for 35 107 Canadian adults (Guo, Willows, Kuhle, Jhangri, & Veugelers, 2009; Vatanparast, Adolphe, et al., 2010). Data from this study indicate that the prevalence of use was significantly higher in women (46.9%) and that supplement users, especially the older adults, were much more likely to reach nutrient adequacy for calcium, when compared to non-

users (Vatanparast, Adolphe, et al., 2010). Another study that analysed the same survey data but focused only on adults found that 40.1% (n = 15 553) reported nutritional supplement use over the past 30 days and that for both sexes, supplement use increased with age (Guo et al., 2009). Additionally, data indicate that supplement use increased with education and household income, and food security; thus, supporting the inverse supplement hypothesis that suggests that those who could benefit from supplementation are not the ones using supplements (Guo et al., 2009; Vatanparast, Adolphe, et al., 2010).

Nutrition- and supplement-related data from the 2004 Canadian Community Health Survey was also analyzed by another group to gain a better understanding of micronutrient inadequacies among the Canadian population and the effect of supplement use on micronutrient adequacy (Shakur, Tarasuk, Corey, & O'Connor, 2012). Table 2.2 shows the prevalence of micronutrient supplement use by Canadian community-dwelling adults, broken down by sex, age group, and nutrient (Shakur et al., 2012). Females over the age of 50 years were more likely (60%) to use any vitamin or mineral supplement when compared to males (41%) of the same age group. The most used supplements by females over the age of 50 years were calcium (48% use) and vitamin D (44% use). In comparison, males of the same age group were most likely to take a vitamin C supplement (32% use), followed by a calcium supplement (29% use). Overall, this study found that vitamin and mineral supplement use aided Canadians in meeting nutrient adequacy but also increased the likelihood of exceeding the UL for one or more nutrients (Shakur et al., 2012).

Table 2.2: Prevalence of Vitamin Mineral Supplement Use by Adults[1]

Consumption of a supplement containing	**Males >50y (n=4324)**	**Females >50y (n=6175)**
	% (SE)	% (SE)
Any VM	41 (1)	60 (1)
MVM[2]	28 (1)	37 (1)
Vitamin A	26 (1)	31 (1)
Vitamin C	32 (1)	38 (1)
Vitamin D	28 (1)	44 (1)
Vitamin B6	26 (1)	31 (1)
Folic Acid	26 (1)	30 (1)
Vitamin B12	27 (1)	32 (1)
Thiamin	26 (1)	30 (1)
Riboflavin	26 (1)	31 (1)
Niacin	26 (1)	30 (1)
Calcium	29 (1)	48 (1)
Phosphorus	18 (1)	18 (1)
Magnesium	25 (1)	31 (1)
Iron	20 (1)	24 (1)
Zinc	23 (1)	28 (1)

[1]Values are percentage (SE). VM, vitamin/mineral

[2]MVM, multi-vitamin/mineral. MVM = any supplement containing 3 or more vitamins/minerals.

Adapted from: (Shakur et al., 2012)

2.3 Dietary Reference Intakes

Dietary Reference Intakes (DRIs) were created to provide reference values for suggested vitamin and mineral intake levels throughout the life cycle for both healthy individuals and groups (Otten et al., 2006). The Estimated Average Requirement (EAR) was established as the estimated amount of a specific nutrient required to meet the needs of half of a healthy population in a specific life stage (Otten et al., 2006). Similarly, the Recommended Dietary Allowance

(RDA) was created for each nutrient as a reference amount that will meet the needs of 97-98% of healthy individuals within a life stage (Otten et al., 2006). When there is not enough evidence available to set an EAR and RDA, an Adequate Intake (AI) level is set based on less evidence and assumed to be an adequate intake amount for healthy people (Otten et al., 2006). Lastly, the Tolerable Upper-Intake Level (UL) was established as a reference amount where no adverse side effects should be observed; although, the risk of experiencing adverse effects increases as intake of a nutrient above its UL increases (Otten et al., 2006).

As shown in Table 2.3, a UL is established for most nutrients but some nutrients do not have enough data available on adverse effects to methodically set a UL (Otten et al., 2006). Nevertheless, this lack of evidence on adverse effects does not imply that nutrients with no defined UL are safe to consume in high doses as this may still pose risk, especially with chronic use (Otten et al., 2006). The UL for a nutrient is set by following a specific method known as the *Risk Assessment Methodology* whereby the literature is critically reviewed and the lowest observed adverse effect level (LOAEL) and/or the highest no observed adverse effect level (NOAEL) are established (Food and Nutrition Board Institute of Medicine, 1998; Munro, 2006). The LOAEL and NOAEL are used in combination with the uncertainty factors to determine the UL, which is then set below the LOAEL/NOAEL (Food and Nutrition Board Institute of Medicine, 1998; Munro, 2006). Thus, each UL is based on specific criteria, as seen in Table 2.3, and assumes chronic intake of the associated nutrient. The evidence used to set each UL is nutrient-specific and will be discussed in further detail in Chapter 6 - Discussion.

Table 2.3: Criteria Used to Set Tolerable Upper-Intake Levels (ULs)

Nutrient	UL	UL for adults was set based on:
Vitamin A	10,000 IU/day retinol	Liver abnormalities
Niacin*	35 mg/day	Flushing
Vitamin B6	100 mg/day	Sensory neuropathy
Folate*	1,000 µg/day	Precipitation or exacerbation of neuropathy in vitamin B12-deficient individuals
Choline	3,500 mg/day	Hypotension with cholinergic side effects and fishy body odor
Vitamin C	2,000 mg/day	Osmotic diarrhea
Vitamin D	4,000 IU/day	Hypercalcemia
Vitamin E*	1,000 mg/day	Increased tendency to hemorrhage
Calcium	2,000 mg/day	Incidence of kidney stones
Copper	10,000 µg/day	Liver damage
Fluoride	10 mg/day	Skeletal fluorosis
Iodine	1,100 µg/day	Elevated serum thyrotropin concentrations
Iron	45 mg/day	Gastrointestinal distress
Magnesium*	350 mg/day	Diarrhea
Manganese	11 mg/day	Manganese neurotoxicity
Molybdenum	2,000 µg/day	Impaired reproduction and growth in animals
Phosphorus	4,000 mg/day (50-70 y) 3,000 mg/day (70+ y)	Elevated serum inorganic phosphorus concentration
Selenium	400 µg/day	Selenosis (hair and nail brittleness/loss; gastrointestinal disturbance; rash; etc.)
Zinc	40 mg/day	Reduced copper status (reduces red blood cell copper-zinc superoxide dismutase activity)

*UL applies only to synthetic and/or supplemental form
Table adapted from: (Office of Nutrition Policy and Promotion Health Products and Food Branch, 2006; Otten et al., 2006; Ross et al., 2011)

2.4 Safety

Vitamin and mineral supplement use in a Canadian LTC was examined, and it was found that over 70% of participants who were classified as consistent (≥ 3 months) supplement users (n = 92) consumed 1-2 dietary supplements per day (Viveky et al., 2012). Overall, 35% of all study participants (n = 189) consumed 1-2 supplements daily (Viveky et al., 2012). Data from this study also showed that patients who took more than one supplement per day were more likely to consume a nutrient from two or more supplement sources (i.e. Vitamin D from a multivitamin and from a separate vitamin D supplement) (Viveky et al., 2012). Data from the same study showed that only 50% of study participants were consuming a form of supplemental vitamin D while Osteoporosis Canada recommends that all adults over the age of 50 should consume a vitamin D supplement of 800 – 2000IU/day to ensure adequate intake (Hanley et al., 2010; Viveky et al., 2012). Another Canadian study had also investigated the use of supplemental vitamin D and found that women between the ages of 51 and 70 had the lowest intake of vitamin D from food when compared to other age groups and sex (Vatanparast, Calvo, Green, & Whiting, 2010).

In addition to intake levels of dietary supplements, the content of vitamin and mineral supplements is also a potential safety issue. A recent study in the Unites States investigated the variability of supplement ingredients (Andrews et al., 2017). Results from this study indicate that the mean ingredient content of multivitamin/mineral (MVM) products exceeded the ingredient quantities that were reported on the supplement label (Andrews et al., 2017). More specifically, data from this study show that 12 nutrients were included in these supplements in amounts at or above the RDA and that all nutrients, with the exception of thiamin, were in quantities greater than that indicated on the label, when analyzed (Andrews et al., 2017).

A nationally representative Canadian study found that adults did not consume nutrients in excess of the UL, from diet alone (Shakur et al., 2012). There was no difference between supplement users and non-users for all age and sex categories. Data from the same study indicate that when a vitamin and/or mineral supplement is consumed, the likelihood of exceeding the UL increases. As seen in Table 2.4, ten nutrients were consumed in amounts exceeding the UL by supplement users. Approximately half of the males (50%) and females (49%) over the age of 50 years who consumed supplements exceed the UL for niacin. Women (15%) over the age of 50 were more likely to have a calcium intake in excess of the UL when compared to men (7%) (Shakur et al., 2012).

Table 2.4: Prevalence of Canadian adults (% (SE)) exceeding the UL from diet + supplement

Nutrient	**Males (>50y)**	**Females (>50y)**
Vitamin A	< 5	< 5
Vitamin C	< 5	< 5
Vitamin D	< 5	< 5
Vitamin B6	<5	< 5
Folic Acid	12 (1)	11 (1)
Niacin	50 (3)	49 (2)
Calcium	7 (2)	15 (1)
Magnesium	< 5	10 (1)
Iron	6 (2)	7 (2)
Zinc	14 (2)	14 (1)

Adapted from: (Shakur et al., 2012)

2.4.1 Polypharmacy

'Polypharmacy' is a term that is used to describe the use of several (usually 6 or more) drugs (Bushardt, Massey, Simpson, Ariail, & Simpson, 2008). A study on older (>75 y)

American adults found that 90% of participants who reported dietary supplement use also reported the use of at least one prescription medication (Nahin et al., 2009). Similarly, the same study reported that over 80% of participants who were prescription drug users reported the use of at least one dietary supplement (Nahin et al., 2009). Of the 3,070 participants, over 70% reported the simultaneous use of at least one prescription drug and one dietary supplement while over 30% reported concurrent use of 3 or more drugs and supplements and 10% reported concurrent use with 5 or more drugs and dietary supplements (Nahin et al., 2009). Another study advocating to change the classification of vitamins from NHPs to drugs highlighted 55 potential vitamin-drug interactions (Rogovik, Vohra, & Goldman, 2010). This list is not extensive as it does not include potential mineral-drug interactions. Although vitamins are not currently classified as drugs in Canada, they have both a physiological and pharmacological impact on the body and thus have the potential to cause equally adverse effects, especially when taken in combination with certain drugs (Rogovik et al., 2010).

A Canadian study done in a Medication Assessment Centre (MAC) in Saskatoon, Saskatchewan that targets complex patients did a retrospective chart audit of all patients seen between March 2014 and July 2015 (Jorgenson et al., 2016). Chart audits were completed on 173 patient files and data on age, gender, referral source, number of appointments attended, number of medications at first appointment, number of medical diagnoses, and number of recommendations made by the pharmacist were extracted (Jorgenson et al., 2016). Data from the study (n = 173) is summarized in Table 2.5. On average, the patient age was considered elderly (64.8 years) but age ranged from 2-93 years. The majority (60.1%, n=104) of patients were females and were referred to the MAC by a physician (52.6%, n=91). Data indicate an average pill count (including prescription drugs, non-prescription drugs, and natural health products) of

13.8 and 6.5 diagnoses per patient, which alludes to the complexity of the patients (Jorgenson et al., 2016).

Table 2.5: Summary of a Study of Patients Receiving Medication Assessments (n = 173)

Mean age in years (range)	64.8 (2-93)
Gender	
Male (%)	69 (39.9)
Female (%)	104 (60.1)
Number of medical diagnoses	
Mean (range)	6.5 (1-16)
Median	6
Number of medications recorded at first appointment*	
Mean (range)	13.8 (1-55)
Median	13
Number of recommendations made by pharmacist	
Mean (range)	6.2 (0-22)
Median	5
Referral Source	
Physician (%)	91 (52.6)
Self-referral (%)	59 (34.1)
Nurse Practitioner (%)	13 (7.5)
Other (%)	10 (5.8)

*Includes prescription drugs, non-prescription drugs, and natural health products

Adapted from (Jorgenson et al., 2016).

Knowing that older adults have the greatest prevalence of dietary supplement use (Bailey et al., 2013; Marques-Vidal et al., 2009; Vatanparast, Adolphe, et al., 2010), and that medication usage increases with age (Rotermann, Sanmartin, Hennesey, & Arthur, 2014) it is important to have a concrete understanding of the risks involved with concurrent use of dietary supplements

and medications. Further research is needed to expand the work done by Jorgenson et al. (2016) to investigate concomitant use of supplemental vitamin/minerals and prescription drugs in a medically-complex population.

2.4.2 Drug-Nutrient Interactions

Drug-nutrient interactions are difficult to summarize or summate due to the indefinite potential of interaction combinations, based on the multitude of factors that are implicated in each interaction (Boullata & Hudson, 2012; Santos & Boullata, 2005). Additionally, many reported interactions are based off of historic case studies and the actual number of interactions that are clinically significant is unclear (Boullata & Hudson, 2012). Broadly, any potential interaction can fit into one of five classifications, which are further broken down into the effect of a nutrient on a drug or a drug on a nutrient, as seen in Table 2.6 (Santos & Boullata, 2005). Tables 2.7 and 2.8 provide a starting point for examining some of the potential drug-nutrient interactions likely to be seen in older adults (Nelms, Sucher, Lacey, & Roth, 2011; Otten et al., 2006; Rogovik et al., 2010; Ross et al., 2011).

Table 2.6: Santos et al., 2005 Classification of Drug-Nutrient Interactions

Precipitating Factor	**Object of Interaction**	**Potential Consequence**
Altered nutrition status	Drug	Treatment failure or drug toxicity
Food or food component	Drug	Treatment failure or drug toxicity
Nutrient or supplement ingredient	Drug	Treatment failure or drug toxicity
Drug	Nutritional status	Altered nutritional status
Drug	Specific nutrient	Altered nutritional status

As seen in Table 2.6, drug-nutrient interactions can occur when the precipitating factor is nutrient related and the object of interaction is a drug or the opposite can occur, where a drug is

the precipitating factor and overall nutrition status or a specific nutrient is the object of interaction (Santos & Boullata, 2005). Each are equally important but a review of the literature indicates limited data on the effect that drugs have on nutrients or overall nutritional status. Table 2.7 highlights a few examples of the effects that nutrients can exhibit on drugs while Table 2.8 provides examples of interactions where drugs exhibit effects on nutrient status (Nelms et al., 2011; Otten et al., 2006; Rogovik et al., 2010; Ross et al., 2011). Tables 2.7 and 2.8 are not meant to be exhaustive lists of potential interactions, but rather illustrate common drug-nutrient interactions that are more likely to occur in older adults.

As seen in Table 2.8, Proton Pump Inhibitor (PPI) drugs interact with several nutrients. PPIs are used extensively to treat upper gastrointestinal (GI) disorders such as gastroesophageal reflux disease (GERD) (Heidelbaugh, 2013). The extensive use of these drugs is a nutrition-related concern based on the potential for malabsorption of vitamin C, vitamin B12, calcium, iron, and magnesium that is caused by chronic use of this drug. Healthy adults are likely at lower risk of experiencing malabsorption of these nutrients while taking PPIs but older adults and malnourished individuals are at a much greater risk of experiencing malabsorption; thus, it is important to acknowledge the value of understanding the prevalence of these interactions, especially when working with older adults who are already at greater risk of malnutrition (Denny, 2008; Heidelbaugh, 2013; Kirkpatrick & Tarasuk, 2008).

From a nutrition standpoint, and due to the lack of literature, it is important to investigate the potential for drug-nutrient interactions in terms of nutrient impairment due to drugs. Although Table 2.8 is not a complete list of drug-nutrient interactions that can affect nutrient status, it is extensive and can be used to gain insight into potential interactions that might be

occurring in a group of community-dwelling older adults. This type of data can be used for a prospective study that would aid in closing literature gap on this clinically important topic.

Table 2.7: Potential Drug-Nutrient Interactions

Nutrient	**Drug**	**Interaction**
Vitamin E	Antiplatelets	May increase risk of bleeding
Vitamin E	Anticoagulants	May increase risk of bleeding
Vitamin E	Iron	May lead to hydroxyl radical production
Vitamin K	Anticoagulants	Antagonist
Folic Acid	Methotrexate	May reduce efficacy in treatment of cancers and can reduce adverse effects when used to treat rheumatoid arthritis and psoriasis.
Folic Acid	Proton Pump Inhibitors	Antagonist
Folic Acid	H2 Receptor Antagonist	Antagonist
Folic Acid	Metformin	Antagonist
Folic Acid	Acetaminophen	May decrease the elimination rate of the drug
Vitamin C	Aluminum	May increase adverse effects (eg. constipation)
Vitamin C	ASA	May increase adverse effects (eg. nausea). Attenuates ASA-induced gastric damage.
Vitamin C	β-blockers	May decrease absorption of the drug.
Vitamin C	Estrogens	May increase plasma estrogen levels up to 55%.
Vitamin C	Iron	May increase absorption of iron
Vitamin C	Anticoagulants	High dosage may reduce response to drug.
Vitamin C	Proton Pump Inhibitors	Antagonist
Vitamin B_{12}	Metformin	Antagonist
Vitamin B_{12}	H2 Receptor Antagonist	Antagonist

Adapted from: (Nelms et al., 2011; Otten et al., 2006; Rogovik et al., 2010; Ross et al., 2011)

ASA: Acetylsalicylic Acid

Table 2.8: Potential Nutrient-Drug Interactions

Nutrient	Drug	Interaction
Vitamin E	Laxatives	Malabsorption of vitamin E
Vitamin D	Thiazide Diuretics	Hypercalcemia
Vitamin D	Phenobarbital	Decreases metabolism and half life
Vitamin D	Phenytoin	Decreases metabolism and half life
Vitamin K	Laxatives	Malabsorption of vitamin K
Vitamin B6	Isoniazid	Decreases serum vitamin B6
Vitamin B6	Levodopa	Decreases serum vitamin B6
Vitamin B12	Proton Pump Inhibitors	Vitamin B12 malabsorption
Vitamin C	Proton Pump Inhibitors	Vitamin C malabsorption
Calcium	Corticosteroids	Calcium depletion
Calcium	Bisphosphonates	Calcium depletion
Calcium	Antihyperlipidemics	Calcium depletion
Calcium	Loop Diuretics	Calcium depletion
Calcium	H2 Receptor Antagonists	Calcium malabsorption
Calcium	Proton Pump Inhibitors	Calcium malabsorption
Calcium	Laxatives	Calcium malabsorption
Folate	Methotrexate	Folate depletion
Folate	Anticonvulsants	Increased folate metabolism
Folate	Pyrimethamine	Antagonist
Folate	Triamterene	Folate depletion
Folate	Sulfasalazine	Folate depletion
Potassium	Thiazide Diuretics	Potassium depletion
Potassium	Loop Diuretics	Increased potassium excretion
Potassium	Laxatives	Potassium malabsorption
Potassium	NSAIDs	Increased potassium excretion
Magnesium	Laxatives	Magnesium malabsorption
Magnesium	Proton Pump Inhibitors	Magnesium malabsorption
Magnesium	Loop & Thiazide Diuretics	Magnesium depletion
Magnesium	Antihyperlipidemics	Hypermagnesuria
Chromium	Antacids	Chromium malabsorption
Sodium	Corticosteroids	Sodium retention
Sodium	Loop Diuretics	Increased sodium excretion
Iron	H2 Receptor Antagonists	Iron malabsorption
Iron	Proton Pump Inhibitors	Iron malabsorption
Iodine	Sulfonylureas	Impair uptake or release of iodine
Iodine	Lithium	Impair uptake or release of iodine

Adapted from: (Heidelbaugh, 2013; Nelms et al., 2011; Otten et al., 2006; Rogovik et al., 2010; Ross et al., 2011)

NSAID: Nonsteroidal anti-inflammatory drug

CHAPTER 3

SCOPING REVIEW

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3.1 Abstract

Vitamin and mineral supplements can assist a person in meeting recommended intakes but excessive use can pose risks. Knowing prevalence of supplement use is the first step toward gauging risk-benefit. This scoping review sought to determine the prevalence of vitamin and mineral supplement use among community-dwelling Canadian and American adults. Medline and Embase were searched using keywords and MeSH headings that encapsulated both vitamin and mineral supplements and community-dwelling adults in Canada and the United States. Search limits were set for study participants over the age of 18, English language articles, and a publication date from the year 2000 to June of 2016. Of the 181 articles originally identified, 30 were deemed relevant for this scoping review. Eleven studies reported on vitamin and mineral supplement use in general, without specifying the prevalence of use for any particular supplement(s). Prevalence of general vitamin and mineral supplement use reported in these studies ranged from 7-85%. Twenty-two studies reported the prevalence of consumption for specific vitamins and minerals; although three of these studies also reported on overall supplement use. Calcium and vitamin D were widely reported, with 10 of 22 studies focusing on these key nutrients. Multivitamin/mineral supplements were also widely studied with 8 of 22

articles reporting their prevalence of consumption. Results from this scoping review indicate that data on the quantity and combination of supplement use is lacking in Canada and United States. These data are key for identifying intake amounts and combinations that have the potential to cause adverse effects.

3.2 Introduction

Vitamin and mineral supplements can aid in meeting daily micronutrient requirements; but they can also pose a risk for toxicity and/or adverse drug-nutrient interactions if not taken appropriately (American Dietetic Association, 2009; Food and Nutrition Board Institute of Medicine, 1998). Consumers, who may not be aware of the potential risks associated with vitamin and mineral supplement use, may be unsure of how to safely consume these products (American Dietetic Association, 2009). Although vitamin and mineral oral supplements are not currently classified as drugs (in Canada and the United States), they have both a physiological and pharmacological impact on the body similar to that of prescription drugs (Health Canada, 2011; Rogovik et al., 2010; U.S. Food and Drug Administration, 2008). Based on their complexity, the use of vitamin and mineral supplements to increase micronutrient intake, especially when taken in combination with over-the-counter and/or prescription medications, can be a concern to health care professionals due to the potential for therapeutic failure of medications and or supplements (American Dietetic Association, 2009; Rogovik et al., 2010).

3.3 Background

Previous research indicates that dietary supplement use, including vitamin and mineral supplements, has increased in many nations, especially Canada and the United States (Guo et al., 2009; Qato et al., 2016). Mainly in response to the rising use of supplements, the Food and

Nutrition Board set Tolerable Upper Intake Levels (ULs) to provide guidance for consumers and health care professionals when choosing dosage amounts for vitamin and mineral supplements. The UL of a vitamin or mineral is defined as "the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects to almost all individuals in the general population." (Food and Nutrition Board Institute of Medicine, 1998). Thus, the UL is a reference level for tolerable, not recommended, consumption of vitamin and mineral supplements (Food and Nutrition Board Institute of Medicine, 1998). Research indicates that although vitamin and mineral supplementation can put people at or above the UL; supplementation increases the percentage of people who attain adequate nutrient intake (Fulgoni, Keast, Bailey, & Dwyer, 2011; Shakur et al., 2012). Vitamin and mineral intake at the UL is not necessarily harmful, although the risk of adverse effect(s) increases as intake passes the UL (Food and Nutrition Board Institute of Medicine, 1998).

3.4 Description of Subject

Nationally representative studies are conducted in both Canada and the United States yet there remains the need for studies that probe for vitamin and mineral supplement usage in specific populations such as clients with complex medical diagnoses. The use and overuse of vitamin and mineral supplements has recently been investigated by Dr. Whiting's group in long-term care/nursing home residents at risk for polypharmacy (Viveky et al., 2012). We sought, however, to determine what studies investigated community-dwelling adults to gain an understanding of vitamin/mineral supplement use in this specific group. We conducted this scoping review on vitamin and mineral supplement use by community-dwelling adults in Canada and the United States to determine prevalence of general and specific use.

3.5 Methods

Using scoping review methodology (Grant & Booth, 2009); two databases (Medline and Embase, both via Ovid) were searched for corresponding literature. MeSH headings and keywords were used, ensuring that at least one term capturing vitamin and mineral supplements, study location, and living arrangements was found in each resulting article. The full list of MeSH headings and keywords are found in Table 3.1.

Table 3.1: List of terms searched in Medline and Embase databases

Key Variables	Medline	Embase
Vitamin and mineral supplements	Dietary supplements	vitamin (exp)
	Vitamins (exp)	mineral (exp)
	Minerals (exp)	trace element (exp)
	Micronutrients (exp)	"dietary supplement*"
	"multivitamin*"	"micronutrient*"
	"micronutrient intake*"	"micronutrient intake*"
	((vitamin* OR mineral* OR liquid* OR micronutrient* OR nutrition* OR food*) AND supplement*)	((vitamin* OR mineral* OR liquid* OR micronutrient* OR nutrition* OR food*) AND supplement*)
Study location	Canada (exp)	Canada (exp)
	United States (exp)	United States (exp)
Living Arrangements	Independent living	independent living
	"community-dwelling*"	"community-dwelling"

exp = explode

Searches in both databases were limited to the English language, human studies on adults (18 years and older), and a publication date from the year 2000 until June of 2016. Search results

from both databases were combined and duplicate results were removed. Articles identified through reference lists were also included. Titles and abstracts of all articles were reviewed using the following inclusion criteria: participants were community-dwelling adults, the study was original research (not a review article), and prevalence of vitamin and mineral supplement use was reported. Next, the eligible full-text articles were examined using the above inclusion criteria. Articles (n = 30) were then placed into two categories: general use of vitamin and mineral supplements (Table 3.2) and specific use of vitamin/mineral supplements (Table 3.3). In the former category, 8 articles were identified as only providing information on general supplement use while 19 articles focused on use of specific supplements. An additional three articles were relevant to both of these categories and thus included in each summary table. See Figure 1 for details regarding this process and reasons for article exclusion. The following data were extracted from all included studies: sample size; location and year of study; a description of the research participants, including their age; nutrients of focus; and the percentage of participants using vitamin and mineral supplements.

Table 3.2: Studies reporting on general supplement use in community-dwelling adults

(Reference); study location	Age (years)	Study Year	Participants (n)	% using supplements	Description of participants
Canadian Studies					
(Bedford & Barr, 2005); CAN	19-84	1999	1,817	60.2%	Adults from the British Columbia Nutrition Survey (BCNS)
(Guo et al., 2009); CAN	19-50	2004	15,553	35.5%	Canadian Community Health Survey (CCHS)
	51-70	2004	4,712	50.5%	
American Studies					
(Beydoun, Beydoun, Boueiz, Shroff, & Zonderman, 2013); USA	20-85	’05-‘06	1,798	62.6%	NHANES participants with complete data sets and depressive symptoms
(Cheung, Wyman, & Halcon, 2007); USA	≥65		445	56.2%	Randomly selected from Minnesota Driver's License/Identification Tape
(Espino et al., 2000); USA	≥65	’93-‘94	2,895	6.97%	Hispanic Established Population for the Epidemiologic Study of the Elderly (EPESE)
(Mursu, Robien, Harnack, Park, & Jacobs, 2011); USA	55-69	1986	38,772	62.7%	Iowa Women’s Health Study
		2004	19,124	85.1%	
(Qato et al., 2008); USA	57-84	’04-‘06	2,976	49.5%	National Social life, Health and Aging Project (NSHAP)
(Qato, Manzoor, & Lee, 2015); USA	57-84	2004	2,975	49.4%	NSHAP
(Qato et al., 2016); USA	62-85	’05-‘06	2,351	51.8%	NSHAP
		’10-‘11	2,206	63.7%	
(Raji, Kuo, Snih, Sharaf, & Loera, 2005); USA	≥77	’95-‘98	365	36.2%	Oldest participants of the Health of the Public Study
(Weeden & Remig, 2010); USA	>80	’07-‘08	113	85.5%	Congregate meal users living in rural communities

Table 3.3: Studies reporting on specific supplement use in community-dwelling adults

(Reference); study location	Size of Study	Study Year	Age of Participants	Nutrient(s) of focus	Supplement Use (%)	Description of Participants
Studies Targeting Calcium and/or Vitamin D						
(Bakhireva, Barrett-Connor, Kritz-Silverstein, & Morton, 2004); USA	507	88-'92 92-'96	45-92	Calcium	17.6%	Cohort of a middle- to upper-class Southern California Community (Rancho Bernardo) - Men Only
(Cline & Worley, 2006); USA	990	2003	45+	Calcium	58.4%	Surveyed 1700 Minnesota residents – Women Only
(Farley, Cline, & Hansen, 2004); USA	990	2003	45+	Calcium	56.7%	Survey sent to 1700 Minnesota residents via a mailing list firm - Women Only
(Barake, Weiler, Payette, & Gray-Donald, 2010); CAN	404	2005-2006	68-82	Vitamin D	30.7%	subset of Quebec Longitudinal Study (NuAge) cohort study; predominantly Caucasian men and women
(Ginter et al., 2013); CAN	224	2012	60-90	Vitamin D	44.8%	Cohort of ethnically diverse individuals - Square One Older Adult Centre in Ontario.
(Bolland, Grey, Gamble, & Reid, 2011); USA	36,282		50-79	Calcium and Vitamin D	47.3 – 53.9%	Post-menopausal women - Women's Health Initiative (WHI)
(Faulkner et al., 2006); USA	9,526	86-'88 89-'90	65+	Calcium and Vitamin D	42.8 – 44.9%	Study of Osteoporotic Fractures
(Saquib, von Muhlen, Garland, &	414	1997-2000	45-95	Calcium and Vitamin D	9.7 – 21.5%	Ranch Bernardo Study - Men Only

Barrett-Connor, 2006); USA						
(Papaioannou et al., 2008); CAN	2,187	1996-2002	50+	Calcium or Vitamin D	29.8%	Canadian Multicentre Osteoporosis Study (CaMOS) - Men Only
Studies Targeting B-Vitamins and Folic Acid						
(Garcia, Day, Zanibbi, & Zunzunegui, 2008); CAN	281	97-'04	avg 73 (±4.9)	B-Vitamins and Folic Acid	27 – 49%	Cohort of older adults with and without voluntary B-Vitamin supplementation
(Gougeon et al., 2016); CAN	1,368	2003-2005	67-84	B-Vitamins & Folic Acid	17.4%	Quebec Longitudinal Study (NuAge)
Studies Targeting Vitamin A						
(Lim, Harnack, Lazovich, & Folsom, 2004); USA	34,703	86-'97	55-69	Vitamin A	35.4%	Iowa Women's Health Study
(Promislow, Goodman-Gruen, Slymen, & Barrett-Connor, 2002); USA	958	1988-1992	55-92	Retinol	45.8%	Cohort of a middle- to upper-class Southern California Community (Rancho Bernardo)
Studies Targeting Multivitamin/minerals vs. Multiple Sources of Key Micronutrients						
(Nelson, Wengreen, Munger, & Corcoran, 2009); USA	3,634	1995	65+	MVM	42.7%	the Cache County Memory Study
(Sternberg, Chandran, & Sikka, 2003); USA	202	2000	avg 80	MVM; Ca; Vitamins A, B, C, E	4.9 – 64.7%	Convenience sample of patients at the University of Chicago primary care clinic
(Nahin et al., 2006); USA	3,072	2000-2002	75+	MVM; Ca; Vitamins A,	7.3 – 59.4%	Ginkgo Evaluation of Memory Study

				B, C, D, E; Mg; Zn		
(Arcury et al., 2006); USA	701	2002	65+	MVM; Ca; Vitamins A, B6, B12, C, E; Folic Acid; Cr; Mg; Se; Zn	0.4 – 34.3%	Evaluating Long-Term Diabetes Self-Management Among Elder Rural Adults Study
(Qato et al., 2016); USA[a]	2,351 2,206	05-'06 10-'11	62-85	MVM; Ca; Vitamins B, C, D, E; Folic Acid; Iron; Mg; K; Niacin; Zn	1.5 – 34.9%	NSHAP
(Mursu et al., 2011); USA[a]	38,772	1986	55-69	MVM; Vitamins A, B_6, B complex, C, D, E; β-carotene; Folic Acid; Ca; Cu; Iron; Mg; Se; Zn	0.59 – 44.9%	Iowa Women's Health Study

Abbreviations: avg, average; BMD, bone mineral density; Ca, calcium; CAM, complementary alternative medicine; Cr, chromium; Cu, copper; K, potassium; OTC, over the counter; Mg, magnesium; MVM, multivitamin/mineral; Se, selenium; Zn, zinc.

[a]Article also appears in Table 2.

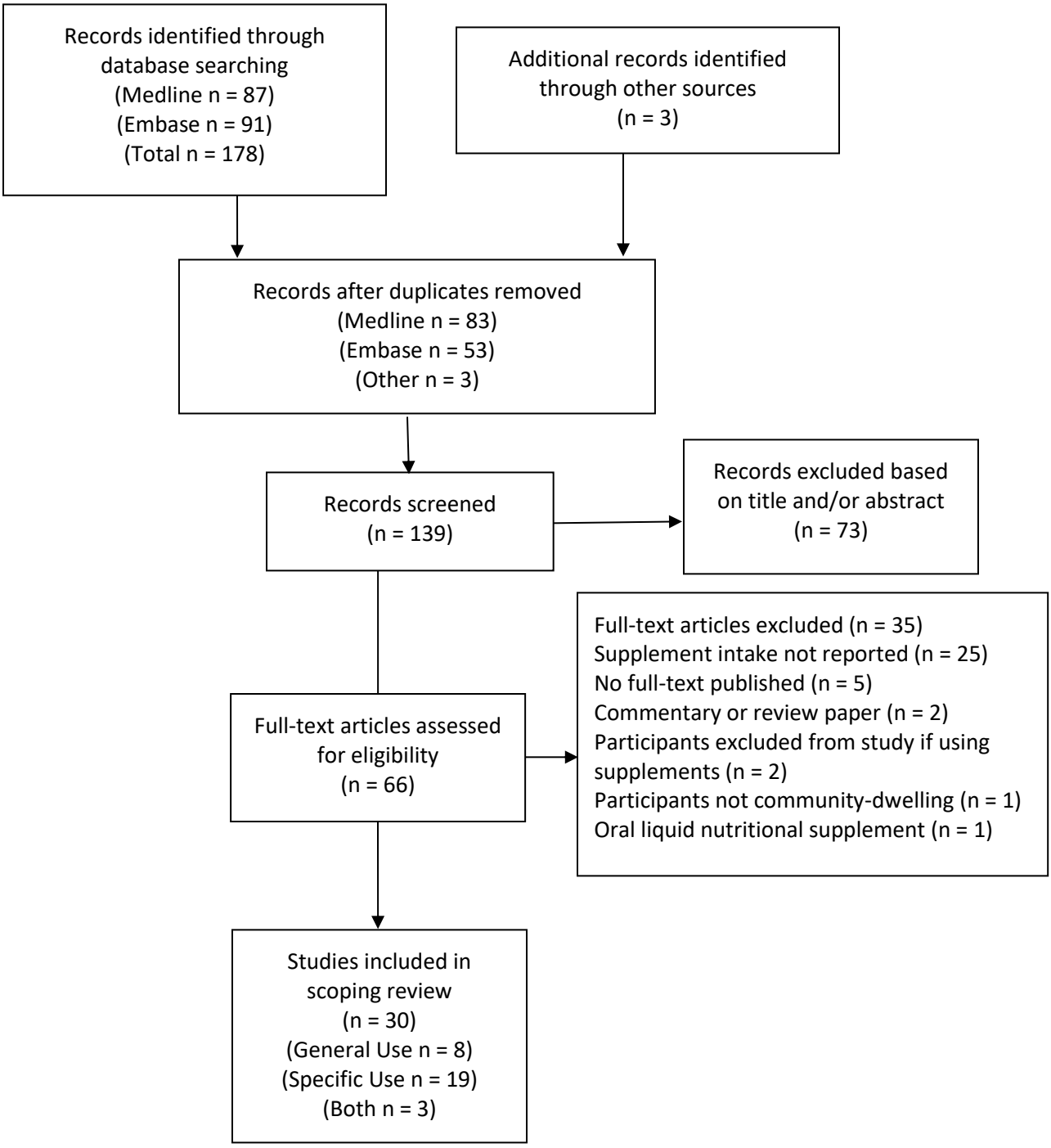

Figure 3.1: Scoping review flow chart of searches, inclusions, and exclusions (Moher, Liberati, Tetzlaff, Altman, & Group, 2009).

3.6 Results

Of the 180 articles originally identified, 30 were deemed relevant for this scoping review. Several of the selected articles reported data on the same cohort of individuals, as noted in Table 3.

3.6.1 General Use of Vitamin and Mineral Supplements

Eleven studies reported on the general use of vitamin and mineral supplements in community-dwelling adults living in Canada or the UnitedStates (Table 2). The majority of these studies used large cohorts of participants (n > 1000) (Bedford & Barr, 2005; Beydoun et al., 2013; Espino et al., 2000; Guo et al., 2009; Mursu et al., 2011; Qato et al., 2008, 2015, 2016) while three studies investigated smaller groups of participants (n < 1000) (Cheung et al., 2007; Raji et al., 2005; Weeden & Remig, 2010). Both Canada (Guo et al., 2009) and the United States (Beydoun et al., 2013; Qato et al., 2008, 2015, 2016) have nationally representative surveys that indicate general use of vitamin and mineral supplements among adults was 40.1% (Guo et al., 2009) and 62.6% (Beydoun et al., 2013) respectively.

Of the above-mentioned studies, eight investigated supplement use of older adults (>55 years of age) (Cheung et al., 2007; Espino et al., 2000; Mursu et al., 2011; Qato et al., 2008, 2015, 2016; Raji et al., 2005; Weeden & Remig, 2010) while only three investigated usage in adults starting at 19 years of age (Bedford & Barr, 2005; Beydoun et al., 2013; Guo et al., 2009). The studies that included a broader age range of participants had a narrow range of supplement users, 40.1% - 62.6% (Bedford & Barr, 2005; Beydoun et al., 2013; Guo et al., 2009), while studies investigating older adults reported a wide range, 6.9% - 85.5%, of supplement users (Cheung et al., 2007; Espino et al., 2000; Mursu et al., 2011; Qato et al., 2008, 2015, 2016; Raji et al., 2005; Weeden & Remig, 2010).

The study with the lowest reported use of supplements (6.9%) was conducted in the early 1990's on a group of elderly Hispanics in the United States (Espino et al., 2000). In contrast, a study done in 2007-2008 on a small group of congregate meal users reported supplement use among 85.5% of the participants (Weeden & Remig, 2010).

3.6.2 Specific Vitamin and Mineral Supplement Use

Ten of the 22 studies reporting on the use of one, or multiple, specific vitamin and mineral supplement(s) focused on the supplementary use of calcium and/or vitamin D (Bakhireva et al., 2004; Barake et al., 2010; Bolland et al., 2011; Cline & Worley, 2006; Dam, von Muhlen, & Barrett-Connor, 2009; Farley et al., 2004; Faulkner et al., 2006; Ginter et al., 2013; Papaioannou et al., 2008; Saquib et al., 2006). Three of these articles analyzed data from the same cohort, the Rancho Bernardo Study, but investigated different associations such as: serum 25-hydroxyvitamin D and bone mineral density; serum vitamin D and physical function; and modifiable predictors of bone loss (Bakhireva et al., 2004; Dam et al., 2009; Saquib et al., 2006). Another two studies used a common cohort of Minnesota residents, with one study looking at calcium and resorptive drug use (Farley et al., 2004) while the other study analyzed health belief patterns and osteoporosis self-care (Cline & Worley, 2006). Overall, supplemental calcium and/or vitamin D use ranged from 9.7% in a small cohort of men (Saquib et al., 2006) to 58.4% in a cohort of women (Cline & Worley, 2006) and all ten studies recruited participants at or over the age of 45 years (Bakhireva et al., 2004; Barake et al., 2010; Bolland et al., 2011; Cline & Worley, 2006; Dam et al., 2009; Farley et al., 2004; Faulkner et al., 2006; Ginter et al., 2013; Papaioannou et al., 2008; Saquib et al., 2006).

Two studies that focused on the combined use of B-vitamins and folic acid included Canadian participants over the age of 65 and looked at the effects of B-vitamin supplementation

on biomarkers (Garcia et al., 2008) and the use of supplemental B-vitamins and folic acid on the risk of depression (Gougeon et al., 2016). Results show that 17-49% of participants were supplementing their B-vitamin and folic acid intake (Garcia et al., 2008; Gougeon et al., 2016).

Supplemental vitamin A was the focus of two studies investigating the effect of excess vitamin A on bone health in older adults (>55 years) (Lim et al., 2004; Promislow et al., 2002). One study examined data from the Rancho Bernardo Heart and Chronic Disease study that used a population-based cohort in California that was comprised mainly of elderly, white, middle- and upper-class residents (Promislow et al., 2002). This data set was also analyzed in three other studies used in this review (Bakhireva et al., 2004; Dam et al., 2009; Saquib et al., 2006).

Of eight American studies investigating the use of multivitamins/minerals and multiple sources of key micronutrients in adults over 55 years of age, two studies analyzed data from the National Social Life, Health, and Aging Project (NSHAP), a nationally representative longitudinal study of community-dwelling American adults (Arcury et al., 2006; Mursu et al., 2011; Nahin et al., 2006; Qato et al., 2008, 2016; Sternberg et al., 2003). One looked at the prevalence and patterns of medication use as well as potential drug-drug interactions (Qato et al., 2008) while the other focused on the changes in prescription, over-the-counter, and dietary supplement usage over a period of five years (Qato et al., 2016). Three studies reported on general supplement use (Table 2) and specific usage (Mursu et al., 2011; Qato et al., 2008, 2016). Seven studies found that multivitamin/mineral use had the highest prevalence of use compared to all other supplement types, ranging from 28% - 64.7% (Qato et al., 2008; Sternberg et al., 2003). The study targeting post-menopausal women was the only study where the highest prevalence of supplement use was calcium, with 44.9% of participants reporting usage (Mursu et al., 2011). Note that this study was completed in the 80's while the remainder of the studies

collected data in the 2000's. With the exception of niacin (Qato et al., 2008), the lowest prevalence of vitamin and mineral supplement use was of minerals, ranging from 0.4% - 7.3% of participants reporting supplemental use of chromium and magnesium, respectively (Arcury et al., 2006; Nahin et al., 2006; Qato et al., 2008, 2016; Sternberg et al., 2003).

3.7 Discussion

The aim of this scoping review was to summarize the existing literature on vitamin and mineral supplement use in community-dwelling Canadian and American adults and to identify any gaps in the literature for this specific population. We compared the prevalence of general vitamin and mineral supplement use with that of specific vitamin and mineral supplements. The majority (n = 22) of the studies focused on specific vitamin and mineral supplements, 11 studies provided data on the use of any, non-specified, vitamin or mineral supplement. Prevalence of supplement use ranged widely in both instances with a higher prevalence (85%) reported for general supplement use, compared to 64% use of a specific supplement (Mursu et al., 2011; Sternberg et al., 2003). It is not surprising that studies reporting on the general use of vitamin and mineral supplements found a higher prevalence of use among study participants as these studies inquired about use of all dietary supplements while studies investigating specific use only reported the prevalence of use for the vitamin and mineral supplement(s) for which they were interested.

Although our search limit was set at all adults 18 years and older for all study participants, by selecting for "community-dwelling" all but three studies (the national surveys) focused on supplement use in older adults. The focus on older adults is justified as it is known that certain nutrient requirements increase or decrease with age (Otten et al., 2006; Ross et al., 2011). Men and women over the age of 50 require an increased amount of vitamin B6 and are

recommended to take a vitamin B12 supplement as their ability to absorb food-bound vitamin B12 decreases with age (Otten et al., 2006). Women over the age of 50 and men over the age of 70 are recommended to increase their calcium consumption to maintain adequate levels of intake (Ross et al., 2011). The suggested intake levels for vitamin D also increases for both sexes after the age of 70 (Ross et al., 2011). After the age of 50, iron requirements for women decrease (Otten et al., 2006). Research on older adults shows that the prevalence of nutrient inadequacy from diet alone is very high for vitamin D and calcium but that the prevalence of inadequacy is significantly reduced when a supplement is included daily (Shakur et al., 2012). Similar findings were also reported for vitamin B6 (Shakur et al., 2012). The risk of vitamin/mineral overconsumption is illustrated by a study that investigated supplement use and mortality in older women and found that high doses of supplemental iron was associated with an increased risk of mortality; whereas, supplemental calcium was inversely related to mortality (Mursu et al., 2011).

Trends in vitamin and mineral supplement use are apparent in Table 3. For example, all studies on calcium that were included in this scoping review were conducted from the 1980's to 2003 while concerns about vitamin A became apparent in the 1980's and 1990's, leading to publications on the implications of this vitamin. Although calcium was already known to have associations with bone health, vitamin A also became a relevant player in bone health, leading to an increase of studies relating to this nutrient. A critical review paper appraised a study on diet and bone health in Europe that found a negative relationship between excess retinol intake and bone mineral density and a positive relationship between excess retinol intake and the risk of hip fracture (Melhus et al., 1998; Whiting & Lemke, 1999).

Multivitamins/minerals were more commonly consumed when compared to individual nutrient supplements. Recent nationally representative data for the United States indicates and

increase in vitamin and mineral supplement use from 51.8% in 2005-2006 to 63.7% in 2010-2011 (Qato et al., 2016). Nationally representative survey data in Canada indicated that 40% of Canadian adults acknowledge use of one, or multiple, vitamin and mineral supplements in 2004 (Guo et al., 2009). The same Canadian survey was repeated in 2015 but results are yet to be disseminated. The second part of the Iowa Women's Study, conducted in 2004, also reported a high prevalence of supplement use, with 85.1% of the over 19,000 participants reporting dietary supplement use, a jump from 62.7% that was reported in 1986 (Mursu et al., 2011). A small Canadian study investigated the use of B-vitamins over time but it was unclear how the participants were assessed for B-vitamin use (Garcia et al., 2008).

From the 30 studies of community-dwelling adults identified as relevant for this scoping review, 23 of them were conducted in the United-States while seven were conducted in Canada. Of the seven articles reporting on Canadian data, two used the same data set, The Quebec Longitudinal Study, one article analyzed nationally representative data from the Canadian Community Health Survey, and the remainder investigated smaller cohorts of participants from different provinces. The American studies focused both on large surveys as well as specific groups of individuals such as the elderly (≥ 77 years) (Raji et al., 2005) or women (Mursu et al., 2011). Nationally representative surveys provide a population overview but studies on targeted cohorts provide an in-depth view that is not likely to be captured at a national level. For example, over 85% of a small cohort of American congregate meal users over the age of 80 were dietary supplement users (Weeden & Remig, 2010) while only 6.9% of participants in a study of elderly Hispanic Americans reported use (Espino et al., 2000). Overall, few Canadian studies investigated dietary supplement use of specific vitamins/minerals in small cohorts and no Canadian studies looked at overall vitamin and mineral supplement use in these types of groups.

The two Canadian studies that focused on adults starting at the age of 19 were a large provincial and a national survey (Bedford & Barr, 2005; Guo et al., 2009). Data from the national survey showed that older adults, 51-70 years, had higher supplement use (50.5%) compared to younger adults (35.5%), indicating greater prevalence of use in older adults (Guo et al., 2009). Unlike North America, dietary surveys in Europe indicate a much lower prevalence of vitamin and mineral supplement use, varying between 9.3-26% (Marques-Vidal et al., 2009; Rovira et al., 2013). This scoping review demonstrates that Canada lacks published studies on specified groups of community-dwelling adults.

3.8 Limitations

A limitation of this scoping review is that many of the research articles did not define "supplement use" in terms of frequency. Thus, our focus could only be on prevalence of use. The majority of the studies relied on self-reported data as opposed to reviewing supplement bottles and packaging as a part of the data collection; nonetheless intervention studies were not included as they would not illustrate voluntary use of supplements. Lastly, the extent to which participants were taking one, or more, vitamin and/or mineral supplement(s) was unclear as 'pill counts' were not typically reported. Thus, due to these limitations, health outcomes of vitamin and mineral supplement use could not be addressed.

3.9 Implications for Practice

This scoping review illustrates the need for further investigation into the risks and benefits of vitamin and mineral supplement use by community-dwelling adults. Supplement use is warranted in many situations while it can also pose risk if not taken appropriately. Health care professionals should inquire about their patient's use of vitamin and mineral supplements and

assist them in understanding appropriate use of supplements to decrease the risk of adverse effects.

3.10 Conclusion

A total of 30 Canadian and American original research articles on the general and specific use of vitamin and mineral supplements were analyzed for this scoping review. The majority of the research pertaining to general use of vitamin and mineral supplements was conducted in the United States and used large, nationally representative cohorts of participants. Interestingly, all research articles that focused on specific supplements investigated the effect that the use (or not) of these supplements had on another variable. Thus, none of the studies used in this scoping review simply looked at what type, the quantity, and in what combination people are consuming vitamin and mineral supplements. This information is important for identifying possibly adverse combinations or amounts of supplement use. Future research should aim to fill this identified gap in literature to provide a better understanding of the types of vitamin and mineral supplements being used by differing cohorts of individuals.

CHAPTER 4

METHODOLOGY

4.1 Study Purpose

The purpose of this research project was to assess vitamin and mineral supplement use in older adults with complex medication use by: identifying use and overuse of vitamin and mineral supplements; determining the extent that people were consuming supplemental nutrients from multiple sources; and investigating the potential for adverse drug-nutrient interactions stemming from presence or absence of supplement use.

4.2 Research Design

The research design for this project was a retrospective chart review of patients who had sought the services of the Medication Assessment Centre (MAC) at the University of Saskatchewan since its inception in January of 2014 up to January 19th, 2017. The primary outcome was to characterize the vitamin and mineral supplement use by MAC patients. Secondary outcomes included identifying potential drug-nutrient interactions that stemmed from supplement use.

The MAC opened in 2011 as a patient care clinic in the College of Pharmacy and Nutrition at the University of Saskatchewan. As a faculty-run patient care clinic it offers complex patients the opportunity, at no personal cost, to have their prescription drugs, over-the-counter (OTC) products, and dietary supplements assessed by a pharmacist, with assistance from

pharmacy students. The MAC accepts patients of all ages through self-referral or by referral of a health care professional (Jorgenson et al., 2016; University of Saskatchewan, n.d.).

4.3 Research Plan

This research proposal was approved by the student researcher's advisory committee and data extraction and analysis has been completed. The student researcher coordinated with the director of the MAC to gain access to the electronic chart database. A data extraction form was created by the student researcher (Appendix A). Each patient chart was assigned a non-identifying code that was linked to their chart number. Demographic data such as gender, age, and postal code was collected. Chronic diseases or health conditions that were noted in the chart were also extracted. Lastly, the product name and reported dosage and frequency of prescription medications, dietary supplements, and OTC products were extracted from each chart.

Statistical analysis of the data was performed using IBM SPSS Statistics software. Standard formulations from brands such as Centrum and Jamieson were used when specific brand names of supplements were not available in the chart, as shown in Table 4.1. For example, if a supplement was listed in the patient chart as "MVM" then the formulation for Centrum Silver was used to calculate the vitamin and mineral intake from this product. Centrum Silver was chosen as there are generic brands (ex. London Drugs) available that mimic the formulation of Centrum Silver. The total amount of each supplemental nutrient was summated and compared to the respective UL. The number of supplements providing a specific nutrient was also recorded (i.e. if a patient reported taking a vitamin D supplement and a multivitamin containing vitamin D). Possible relationships were analyzed between product and demographic data.

Table 4.1: Brand name formulations used for data when specific brand not available in chart

Information in Patient Chart	Brand Formulation used for Data
MVM	Centrum Select Essentials Adults 50+
50+ MV	Centrum Select Essentials Adults 50+
Women's MV	Centrum Women
B Complex	Jamieson B50 Complex
B50 Complex	Jamieson B 50 Complex
B100 Complex	Jamieson B100 Complex
Vitamin B 100mg	Jamieson B100 Complex
Ca/Mg	Jamieson Calcium Magnesium
Ca/Mg/Zn	Jamieson Calcium Magnesium Zinc
Ca/Mg/D3	Jamieson Calcium Magnesium + Vitamin D3

A list of potential nutrient-drug interactions was modified from four sources and can be found in section 2.4.2 of the literature review. This was not an exhaustive list but rather a list of interactions with a high likelihood of occurrence in the study population, derived as follows. The primary MAC pharmacist reviewed an extensive list of drug-nutrient interactions (Heidelbaugh, 2013; Nelms, Sucher, Lacey, & Roth, 2011; Office of Nutrition Policy and Promotion Health Products and Food Branch, 2006; Rogovik, Vohra, & Goldman, 2010; Ross, Taylor, Yaktine, & Del Valle, 2011) and noted the drugs that he never encountered, rarely encountered, and often encountered with MAC patients over the previous six years. The drugs that he often encountered were listed with possible interactions to common vitamin and minerals.

As discussed in section 2.4.2 of the literature review, drug-nutrient interactions are difficult to summate due to the multitude of possible combinations and factors that affect the interactions. Likely, this is a reason that much of the literature on drug-nutrient interactions is displayed in the form of case studies. For this study, the data extraction form (Appendix A) and the list of interactions (Table 2.8) were used to link potential interactions and highlight their

occurrences by means of case studies. The case studies were chosen based on the top four drug users in our data set as they were assumed to be the most likely to experience the effect of drugs on nutrient status.

4.4 Sample Selection

The inclusion criteria for this retrospective chart review were all MAC clients who were 50 years of age or older at the time of their initial assessment and had at least one drug or dietary supplement recorded in their chart. MAC client interactions with the pharmacist are often audio and video recorded for teaching purposes and all MAC clients are offered the opportunity to decline video and audio recording of their appointment(s). As a safeguard, any client who declined video and audio recording was assumed to have declined that their data be used for research purposes, and thus their chart information was not extracted as a part of data collection for this study. A total of 286 patient charts were reviewed.

4.5 Statistical Analysis

As seen in the Data Extraction Form (Appendix A), gender, age, postal code, reported chronic disease and health issues, prescribed drugs, dietary supplements, and OTCs were extracted from patient charts for those who were over the age of 50 at the time of their initial appointment. SPSS software was used to statistically analyze the data. Descriptive statistics such as prevalence, frequencies, and means were calculated. Associations such as Chi-Square tests for independence were also used to analyze relationships.

For this research project, dietary supplements were defined as any vitamin and/or mineral-containing supplement. Patients of the MAC were instructed to bring all medications, OTCs, and supplement bottles to their first appointment for the pharmacist to review and record

name, dosage, and frequency of each drug and/or supplement. Only oral prescription and OTC products were tabulated for the purpose of this study; thus, drugs and OTC products that were taken via injection, topical application, inhalation, etc. were not included as these formulations rarely involve vitamins and/or minerals. Pill count was defined as the total number of prescription medications, dietary supplements, and OTC drugs, with the acknowledgement that the patient may consume more than one tablet per day to meet their prescribed, recommended, or chosen dosage. 'Overuse' of vitamin and mineral supplements was determined by summating the total amount of each nutrient consumed and comparing the total intake to the respective UL. As discussed in the literature review, some nutrients do not have a set UL thus these nutrients were not considered when discussing 'overuse' as there was no comparative measure available. For the nutrients with a defined UL, a patient was considered to have 'overused' a supplement if their intake was equal to or greater than the defined UL. Since dietary intake was not assessed, it in important to include those who consumed supplemental nutrients at the UL because when food is taken into consideration, it is likely that they would surpass the ULs for nutrients where food contributes to nutrient intake levels. "Non-vitamin/mineral supplements" included dietary supplements that did not contain any vitamins or minerals.

4.6 Ethics Approval

This study was approved by the University of Saskatchewan Biomedical Research Ethics Board on July 20th, 2016 and re-approved on June 29th, 2017 (Bio 16-169). Formal patient consent was not required as this was a retrospective study and the researcher did not extract any identifiable information as a part of the data collection process.

CHAPTER 5

RESULTS

5.1 Demographic Data

A total of 286 patient charts were available for review but 48 charts were excluded due to age (< 50 y), 8 charts were excluded because the patient was never seen for their initial assessment at the MAC (and no medications were recorded in their chart), and 1 chart was excluded because there were no medications listed on file at the time of data extraction. Thus, 229 charts met all inclusion criteria. Subject age at the time of initial assessment ranged from 50 to 93 years, with a mean age of 68.9 (median: 69) years. Females represented 57.2% of the sample (n = 131). Health conditions, tabulated based on those reported by subjects and recorded in the medical chart, numbered from 1 to 16 per person, with an average of 4.8 (median: 5.0) reported health conditions per person, as seen in Table 5.1.

Table 5.1: Summary of Demographics and Product Usage

	Minimum	**Maximum**	**Mean**	**Median**
Age (y)	50	93	68.9	69
Reported Health Conditions	1	16	4.8	5
Prescription Drugs + OTC's	0	18	6.5	6
Vitamin and Mineral Supplements	0	19	2.4	2
NVM Supplements	0	23	0.9	0
Total Product Count	1	45	9.8	9

Prescription drugs and medications that can be bought over-the-counter (OTC) were tabulated as one category because it was often unclear in the chart whether the OTC product was prescribed by a health care professional or taken based on personal preference. Prescription drug and OTC use ranged up to 18 products per person, with an average product count of 6.5 (median: 6.0) per person. Pill count was not done but would be equal or greater than the product count.

In the MAC population, vitamin and mineral supplement use ranged from no use (0) to the use of 19 various products. The mean use of vitamin and mineral supplements was 2.4 (median: 2.0) products per person. The use of non-vitamin/mineral (NVM) supplement products was less, overall, with a mean usage of 0.9 (median: 0) products per person but the range was higher than that of the vitamin and mineral supplement usage, with one subject reporting use of 23 NVM supplement products.

Prescription drugs, OTC products, vitamin and mineral supplements, and NVM supplements were summated to give a total product count. All subjects had a product count of at least 1 and some ranged to as high as 45 products. The average product count was 9.8 products per person with a median of 9. Again, this does not encompass the total number of pills taken daily.

5.2 Use of Vitamin and Mineral Supplements

Data indicate that 76.9% (n = 176) of patients aged 50+ years reported using one or more vitamin and/or mineral supplement(s) daily (Table 5.2). Vitamin D was the supplement taken the most frequently, with 78% of supplement users reporting use. A multivitamin/mineral product was the next most reported supplement, with 54% of supplement users and 41% of patients reporting daily consumption. The third most reported supplement was vitamin C, with 29% of

supplement users reporting daily use. As seen in Table 5.3, vitamin and mineral supplement use was independent ($p > 0.05$) of age both when ages were grouped by decades or when looked at as subjects who were 50-69 years old (n = 118) and those 70+ years of age (n = 111). Based on the percentage of supplement users in each age group, there was a slight but not significant increase in supplement use as age increased. Similarly, vitamin and mineral supplement use was independent of sex ($p > 0.05$) with 77.5% (n = 76/98) of males and 76.3% of females (n = 100/131) reporting daily usage.

Table 5.2: Vitamin and/or mineral supplement (VMS) use by different population variables

		VMS Use	
	No. of Subjects	No. of Subjects	%
Overall	229	176	76.9
Age Group, years			
50-59	56	38	67.8
60-69	62	47	75.8
70-79	69	57	82.6
80-89	38	30	78.9
90+	4	4	100
Sex			
Male	98	76	77.5
Female	131	100	76.3
Self-Reported Health Conditions			
≤ 6	182	135	74.2
≥ 7	47	41	87.2
Medication/OTC Use			
≤ 7	146	108	74.0
≥ 8	83	68	81.9

Vitamin and mineral supplement use and the number of self-reported health conditions are also independent of one another ($p > 0.05$). Table 5.2 shows that the percentage of supplement users increases for those who reported seven or more health conditions (87.2%), when compared to those who reported 6 or less health conditions (74.2%). Similarly, reported use of vitamin and mineral supplements was independent of prescription drug and OTC use ($p > 0.05$) but Table 5.2 shows that the percentage of patients using vitamin and mineral supplements is greater in those who take eight or more prescription drugs and OTC products (81.9%) when compared to those who take seven or less (73.9%).

Table 5.3: Associations between supplement use and patient characteristics

Variable 1 (Y/N)	**Variable 2**	**P-Value**
VM Supplement Use	Age (by decades)	0.234
VM Supplement Use	Age (<70/70+)	0.074
VM Supplement Use	Sex (M/F)	0.829
VM Supplement Use	Health Conditions (<7/7+)	0.058
VM Supplement Use	Drug + OTC (<8/8+)	0.170
≥ 400 IU Vitamin D	Age (<70/70+)	0.010
≥ 400 IU Vitamin D	Sex (M/F)	0.226
≥ 400 IU Vitamin D	Nutrients from Multiple Sources (Y/N)	<0.001
Nutrients from Multiple Sources	Nutrient intake at or above UL (Y/N)	<0.001

5.2.1 Supplemental Vitamin D

Daily use of supplemental vitamin D (≥ 400 IU) was reported by 64.6% (n = 148) of patients. The percentage of subjects taking supplemental vitamin D at or above 400 IU per day increased with age, with 56.8% of subjects between the ages of 50 and 69 reporting daily use while 72.9% of those patients 70 years and older reported taking 400 IU or more of supplemental vitamin D daily (Table 5.4). Daily use of supplemental vitamin D (≥ 400 IU) was associated with

age (p 0.01 < 0.05) when comparing patients aged 50-69 years with those 70+ years of age. Females were more likely (67.9%; n = 89/131) to take supplemental vitamin D at or above the recommended daily dose (400 IU) compared to men (60.2%; n = 59/98). The association between supplemental vitamin D use of 400 IU/day or more and sex was not statistically significant (p > 0.05).

Table 5.4: Supplemental vitamin D use by population variables

			≥ 400 IU Daily Supplemental Vitamin D	
		No. of Subjects	No. of Subjects	%
Overall		229	148	64.6
Age				
	50-69	118	67	56.8
	70+	111	81	72.9
Sex				
	Male	98	59	60.2
	Female	131	89	67.9

5.3 Overuse of vitamin and mineral supplements

Data from this study indicate that 63 of the 229 patients (27.5%) exceeded the UL for at least one nutrient, from supplements alone. Data also indicate that 6.5% (n = 15) of patients in this study consumed supplemental nutrient(s) in amounts equal to the UL. Dietary intake data was not available for this study but it is highly probable that if dietary intake were considered, many of these patients would have exceeded the UL for nutrients where food intake contributes to the UL, suggesting that this was an underestimation of the risk. In total, 70 patients (30.6%) in this study consumed supplemental nutrients at or above the UL. Of reported supplement users (n = 176), 39.8% reported overuse of supplements. As seen in Table 5.5, since some patients

consumed more than one nutrient at or above the UL, the total number of patients that overused supplements is not a direct summation of those who consumed nutrients at the UL plus those who consumed nutrients above the UL.

Table 5.5: Overuse[*] of supplemental nutrients by reported supplement users (n = 176)

Nutrient	**At UL**	**Over UL**	**Total Overuse[*]**	**UL[†]**	**Average Intake at or over UL**
	N (%)	**N (%)**	**N (%)**	**mg/day**	**mg/day**
Niacin[^]	0 (0)	26 (14.7)	26 (14.7)	35	155
Magnesium[^]	1 (0.6)	22 (12.5)	23 (13.1)	350	586
Iron	0 (0)	14 (7.9)	14 (7.9)	45	135
Vitamin D	2 (1.1)	11 (6.2)	13 (7.4)	4000 IU/day	5223 IU/day
Folate[^]	3 (1.7)	9 (5.1)	12 (6.8)	1	2.5
Zinc	2 (1.1)	10 (5.7)	12 (6.8)	40	60
Vitamin B6	6 (3.4)	5 (2.8)	11 (6.2)	100	139
Vitamin C	1 (0.6)	6 (3.4)	7 (3.9)	2000	3070
Calcium	1 (0.6)	1 (0.6)	2 (1.1)	2000	2100
Manganese	0 (0)	1 (0.6)	1 (0.6)	11	30

[*]Overuse defined as consumption at and over UL
[^]UL only applies to synthetic form
[†](Otten, Pitzi Hellwig, & Meyers, 2006; Ross et al., 2011)

Data from this study indicate that niacin (also called vitamin B3) was taken in excess of the UL most frequently (26 times) in comparison to the other micronutrients. Of those who exceeded the UL for niacin, 84.6 % were taking a B Complex vitamin product. No patients reported supplemental intake of niacin equal to the UL of 35 mg/day. Supplemental magnesium was taken in excess of the UL by 22 patients and in an amount equal to the UL by one patient. Iron was taken in excess of the UL by 14 patients and no supplement users reported intake equal to the UL. Of the 148 patients who took a vitamin D supplement at or above the recommended amount for this age group (400 IU/day), only 11 patients (7.4%) took it in an amount above the

UL and 2 patients reported supplemental vitamin D intake of 4000 IU/day (UL). As seen in Table 5.5, other nutrients were also taken in amounts equal to or exceeding the UL, from supplements alone, include folate (12 patients), zinc (12 patients), vitamin B6 (11 patients), vitamin C (7 patients), calcium (2 patients), and manganese (1 patient). Nutrients with a defined UL that was not exceeded include: vitamin A, vitamin E, choline, copper, fluoride, iodine, molybdenum, nickel, phosphorus, selenium, vanadium, sodium, chloride, and boron.

The average vitamin and mineral supplement intake of reported supplement users who consumed nutrients at or above the UL is compared to the UL for each nutrient in Table 5.5. The average intake of supplemental niacin, among VMS users who reported an intake of supplemental niacin above the UL, was 155 mg/day which is 4.4 times the UL for this nutrient (35 mg/day). Of the 14 patients who consumed supplemental iron in excess of the UL (45 mg/day), the average intake was 135 mg/day which is three times the UL. Folate was consumed in amounts equal to the UL by 3 patients while 9 other patients consumed folate in amounts greater than the UL. The average folate intake of these patients was 2570 µg/day, more than 2.5 times the UL of 1000 µg/day. Table 5.5 shows the extent to which other nutrients were consumed in excess of the UL.

5.4 Vitamin and Mineral Supplement Use from Multiple Sources

Results from this study show that 76 of the 229 subjects (33.2%) or 76 of the 176 supplement users (43.2%) reported taking one or more supplemental nutrients from multiple sources. For example, taking a multivitamin containing niacin and taking a B complex that also contains niacin. Up to 16 supplemental nutrients were taken from more than one source by patients. On average, those who reported nutrient consumption from more than one source did so for 3.1 nutrients (median: 2.0).

Of the 76 subjects who took supplemental nutrients from multiple sources, 53.9% (n = 41) took supplemental nutrient(s) in amounts equal to or greater than the UL. As seen in Table 3.3, nutrient intake from multiple supplemental sources was significantly associated ($p < 0.001 < 0.05$) with intake of supplemental nutrients in amounts at or above the UL. Similarly, of the 76 patients who took supplemental nutrients from multiple sources, 86.8% (n = 66) reported taking supplemental vitamin D from 2 or more sources. Additionally, supplemental vitamin D intake at or above the recommended intake level of 400 IU per day was significantly associated ($p < 0.001 < 0.05$) with reported intake of nutrients from multiple sources.

5.5 Potential Drug-Nutrient Interactions

For the purpose of this study, drug-nutrient interactions were investigated in the context of how a drug affects nutrient status. Due to the retrospective nature of this study, it is impossible to know whether the patient exhibited symptoms of the potential drug-nutrient interactions. As discussed in the literature review, the multitude of factors affecting drug-nutrient interactions makes for an extensive list of potential interactions thus, drug-nutrient interactions were investigated through four case studies, as shown in Tables 5.7-5.10. The case charts selected for case study were chosen based on the top oral drug users in the population. A summary of likely drug-nutrient interactions from the 4 case studies is shown in Table 5.6.

Case 1 (Table 5.7) was a 53-year-old male who reported taking 18 drugs and no nutritional supplements. Of the 18 drugs being taken by this patient, 3 of the drugs had the potential to interact with nutrients. Firstly, the docusate sodium (a laxative) could potentially have led to malabsorption of vitamin E, vitamin K, calcium, potassium, and magnesium. The patient was also taking rabeprazole sodium (a PPI), with had the potential to cause malabsorption of vitamin C, vitamin B12, calcium, iron, and magnesium. The last drug that this patient was

taking that had the potential to interact with nutrient status was ranitidine (an antacid) that could cause malabsorption of chromium. Since this patient was not taking any supplemental nutrients, there was a greater potential for heightened risk of long term negative impacts on health status from chronic malabsorption due to the laxative, PPI, and antacid.

Table 5.6: Summary of potential drug-nutrient interactions from 4 case studies

Drug	**Nutrient**	**Interaction**
Bisphosphonate	Calcium	Calcium depletion
NSAID	Potassium	Risk for hyperkalemia
H2 Receptor Antagonist	Calcium Iron Chromium	Risk for nutrient malabsorption
Laxative	Vitamin E Vitamin K Calcium Potassium Magnesium	Risk for nutrient malabsorption
Loop Diuretic	Calcium Potassium Magnesium	Risk for nutrient depletion
Thiazide Diuretic	Potassium Magnesium	Risk for nutrient depletion
Thiazide Diuretic	Calcium	Stimulate calcium reabsorption
Anticonvulsant	Folate	Risk for nutrient depletion
Proton Pump Inhibitor (PPI)	Vitamin C Vitamin B12 Calcium Iron Magnesium	Risk for nutrient malabsorption

Table 5.7: Case #1 of potential drug-nutrient interactions

Sex	Oral drugs	Supp. Use	Drug	Nutrient	Interaction	Effect of Supplement Use
M	18	0	Docusate Na^+ (Laxative)	Vitamin E Vitamin K Calcium Potassium Magnesium	Malabsorption	No nutrient supplementation by patient.
			Rabeprazole Na^+ (PPI)	Vitamin C Vitamin B12 Calcium Iron Magnesium	Risk for nutrient malabsorption.	No nutrient supplementation by patient.
			Ranitidine (H2 Receptor Antagonist)	Chromium	Risk for malabsorption.	No nutrient supplementation by patient.

Case 2 (Table 5.8) was a 60-year-old female with 18 oral drugs listed in her chart and 10 dietary supplements (vitamin/mineral and non-vitamin/mineral). The daily use of esomeprazole (a proton pump inhibitor (PPI)) may have put the patient at risk for malabsorption of vitamin C, B12, calcium, iron, and magnesium. This patient was on 6 supplements containing vitamins and minerals, thus was receiving supplemental doses of the potentially affected nutrients on a daily basis. The patient was consuming 1090 mg/day of supplemental vitamin C; 1000 mcg/day of supplemental vitamin B12; 800 mg/day of supplemental calcium; 10 mg/day of supplemental iron, and 550 mg/day of supplemental magnesium. The daily dose of magnesium (550 mg) that this patient reported taking was well above the tolerable upper intake level (UL) for magnesium, which is 350 mg/day. This patient was also taking Celebrex (an NSAID) daily, which could

increase the risk for hyperkalemia. Additionally, this patient was consuming supplemental potassium daily, which could further add to the risk for hyperkalemia.

Table 5.8: Case #2 of potential drug-nutrient interactions

Sex	Oral drugs	Supp. Use	Drug	Nutrient	Interaction	Effect of Supplement Use
F	18	10	Esomeprazole (PPI)	Vitamin C Vitamin B12 Calcium Iron Magnesium	Risk for malabsorption.	All nutrients supplemented. Supplemental magnesium over UL (550mg).
			Celecoxib (NSAID)	Potassium	Risk for hyperkalemia	80mg/day supplemental potassium

The third case (Table 5.9) was a 64-year-old female who reported the use of 15 oral drugs and 2 nutritional supplements. This patient was taking 4 types of drugs (a total of 6 different drugs) that had the potential to interact with one or more nutrients. Firstly, the patient was taking cetirizine (an H2 receptor antagonist) that has the potential to interact with both calcium and iron, with the possibility of malabsorption of both nutrients. Neither of the nutritional supplements that this patient was consuming contained calcium or iron. The patient was also taking diuretics, which had the potential to interact with one or more nutrients. This patient was taking both furosemide and hydrochlorothiazide, each of which could affect the status of calcium, potassium, magnesium, and sodium. This patient was being supplemented with potassium daily but was not taking any supplements containing calcium, magnesium, or sodium. Anticonvulsants can impact the status of folate and this patient was taking gabapentin and lamotrigine. Neither of the nutritional supplements that this patient was taking contained folate,

likely placing the patient at increase risk of impaired folate status. Lastly, this patient was taking ranitidine, an antacid, which can affect the absorption of chromium. The patient was not taking any supplements that contained chromium. Overall, this patient was potentially at greater risk for malabsorption of calcium, iron, magnesium, sodium, folate, and chromium due to the types of medications that she was taking.

The fourth case analyzed (Table 5.10) was a 74-year-old woman who reported taking 14 oral drugs and 5 oral nutritional supplements. This patient was taking 6 types of drugs that had the potential to impact her nutrient status. In addition to pantoprazole (a PPI), celecoxib (an NSAID), docusate sodium (a laxative), sennosides/docusate (a laxative), gabapentin (an anticonvulsant), and hydrochlorothiazide (a diuretic), the patient was also consuming alendronate. Alendronate is a bisphosphonate that can cause calcium depletion. Of the nutritional supplements that this person reported taking, they were receiving 200 mg/day of supplemental calcium. Nutrients with the potential for interaction with her other medications included vitamin C, vitamin B12, vitamin E, vitamin K, iron, magnesium, potassium, and folate. This patient was not consuming supplemental vitamin B12, vitamin E, vitamin K, iron, potassium, folate, or sodium, likely putting her at increased risk of impaired nutrient status.

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Table 5.9: Case #3 of potential drug-nutrient interactions

Sex	Oral drugs	Supp. Use	Drug	Nutrient	Interaction	Effect of Supplement Use
F	15	2	Cetirizine (H2 receptor antagonist)	Calcium Iron	Risk for nutrient malabsorption.	No nutrient supplementation by patient
			Furosemide (Loop diuretic)	Calcium Potassium Magnesium Sodium	Risk for nutrient depletion	Potassium supplementation daily. No other nutrient supplementation by patient.
			Hydrochlorothiazide (Thiazide diuretic)	Calcium	Risk for hypercalcemia	No calcium supplementation by patient.
			Gabapentin (anticonvulsant) Lamotrigine (anticonvulsant)	Folate	Risk for folate depletion	No nutrient supplementation by patient.
			Ranitidine (Antacid)	Chromium	Risk for malabsorption.	No nutrient supplementation by patient.

Table 5.10: Case #4 of potential drug-nutrient interactions

Sex	Oral Drugs	Supp. Use	Drug	Nutrient	Interaction	Effect of Supplement Use
F	14	5	Pantoprazole (PPI)	Vitamin C Vitamin B12 Calcium Iron Magnesium	Risk for nutrient malabsorption.	No nutrient supplementation of vitamin B12 or iron by patient.
			Alendronate (bisphosphonate)	Calcium	Calcium depletion.	200mg/day supplemental calcium.
			Celecoxib (NSAID)	Potassium	Risk for hyperkalemia.	No potassium supplementation.
			Docusate Na (Laxative) Sennosides/ Docusate (laxative)	Vitamin E Vitamin K Calcium Potassium Magnesium	Malabsorption.	No supplemental vitamin E, K, potassium.
			Gabapentin (anticonvulsant)	Folate	Risk for folate depletion.	No nutrient supplementation by patient.
			Hydrochlorothiazide (Thiazide diuretic)	Calcium Potassium Magnesium Sodium	Risk for hypercalcemia and potassium, magnesium, sodium depletion.	Calcium and magnesium supplementation daily. No other nutrient supplementation by patient.

CHAPTER 6

DISCUSSION

6.1 Discussion

The overarching aim of this research project was to identify initial data needed to implement nutritional interventions to medically complex patients, particularly to ensure the safe usage of vitamin and mineral supplements at the primary care level. Such intervention could aid in improving the health status of older adults with chronic disease. In addition, this project aimed to highlight the positive attributes that a collaborative interdisciplinary approach could bring to a pharmacist-led medication assessment centre, such as the integration of a dietitian into the assessment and counselling of high-risk patients. Thus, the purpose of this study was to assess the personal vitamin and mineral supplement use of older adults with complex medication use. Specifically, the three objectives of this study were to: 1) identify use and overuse of vitamin and mineral supplements; 2) learn the extent to which people were consuming supplemental nutrients from multiple sources; 3) investigate the potential for adverse drug-nutrient interactions.

6.1.1 Demographics

For a patient chart to be included in this study and have their data extracted, the patient had to be 50 years of age or older at the time of their initial assessment and have at least one drug or supplement listed in their chart. Age was a component of the inclusion/exclusion criteria for this study because 50 is a pivotal age at which the recommended intake for many nutrients changes (Otten et al., 2006; Ross et al., 2011). Furthermore, an evaluation study (n = 173) of the

patient care clinic, the Medication Assessment Centre (MAC), that we used for the current study was completed in 2014/2015 and looked at demographic data that spanned all ages of patients (Jorgenson, Landry, & Lysak, 2016). Thus, the current study looked at a subpopulation, patients 50 years of age and older. The current study (n = 229) found that patient ages ranged from 50-93 years, with a mean and median age of 69 years. In 2014/2015, the average age of a patient attending the MAC was 64.8 years with ages ranging from 2-93 y (Jorgenson et al., 2016). As seen by comparing the size of the current study (n= 229) to that of the one completed in 2014/15 (n = 173), the patient group at the MAC has grown significantly.

The current study looked at many patient characteristics that were also investigated in the study done by Jorgenson et al. (2016) such as gender, number of medical diagnoses, and number of medications recorded at first appointment. The current study found that 57.2% (n = 131) patients were female similar to the study by Jorgenson et al. (2016) who found 60.1% were female for all ages. Thus, as the patient population at the MAC has grown, the distribution between males and females has remained relatively stable. When Jorgenson et al. (2016) looked at the number of medical diagnoses reported by patients, they found that diagnoses ranges from 1-16, with an average of 6.5 diagnoses per patient. Although the currently study only looked at older adults, we found that the reported number of health conditions in this group also ranged from 1-16, but had a lower average (4.8 conditions per patient). As for the number of medications recorded at the first appointment, the study by Jorgenson et al. (2016) included both drugs and supplements as the number of medications recorded at first appointment whereas the current study looked at drugs and supplements separately and then summed the groups to obtain a total product count per patient. We found that product use ranged from 1 - 45 products per patient, with an average of 9.8 and a median of 9 products per patient. The study by Jorgenson et

al. (2016) found a greater range (1-55) and average (13.8) for total product use, when compared to our study.

6.1.2 Vitamin and Mineral Supplement Use

This study found that supplement use was prominent (76.9%) in a group of medically-complex older adults, with 176 patients reporting use of at least one vitamin or mineral supplement (VMS) daily. VMS use did not vary significantly between sexes, with 77% of males (n = 76/98) and 76% of females (n = 100/131) reporting daily use. Although the current study did not find a significant difference in VMS use between sexes, a nationally representative Canadian study of supplement use in community-dwelling individuals found that VMS use was closely related to age and was significantly higher in females than males, both for overall use and for use in adults 50 years of age and older (Vatanparast, Adolphe, & Whiting, 2010).

Vitamin D was the most used supplement in the current study, with 64.6% of patients reporting the use of a vitamin D supplement daily. Of the reported supplement users in this study, 78.4% reported taking a vitamin D supplement daily. A multivitamin/mineral (MVM) product was the next most used supplement by this group, with 41.5% of the patients reporting daily use and 54% of supplement users reporting daily consumption. The third most used supplement in this study was vitamin C, with 22% of the patients and 29% of the supplement users reporting daily use. These results vary slightly from a study that looked at nationally-representative data on supplement use of Canadians and found that vitamin D was the most common supplement used in women over the age of 50 years but for men of the same age group, vitamin C was the most commonly consumed supplement (Shakur, Tarasuk, Corey, & O'Connor, 2012). For all age groups, vitamin C was the most commonly used supplement, followed by vitamin D and a multivitamin/mineral product (Shakur et al., 2012).

Health Canada recommends that all adults over the age of 50 take a 400 IU supplement of vitamin D daily to ensure vitamin D adequacy (Health Canada, 2012). Furthermore, Osteoporosis Canada suggests 800-2000 IU/day of supplemental vitamin D to maintain vitamin D adequacy in older adults (Hanley et al., 2010). Despite these recommendations, the current study found that only 64.6% of patients consumed a vitamin D supplement of 400 IU or more per day. In comparison to other studies, this finding is relatively high. For example, a Canadian study of long term care (LTC) residents found that only 35.4% of residence (n = 189) took a vitamin D supplement daily (Viveky et al., 2012). A nationally representative study also found relatively low prevalence of vitamin D supplement use. Results showed that 28% of males and 44% of females 51 years of age and older took supplemental vitamin D daily (Shakur, Tarasuk, Corey, & O'Connor, 2012). The current study found that women were more likely to take a daily vitamin D supplement, when compared to men, with 67.9% of females and 60.2% of males reporting vitamin D supplement use on a daily basis. Despite the apparent difference in supplemental vitamin D use, the association between sex and supplemental vitamin D was not significantly associated.

6.1.3 Overuse of Vitamin and Mineral Supplements

For the purpose of this study, overuse of vitamin and mineral supplementation was defined as intake at or above the Tolerable Upper Intake Level (UL). The current study investigated the overuse of vitamin and mineral supplements in a group of older adults with multiple morbidities and compared their intake to the UL to investigate overuse. Notably, the Dietary Reference Intakes, including the ULs are set for a healthy population and the effect of nutrient intake in excess of the UL in individuals with multiple morbidities is unknown. Presumably, medically-complex individuals may have a lower tolerance to the UL, based on

their individual medical conditions. Further research into ULs for groups with multiple morbidities is needed.

Overall, 70 participants (30.6%) in this study reported overuse of at least one supplemental nutrient. A nationally representative study that looked at diet and supplement intake found that Canadian adults did not exceed the UL from diet alone for any nutrient; but when supplements were considered, over 10% of some age and sex groups exceeded the UL for several nutrients (Shakur et al., 2012). The current study found that niacin (vitamin B3) was the most overused nutrient, with 26 patients (14.7% of supplement users) reporting daily intake of supplemental niacin that exceeded the UL. Of those who reported overuse of niacin supplements, the average intake was 155 mg/day, over four times the UL of 35 mg/day. Similarly, the study by Shakur et al. (2012) found that 50% of adult supplement users over the age of 50 years had a niacin intake above the UL. The UL for niacin only applies to synthetic forms of the nutrient and is based on the adverse effect of flushing (Otten, Pitzi Hellwig, & Meyers, 2006). In addition to flushing, side effects of large doses of niacin include vomiting, liver toxicity, blurred vision, and impaired glucose tolerance (Otten et al., 2006). It is likely that many patients in the current study were at greater risk for adverse effects from overuse, secondary to their medical complexity. For example, individuals suffering from liver dysfunction, diabetes, peptic ulcers, gout, cardiac arrhythmias, or inflammatory bowel disease are at an increased risk of observing adverse effects from niacin at or above the UL (Otten et al., 2006).

Magnesium was the second most overused nutrient in this study. Only pharmacological agents contribute to the UL for magnesium, meaning that intake from food is not a factor of consideration. The UL of 350 mg/day of magnesium was set based on several studies showing diarrhea when high doses of non-food sources of magnesium were consumed (Otten, Pitzi

Hellwig, & Meyers, 2006). In the current study, 23 patients consumed magnesium supplements at or over the UL of 350 mg/day, with an average intake of 586 mg of supplemental magnesium per day. When taken in very high doses, magnesium can cause metabolic alkalosis, hypokalemia, or a paralytic ileus (Otten et al., 2006). It is important to note that older adults are more likely to experience decreased magnesium absorption through the intestine and increased urinary magnesium excretion while individuals with impaired renal function are at a greater risk of experiencing magnesium toxicity from pharmacological sources (Otten et al., 2006). Although high doses of magnesium may prove to be beneficial for certain medical conditions, the age of patients in the current study suggests that they are at an increased risk for experiencing adverse side effects from their high doses of magnesium. Supplemental magnesium intake for this age group should be overseen by a health care professional to decrease the potential from adverse side effects, especially in patients who are taking acute doses of magnesium that exceed the UL.

Following niacin and magnesium, iron supplements were next most likely taken in doses that exceeded the UL by 14 patients (6.1%) in the current study. Unlike niacin and magnesium, dietary intake of iron contributes to the UL thus if dietary intake was considered in this study there would likely be higher intakes of total iron. The average intake of supplemental iron from the patients that exceeded the UL was 135 mg/day, substantially greater than the UL of 45 mg/day. The UL for iron is based on gastrointestinal distress but some populations such as people with hemochromatosis, chronic alcoholism, or other liver disorders may not be protected by this UL (Otten et al., 2006). Individuals who follow a vegetarian diet may find it a challenge to consume adequate amounts of iron from their diet alone because the bioavailability of plant-based sources of iron is approximately 10% (Otten et al., 2006). Data on dietary patterns or intake was not available in this study thus we cannot comment on the association between a

vegetarian diet and increased prevalence of iron supplement use. Data from a nationally-representative study indicate that the use of supplements greatly increased the likelihood of exceeding the UL for many nutrients, including iron (Shakur, Tarasuk, Corey, & O'Connor, 2012). Special recommendations exist for iron supplementation in men and postmenopausal women, suggesting that iron supplementation should be avoided in these groups because the relationship between excessive intake and heart disease and cancer is unclear (Otten et al., 2006). Based on the age of our study population, the women in our study were more likely to be postmenopausal. Of those who exceeded the UL for iron in this study, 7 were men and 7 were women who ranged from 54-86 years of age.

In Canada, vitamin D supplementation of 400 IU/day is recommended for all adults over the age of 50 years (Health Canada, 2012). Vitamin D supplements were overused by 13 patients (5.7%) in this study. Of the 13 patients, two consumed 4000 IU of vitamin D daily, which is equivalent to the UL. The average vitamin D intake from supplements alone, for those who exceeded the UL, was 5223 UL/day. One patient consumed 8000 IU daily, a dose that is double that of the UL. The UL for vitamin D is based on hypercalcemia, which is an indicator of vitamin D intoxication (Ross, Taylor, Yaktine, & Del Valle, 2011). Unfortunately, similar to the other nutrients, there is uncertainty surrounding the long-term effects of vitamin D consumption at or above the UL.

Calcium is also a nutrient of concern for older adults. The recommended intake of calcium increases from 1000mg/day to 1200mg/day after the age of 70 years for males while this increase happens after the age of 50 for females (Ross, Taylor, Yaktine, & Del Valle, 2011). Based on these recommendations, older adults may be more inclined to consume a calcium supplement, potentially leading to overuse. In the current study, calcium supplement use was

common (21% of supplement users) but was only overused by two female patients in the study. Data from a nationally representative Canadian survey indicate that 15% of female supplement users who were over the age of 50 years exceeded the UL for calcium, from a combined intake of diet and supplements (Shakur, Tarasuk, Corey, & O'Connor, 2012). The UL for calcium is based on the following indicators: hypercalcemia, hypercalciuria, vascular and soft tissue calcification, renal stone development, prostate cancer, interactions with iron and zinc, and constipation; with kidney stone formation being the key marker for older adults (Ross et al., 2011). It is difficult to exceed the UL and experience the previously mentioned adverse effects from dietary calcium intake alone (Ross et al., 2011). People with multiple morbidities should be aware that renal failure or the use of thiazide diuretics put them at an increased risk of experiencing adverse effects from calcium (Otten, Pitzi Hellwig, & Meyers, 2006).

A total of 12 patients (5.2%) reported taking daily folate supplements at or above the UL of 1 mg/day. The average folate intake for these patients was 2.57 mg/day, more than double the UL for this age group. Folate from non-fortified food sources does not contribute to the UL, which was set based on the exacerbation of neuropathy in vitamin B12-deficient individuals (Otten et al., 2006). Essentially, excessive folate intake can mask a vitamin B12 deficiency, which if left untreated can lead to neurological damage (Otten et al., 2006). A study of nationally-representative Canadian survey data indicate that 3.3-4.2% of men and women over the age 50 years exceed the UL for folate when the use of dietary supplements was considered (Shakur, Garriguet, Corey, & O'Connor, 2010). The same study looked at dietary intake and concluded that there was minimal risk of exceeding the UL for folate, from fortified dietary sources alone (Shakur et al., 2010).

For men and women over the age of 50 years, the UL for zinc is 40 mg/day (Otten et al., 2006). Both dietary and supplemental sources of zinc contribute to the UL, which is based on a zinc-induced decrease in copper absorption (Otten et al., 2006). A total of 12 patients (5.2%) took zinc supplements in daily doses equal to or greater than the UL, with an average intake of 60 mg/day. If dietary intake was a component of this study, it is likely that we would have seen a greater proportion of patients exceed the UL for zinc. A nationally representative study on Canadian community-dwelling adults found that 14% of adults over the age of 50 years exceeded the UL for zinc (Shakur, Tarasuk, Corey, & O'Connor, 2012). Although both dietary and supplemental intakes of zinc contribute to the UL, chronic intake of supplemental zinc can cause gastrointestinal distress, headaches, impaired immune function, and changes in cholesterol levels (Otten et al., 2006).

The UL for vitamin B6 is 100 mg/day, based on the critical adverse effect of sensory neuropathy (Otten et al., 2006). In the current study, vitamin B6 is the only nutrient that was consumed in amounts equal to the UL more frequently than in amounts exceeding the UL. A total of 11 patients (4.8%) consumed supplemental B6 at or in excess of the UL, with 6 patients reporting intake of 100 mg/day. Dietary vitamin B6 intake contributes the UL thus it is likely that the majority of these patients are actually exceeding the UL for vitamin B6. The largest dose of supplemental vitamin B6 in this group was 300 mg/day, which is well below the dose (2000 mg/day chronic use) that has been shown to cause sensory neuropathy and skin lesions (Otten et al., 2006). Interestingly, 81.8% (n = 9/11) of patients who took supplemental vitamin B6 at or in excess of the UL reported use of a B complex supplement. A study of nationally-representative Canadian survey data found that less than 5% of adults over the age of 50 years had a vitamin B6 intake that exceeded the UL when both dietary and supplement intake was considered (Shakur et

al., 2012). Despite the low prevalence of vitamin B6 overuse, the same study found that 26% of males and 31% of females over the age of 50 reported taking a vitamin B6-containing supplement on a daily basis (Shakur et al., 2012).

Despite being the third most consumed supplement of patients in this study, vitamin C was only taken in amounts equal to or greater than the UL by 3% of patients. The UL for vitamin C is 2000 mg/day, a value that is set based on osmotic diarrhea and gastrointestinal distress (Otten et al., 2006). The average intake of supplemental vitamin C for those patients who reported excess use was 3070 mg/day, approximately one and a half times the UL for this nutrient. One patient in the study reported a daily supplemental vitamin C intake of 5250 mg/day. Adverse effects such as osmotic diarrhea and gastrointestinal distress have been documented with intakes greater than 3000 mg/day (Otten et al., 2006). The study by Shakur et al. (2012) had similar findings to our study, with high use (32% females; 38% males) of vitamin C supplements but low prevalence (<5%) of exceeding the UL for vitamin C. Lastly, one patient in the study exceeded the UL for manganese, reporting a daily intake of 30 mg/day. The UL for manganese is 11 mg/day, based on the critical outcome of neurotoxicity secondary to elevated blood manganese (Otten et al., 2006).

6.1.4 Vitamin and Mineral Supplement Use from Multiple Sources

Patients in this study who reported daily use of supplements were likely to obtain their nutrient intake from two or more supplement products. Of the supplement users in this study, 43.2% of them reported nutrient intake from more than one supplement. Overall, 33.2% of patients in this study consumed nutrients from two or more supplement sources. For example, a patient who took a multivitamin, vitamin D, and a magnesium supplement would have had intake of both vitamin D and magnesium from two sources as both nutrients are found in the

multivitamin product. An American study looked at data from 3469 adults over the age of 60 years and found that 69% reported taking two or more dietary supplements daily (Gahche, Bailey, Potischman, & Dwyer, 2017). Furthermore, this study found that older adults who reported the use of three or more daily prescription drugs were more likely to take a dietary supplement (Gahche et al., 2017).

Of the 76 patients who reported nutrient consumption from more than one product, 86.8% were consuming supplemental vitamin D from two or more sources. Furthermore, this group of supplement users consumed an average of 3.1 different nutrients from multiple supplement products. In this study, the vitamin D intake of 400 IU/day or more was significantly associated with nutrient intake from multiple sources ($p < 0.001$). Additionally, reporting uptake of nutrients from more than one supplement product was significantly associated with supplemental nutrient intake at or in excess of the UL ($p < 0.001$). Consuming supplemental nutrients from more than one source raises concerns as it is more likely for the patient to exceed the UL for a nutrient, as found in the current study and elsewhere (Viveky et al., 2012). Dietary intake should be taken into consideration when completing medication assessments for complex patients, especially in those who are reporting the use of multiple supplements, in order to mitigate the risks of supplement consumption in conjunction with medication use.

6.1.5 Potential Drug-Nutrient Interactions

Drug-nutrient interactions are a concern for health care providers, especially when working with medically-complex patients such as those in the current study. Additionally, the multitude of factors that affect the likelihood of a drug-nutrient interaction occurring make it difficult for practitioners to mitigate all risks associated. A recent American study on supplement and drug use in 3469 older adults (over 60 years of age) concluded high (29%) use of dietary

supplements and concurrent use with prescription drugs (Gahche, Bailey, Potischman, & Dwyer, 2017). Furthermore, a recent review found that the concurrent use of prescription drugs and dietary supplements is becoming increasingly common; thus there is growing risk of adverse effects from such interactions (Harris, Morrow, Titgemeier, & Goldberg, 2017; Qato et al., 2008; Qato, Wilder, Schumm, Gillet, & Alexander, 2016). As the uptake of prescription drugs (average 6.5/patient) and supplements (average 2.4/patient) was high in this study population, the potential for drug-nutrient interactions was investigated through four case studies. These case studies were chosen based on the top drug users in this study.

The first case study investigated the potential for drug-nutrient interactions in a 53-year-old male who reported the use of 18 drugs and no nutritional supplements, as seen in Table 5.7. This patient was taking three different drugs that had the potential to cause nutrient depletion including a laxative, proton pump inhibitor (PPI), and an H2 receptor antagonist. Overall, these three drugs had the potential to cause depletion of nine nutrients. Both the laxative and the proton pump inhibitor could cause calcium depletion (Heidelbaugh, 2013; Nelms, Sucher, Lacey, & Roth, 2011). As this patient was not consuming any supplemental nutrients, they were at greater risk of experiencing nutrient depletion from the drugs that they consume. The Dietary Reference Intakes (DRIs) are set for healthy populations and do not account for nutrient depletion cause by drugs (Otten, Pitzi Hellwig, & Meyers, 2006). Thus, this patient was potentially at risk for nutrient depletion, especially calcium. Iron, vitamin B12, calcium, and magnesium should all be monitored if PPI use is chronic as PPIs inhibit gastric acid secretion, decreasing the absorption of these nutrients (Heidelbaugh, 2013). Unfortunately, the clinical significance of PPI-induced nutrient depletion remains unclear in the literature (Heidelbaugh,

2013). Overall, risk of nutrient depletion for this patient could be mitigated through low-dose nutrient supplementation.

The second case study, shown in Table 5.8, was a 60-year-old female who also reported the use of 18 drugs, but took 10 nutritional supplements as well. Of the 18 drugs, one had the potential to deplete her nutrient status, while another could cause high potassium (hyperkalemia). As discussed in the first case, the use of a PPI has the potential to cause depletion of several nutrients including vitamin C, vitamin B12, calcium, iron, and magnesium. In this case, the patient was taking all potentially affected nutrients in supplemental form. This patient was taking 550 mg/day of supplemental magnesium, a dose much greater than the UL, which may be justified by her use of a PPI. The non-steroidal anti-inflammatory drug (NSAID) that this patient was taking could potentially cause hyperkalemia. In addition to this risk, the patient was consuming additional potassium in her supplements, which could exacerbate this issue. Overall, this patient was potentially at risk for nutrient depletion of vitamins C and B12, calcium, iron, and magnesium secondary to her PPI use. She likely mitigated the potential for adverse nutrient depletion by consuming supplemental forms of the affected nutrients.

The third case study illustrated the concomitant drug and supplement use of a 64-year-old female, as shown in Table 5.9. She reported the use of 15 drugs and 2 supplements. Of the drugs that she reported using, five had the potential to cause nutrient depletion while one had the potential to cause hypercalcemia. Two of the drugs that this patient was consuming had the potential to cause calcium depletion. The H2 receptor antagonist and the loop diuretic that this patient took could cause nutrient depletion of calcium, iron, potassium, magnesium, and sodium (Nelms, Sucher, Lacey, & Roth, 2011). Of these nutrients, only potassium was being supplemented daily. Although this patient was not consuming any supplemental calcium, she

was on a thiazide diuretic which may cause excess calcium retention. It is possible that the use of a thiazide diuretic could decrease the impact of the potential drug-induced calcium depletion that was previously mentioned. Of note, this patient was on two anticonvulsant drugs which have the potential to cause folate depletion. Folate depletion from anticonvulsant drugs can be corrected through folate supplementation (Linnebank et al., 2011). Overall, this patient's supplement use could be modified to aid in mitigating potential drug-related nutrient depletion.

The last case analyzed was of a 74-year-old female who reported taking 14 drugs and 4 supplements daily. Seven of the drugs that she used had the potential to cause impair her nutrient status. As already discussed, the use of a PPI, NSAID, and anticonvulsant, can cause nutrient depletion. In total, this patient was taking four drugs, a PPI, bisphosphonate, and two laxatives, that could cause calcium depletion (Heidelbaugh, 2013; Nelms et al., 2011; Pronsky & Crowe, 2012). Although she reported supplementing her dietary calcium intake with 200 mg of supplemental calcium daily, she was also on a thiazide diuretic which can potentially lead to hypercalcemia. It is possible that between her calcium supplement and the use of a thiazide diuretic, the risk of calcium depletion from the four other drugs was mitigated. Lastly, this patient was on a PPI, potentially placing her at greater risk for iron and vitamin B12 depletion (Heidelbaugh, 2013). As vitamin B12 stores take several years to deplete, her vitamin B12 status should be monitored if her use of a PPI is chronic. Overall, this case study along with #2 and #3 highlight that despite the use of supplemental nutrients, if they are not systematically chosen then they may not aid in mitigating the potential risks associated with drug-induced nutrient depletions.

Overall, dietary Reference Values such as RDAs and ULs do not account for nutrient impairment (depletion or retention) that can be caused by drugs. Thus, individuals who are

prescribed drugs that have the potential to have impaired nutrient status should be counselled on the appropriate use of nutritional supplements. Furthermore, as the literature does not focus on the effect of drugs on nutrient status, this area requires further research (Péter et al., 2017). The above-mentioned case studies illustrate the need for further work in the area of drug-nutrient interactions that affect the nutrient status of patients. The development of a screening tool or checklist for healthcare providers would greatly aid in identifying and mitigating the risks associated with drug-induced altered nutrient status. Additionally, these cases highlight the need for interdisciplinary collaboration between healthcare practitioners, especially for medically-complex patients.

6.2 Limitations

A limitation of the current study was that the data on drugs, supplements, and health conditions was self-reported. Although patients were asked to bring in the bottles for the drugs and supplements that they used, their actual usage was self-reported. A second limitation of this study was that many supplements were recorded in the medical chart without a brand name, thus standard formulations were used to collect data on supplemental nutrient intake. It is likely that this limitation had minimal impact on the study outcomes as the formulations for most vitamins and minerals are very similar. Lastly, no dietary intake or dietary assessment data were available, and as this study was retrospective in nature, information on diet could not be obtained. Thus, the study was only able to look at nutrient intake from supplements. As previously discussed, many ULs for nutrients consider dietary intake and it is likely that if dietary intake were to be factored in then more patients would have exceeded the UL. Further, for the drug-nutrient interactions where nutrient depletion or malabsorption was the main risk factor, this study was unable to comment on the impact of dietary intake on the potential interactions. Nonetheless, the

importance of monitoring supplement intake was highlighted through the high prevalence of use and frequency of consumption over the UL for several nutrients.

6.3 Conclusion

A total of 229 patient charts were reviewed for this study, and we found that 76.9% of adults over the age of 50 reported consuming a vitamin or mineral supplement daily. Of these patients over the age of 50 years, only 64.6% reported taking a vitamin D supplement daily. Overuse of supplements was observed in 70 patients (30.6%) and niacin (vitamin B3) was taken in excess the most frequently (by 26 patients). Additionally, 43.2% of patients who reported daily supplement use were consuming the same nutrient(s) from more than one supplement. These factors, in combination with the potential for drug-nutrient interactions in this population, are cause for concern and suggest that an interdisciplinary approach to care would benefit this medically-complex group of patients. The addition of dietitian services to complex medication assessments would aid patients in achieving maximal benefit and minimal adverse effects from their vitamin and mineral supplement use.

6.4 Future Research

This study sought to identify data needed to investigate the potential for adverse drug-nutrient interactions and was a hypothesis-generating study with the aim of identifying a possible prospective study. Future research should consider a prospective study of vitamin and mineral supplement use in a medically-complex group that also gathers dietary intake data. Such study would provide greater insight into drug-nutrient interactions and the effect that dietary intake can have in aiding or worsening the nutritional-impact of the interaction. Further, such a study could

collect data showing whether or not the patient actually experienced the drug-nutrient interaction.

6.5 Implications for Practice

This study highlights the importance of an interdisciplinary team approach to complex medication assessments. The case studies presented in this study highlight the potential interactions that could have been identified by health care professionals. The addition of a Registered Dietitian to a patient care clinic such as the Medication Assessment Centre would benefit patient care as they bring specialized knowledge in dietary intake and the role of supplements in individualized patient care. Furthermore, the data from this study can aid in the development of resources that would be aimed at maximizing the benefits of vitamin and mineral supplements while mitigating the potential effects related to overuse of supplements or drug-nutrient interactions.

CHAPTER 7

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APPENDIX A

Data Extraction Form

Participant Code: _____ Male / Female Age: _____ Postal Code: _____

Chronic Diseases/Health Conditions:

- o Cardiovascular Disease
- o Hypertension
- o Osteoporosis
- o Diabetes
- o Obesity
- o Cancer (specify: _____)
- o Other (specify: _____)

Pill Count:

Prescription Medications	Dietary Supplements	Over-the-Counter
1. _____	1. _____	1. _____
2. _____	2. _____	2. _____
3. _____	3. _____	3. _____
4. _____	4. _____	4. _____
5. _____	5. _____	5. _____
6. _____	6. _____	6. _____
7. _____	7. _____	7. _____
8. _____	8. _____	8. _____
9. _____	9. _____	9. _____
10. _____	10. _____	10. _____
11. _____	11. _____	11. _____
12. _____	12. _____	12. _____
13. _____	13. _____	13. _____
14. _____	14. _____	14. _____
15. _____	15. _____	15. _____
16. _____	16. _____	16. _____
17. _____	17. _____	17. _____
18. _____	18. _____	18. _____
19. _____	19. _____	19. _____
20._____	20. _____	20. _____

Notes:

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