The Lifetime Prevention Schedule

Establishing Priorities among Effective Clinical Prevention Services in British Columbia

Summary and Technical Report
March 2017 Update

Screening for hearing loss in newborns, screening for cardiovascular disease risk in adults, routine aspirin use and folic acid supplementation

BRITISH COLUMBIA

Update completed by H. Krueger & Associates Inc.

Acknowledgments

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Establishing Priorities among Effective Clinical Prevention Services in British Columbia: *2017 Update*

Executive Summary

The report, *A Lifetime of Prevention*, was published by the Clinical Prevention Policy Review Committee (CPPRC) in December of 2009.[1] A key goal of the CPPRC was to determine which clinical prevention services are worth doing in British Columbia (BC), culminating in a proposed Lifetime Prevention Schedule (LPS). Clinical prevention services were included on the LPS if they were considered to be effective, had a significant impact on population health and were cost-effective.

Clinical prevention services (CPS) are defined as:

> *Manoeuvres pertaining to primary and early secondary prevention (i.e., immunization, screening, counselling and preventive medication) offered to the general population (asymptomatic) based on age, sex, and risk factors for disease, and delivered on a one-provider-to-one-client basis, with two qualifications:*
>
> > *(i) the provider could work as a member of a care team, or as part of a system tasked with providing, for instance, a screening service; and*
> >
> > *(ii) the client could belong to a small group (e.g., a family, a group of smokers) that is jointly benefiting from the service.*

This definition does not refer to the type of provider or the type of funding. This allows for the evaluation of the appropriate implementation of the service as a separate program planning matter.

In 2013/14, a Lifetime Prevention Schedule Expert Advisory Committee was formed by the Ministry of Health and tasked with updating and potentially expanding the number of clinical prevention services included on the LPS. That process involved calculating the clinically preventable burden (CPB) and cost-effectiveness (CE) associated with the clinical prevention service. CPB is defined as "the total quality-adjusted life years (QALYs) that could be gained if the clinical preventive service were delivered at recommended intervals to a BC birth cohort of 40,000 individuals over the years of life that a service is recommended." CE is defined as "the average net cost per QALY gained in typical practice by offering the clinical preventive service at recommended intervals to a BC birth cohort over the recommended age range."

The updated list reviewed in 2013/14 included the 10 services on the original 2009 LPS together with 9 additional services (highlighted in *italics* below) to be considered for inclusion on the updated LPS:

[1] Clinical Prevention Policy Review Committee. *A Lifetime of Prevention: A Report of the Clinical Prevention Policy Review Committee*. 2009. Available at http://www.health.gov.bc.ca/library/publications/year/2009/CPPR_Lifetime_of_Prevention_Report.pdf. Accessed July 2017.

Screening for Asymptomatic Disease or Risk Factors – Children/Youth

- Newborn screening for hearing
- Vision (amblyopia) screening

Behavioural Counseling Interventions – Children/Youth

- *Preventing tobacco use*

Preventive Medication – Children/Youth

- Fluoride varnish and sealants to prevent dental caries

Screening for Asymptomatic Disease or Risk Factors – Adults

- Breast cancer screening - women 50-74
- Cervical cancer screening - women 25-69
- Colorectal cancer screening - adults 50-74
- Hypertension screening and treatment - adults 18+
- Cholesterol screening and treatment - men 35+, women 45+
- *Screening for hepatitis C virus - adults born between 1945 and 1965*

Routine Offer of Screening for STIs in Sexually Active Young Adults

- *Screening for human immunodeficiency virus (HIV) – adolescents/adults 15-65*
- *Screening for gonorrhea - females 15-29*
- *Screening for chlamydia - females 15-29*
- *Screening for syphilis*

Behavioural Counseling Interventions – Adults

- Smoking cessation advice and help to quit
- *Alcohol screening and brief counseling*
- *Prevention of fetal alcohol spectrum disorder (FASD)*

Preventive Medication – Adults

- Discuss daily aspirin use - men 45-79, women 55-79
- *Preventing falls in community–dwelling elderly - adults 65+*

In 2015, the Lifetime Prevention Schedule Expert Advisory Committee requested an assessment of the estimated CPB and CE associated with the following four additional clinical prevention services:

Behavioural Counseling Interventions – Children/Youth

- Promotion of breastfeeding

Screening for Asymptomatic Disease or Risk Factors - Adults

- Screening for type 2 diabetes mellitus

Behavioural Counseling Interventions – Adults

- Prevention of sexually transmitted infections
- Screening for and management of obesity

In 2016, the Lifetime Prevention Services Expert Oversight Committee requested an assessment of the estimated CPB and CE associated with the following five additional clinical prevention services:

Behavioural Counseling Interventions – Children/Youth

- Screening for and management of obesity in children/youth ages 2-17

Screening for Asymptomatic Disease or Risk Factors - Adults

- Screening for lung cancer in adults ages 55 - 79 who have a 30 pack-year smoking history
- Screening for depression in non-pregnant adults ages 18+
- Screening for depression in pregnant and postpartum women
- The addition of HPV-based screening for cervical cancer in women ages 30-69

In order to avoid duplicating evidence reviews, the LPSEOC decided to refer any recommendations regarding immunizations to the BC Immunization Schedule and any recommendations regarding prenatal care, intrapartum care and immediate postpartum care to Perinatal Services BC (PSBC) or to other relevant Provincial Health Services Authority (PHSA) guidelines.

In the 2016 update, three of the services that were analysed in the 2015 update were excluded. *Screening for hearing in newborns* was considered to be part of immediate postpartum care, *screening for syphilis* was excluded as the LPSEOC determined that the targeted population was too specific to meet the definition of a clinical prevention service, and *discuss daily aspirin use* was excluded as the evidence available at that time called into question the effectiveness of this service.

In addition, *screening for chlamydia* and *screening for gonorrhea* were combined as there is a strong overlap in at-risk populations and both STIs are often seen in the same individual.

Finally, *fluoride varnish and sealants to prevent dental caries* was divided into two separate models; 1) *fluoride varnish for the prevention of dental caries in primary teeth* and 2) *sealants for the prevention of caries in permanent teeth*.

As of 2016, a total of 25 services have been assessed for their potential inclusion in the Lifetime Prevention Schedule.[2]

The Lifetime Prevention Services Expert Committee (LPSEC) is currently seeking an assessment of the estimated CPB and CE associated with the following four clinical prevention services (highlighted with shading on Table ES-1):

Screening for Asymptomatic Disease or Risk Factors – Children/Youth

- Screening for hearing loss in newborn and preschool children

Screening for Asymptomatic Disease or Risk Factors – Adults

- Screening for cardiovascular disease risk and treatment with statins

Preventive Medication / Devices – Adults

- Routine aspirin use for the prevention of cardiovascular disease and colorectal cancer
- Folic acid supplementation in reproductive-age women for the prevention of neural tube defects

Note that in several cases this represents a re-assessment or enhancement of a service previously considered for inclusion on the LPS. Screening for hearing loss in newborns was previously excluded as it was considered to be part of immediate postpartum care. Routine aspirin use had initially been included on the LPS but, based on new evidence at the time, was excluded in the 2013 update. Screening for cardiovascular disease risk and treatment with statins represents an update (previously called 'cholesterol screening and treatment') based on a new evidence review compiled by the USPSTF.

Table ES-1 provides an overview of the results for all 29 services. The *estimated coverage* columns include information on current coverage in BC for a specific service as well as information indicating the best coverage in the world (BiW). For example, 37% of adults ages 50-74 in BC are currently being screened for colorectal cancer. Evidence from other jurisdictions suggests that this coverage could be increased to 73%.

[2] See http://www2.gov.bc.ca/gov/content/health/about-bc-s-health-care-system/office-of-the-provincial-health-officer/current-health-topics/lifetime-prevention for an overview of LPS services and supporting documentation.

The *CPB* columns identify the clinically preventable burden (in terms of quality adjusted life years or QALYs) that is being achieved in BC based on current coverage, and the potential CPB if BiW coverage is achieved. For example, if coverage for colorectal cancer screening were as high as the BiW (73%), we would expect a CPB of 10,384 QALYs. Since BC's coverage is at 37%, a CPB of 5,263 QALYs is being achieved. This is 5,121 QALYs short of the potential 10,384 QALYs achievable based on BiW coverage, as identified in the *Gap* column.

The *CE* columns identify the cost-effectiveness ratio associated with a service stated in terms of the cost per QALY. The ratio is given based on the use of a 3% and a 0% discount rate. For example, the cost/QALY associated with colorectal cancer screening in BC is estimated at $2,804, based on a discount rate of 3%. If a 0% discount rate is used, then the cost/QALY would be reduced to $2,777.

Table ES-1: Effective Clinical Prevention Services in B.C.

Summary *(Not including Immunizations or Perinatal Care)*

Clinical Prevention Services	Estimated Coverage B.C.	Estimated Coverage 'BiW'(1)	CPB(2) (0% Discount) QALYs B.C.	CPB(2) (0% Discount) QALYs 'BiW'(1)	CPB(2) (0% Discount) QALYs Gap	CE(3) (% Discount) Cost/QALY 3%	CE(3) (% Discount) Cost/QALY 0%
Screening for Asymptomatic Disease or Risk Factors - Children							
Universal newborn hearing screening (UNHS)	97%	97%	312	312	-	$27,159	$10,516
Vision screening for amblyopia - children, 3-5	93%	93%	25	25	-	$879,199	$179,901
Behavioural Counseling Interventions - Children/Youth							
Preventing tobacco use - children/youth	Unknown, assume 0%	65%	-	1,299	1,299	($7,262)	($16,750)
Promotion of breastfeeding	41%	60%	7,031	10,370	3,339	$397	($4,586)
Screening for and management of obesity - children/youth ages 2-17	Unknown, assume 15%	30%	159	318	159	$41,106	$14,971
Preventive Medication - Children							
Fluoride varnish - children	92%	92%	407	407	-	$19,292	$19,292
Dental sealants - children/youth	30%	70%	239	558	319	($15,140)	($18,917)
Screening for Asymptomatic Disease or Risk Factors - Adults							
Breast cancer screening - women 50-74	53%	70%	871	1,150	279	$25,412	$22,125
Cytology-based cervical cancer screening for women ages 25-69	67%	80%	1,243	1,477	234	$18,217	$16,781
Addition of HPV-based cervical cancer screening for women ages 30-69	0%	70%	-	355	355	($5,181)	($6,877)
Colorectal cancer screening - adults 50-74	37%	73%	5,263	10,384	5,121	$2,804	$2,777
Hypertension screening and treatment - adults 18+	85%	85%	8,791	8,791	-	$15,131	$5,573
Screening for cardiovascular disease risk and treatment with statins	Unknown, assume 15%	30%	1,755	3,510	1,755	$20,440	$11,033
Screening for Type 2 Diabetes Mellitus	Unknown, assume 0%	70%	-	3,693	3,693	($3,777)	($4,045)
Screening for lung cancer - adults 55 - 74 who have a 30 pack-year smoking history	Unknown, assume 0%	80%	-	2,736	2,736	$1,556	$1,553
Screening for depression - nonpregnant adults ages 18+	Unknown, assume 0%	5%	-	50	50	$67,322	$67,322
Screening for depression - pregnant and postpartum women	Unknown, assume 0%	40%	-	102	102	$26,670	$19,181
Screening for Sexually Transmitted Infections - Adults							
Screening for Human Immunodeficiency Virus - adults 15-65	20%	70%	111	387	276	$43,846	$43,846
Screening for Chlamydia/Gonorrhea - women 15-29	29%	50%	647	1,115	468	$9,900	$7,980
Screening for Syphilis	*Not for general population*						
Screening for Hepatitis C Virus - adults born between 1945 and 1965	33%	90%	2,895	7,895	5,000	$4,751	$3,321
Behavioural Counseling Interventions - Adults							
Smoking cessation advice and help to quit - adults	50%	75%	10,743	16,034	5,291	$7,277	$1,749
Alcohol screening and brief counseling - adults	Unknown, assume 0%	35%	-	1,136	1,136	$1,175	($12,636)
LARC(4) and screening/counseling to reduce FASD(5) and unplanned pregnancies	Unknown, assume 0%	70%	-	3,752	3,752	($2,829)	($4,980)
Prevention of sexually transmitted infections - adults 15-59	Unknown, assume 0%	30%	-	3,543	3,543	$7,142	$7,142
Screening for and management of obesity	Unknown, assume 0%	30%	-	3,233	3,233	$10,346	$8,005
Preventing falls in community–dwelling elderly - adults 65+	Unknown, assume 0%	30%	-	2,394	2,394	$5,615	$5,615
Preventive Medication / Devices - Adults							
Routine aspirin use for the prevention of cardiovascular disease and colorectal cancer - adults age 50-59 at low risk of bleeding	Unknown, assume 15%	30%	224	448	224	$37,758	$19,938
Folic acid supplementation in reproductive-age women for the prevention of neural tube defects	7.5 NTDs / 10,000 Births	5.8 NTDs / 10,000 Births	-	94	94	$237,088	$88,818

(1) 'BiW' = best in world; (2) CPB = clinically preventable burden; (3) CE = cost-effectiveness; (4) LARC = long-acting reversible contraception; (5) FASD = fetal alcohol spectrum disorder

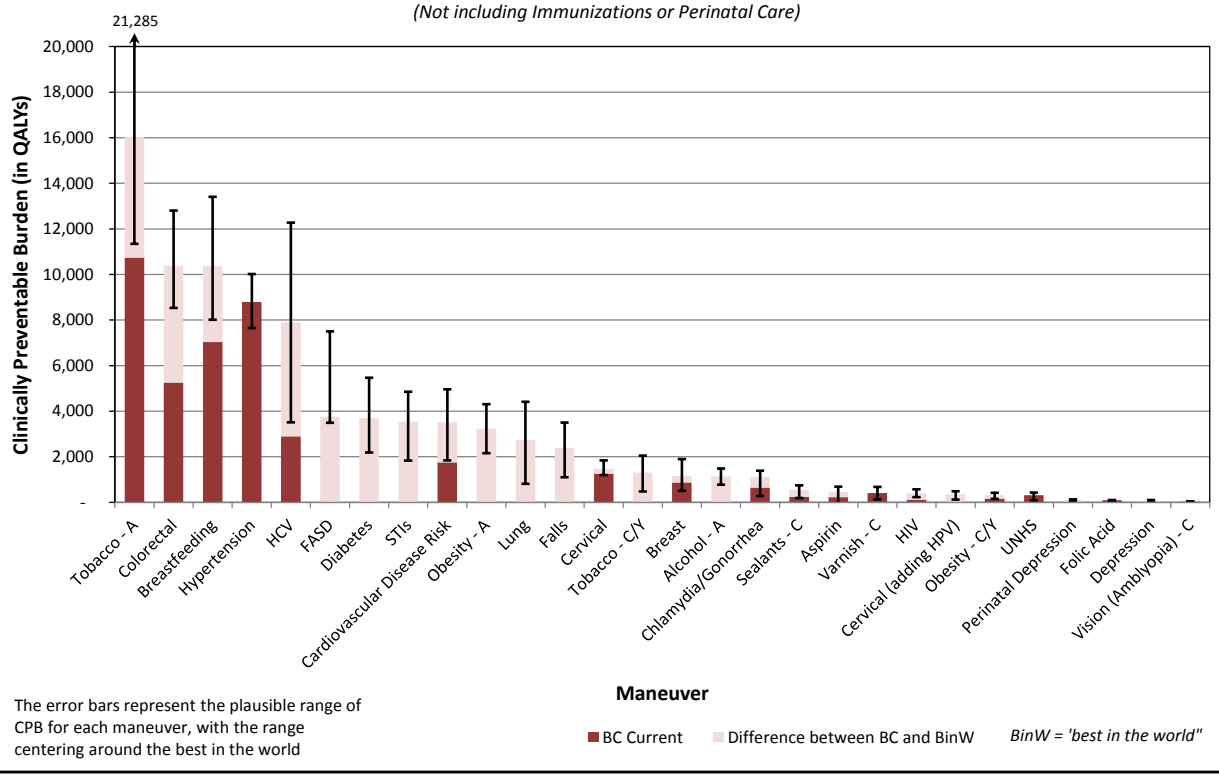
Figure ES-1 provides a summary of the CPB associated with each service. Results are displayed based on a 0% discount rate and results based on a 3% discount rate are available in the body of the text. Using a 3% discount rate tends to reduce the CPB. The results are organized from left to right based on the services with the highest to lowest potential CPB. For example, full implementation of the service *smoking cessation advice and help to quit – adults* (Tobacco-A) (i.e., achieving levels that are comparable to the best in the world) would result in a CPB of 16,034 QALYs, the highest of any service reviewed. Our best estimates suggest that approximately 50% of adults in BC are receiving the service, resulting in a CPB of 10,743 QALYs. This would leave a gap of 5,291 QALYs between current services in BC and the potential full implementation of this service in the province.

The black error bars / whiskers associated with each service represent a potential range in CPB based on one-way sensitivity analysis. That is, the range is based on varying (over a plausible range) the one assumption that has the largest effect on the results generated by the model. Simultaneously varying more than one assumption would increase the potential range. A larger range suggests a higher sensitivity to the assumptions used.

Figure ES-1: ***Clinically Preventable Burden*** Based on Providing Clinically Effective Services to a B.C. Birth Cohort of 40,000

0% Discount Rate

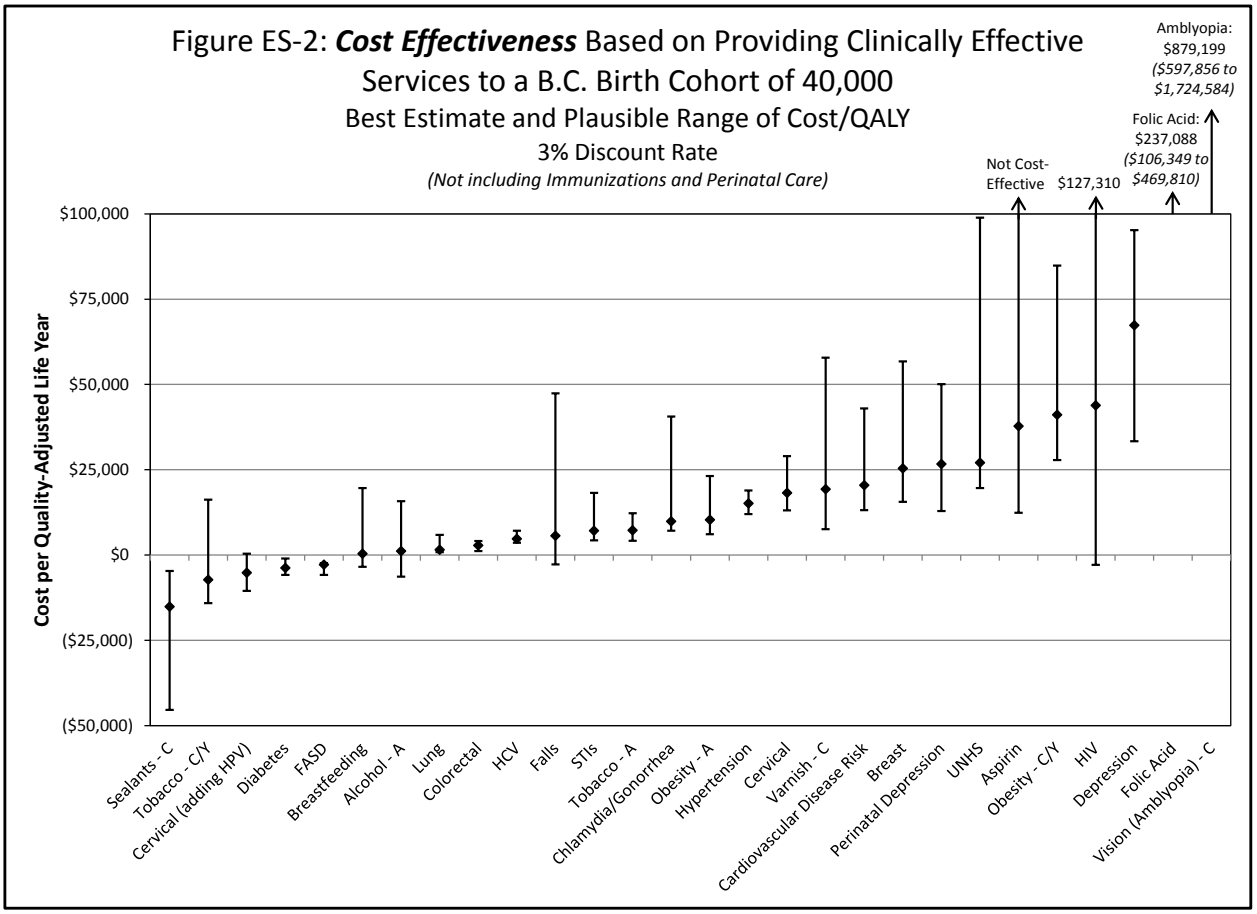
(Not including Immunizations or Perinatal Care)



The error bars represent the plausible range of CPB for each maneuver, with the range centering around the best in the world

Note that the labels on the horizontal axis in Figures ES-1 and ES-2 refer to the CPS included in Table ES-1. The 'A' refers to 'adults', the 'C' to children and the 'C/Y' to children/youth.

Figure ES-2 provides a summary of the CE associated with each service. Results are displayed based on a 3% discount rate. Results based on a 0% discount rate are available in the body of the text. Using a 0% discount rate tends to improve the CE. Furthermore, the results are organized from left to right based on the services with the best to worst potential CE, including a plausible range for each service based on sensitivity analysis. The use of *dental sealants for the prevention of caries in permanent teeth* has the best CE result of any service reviewed. That is, this service is considered to be cost-saving, with a cost per QALY of -$15,140 (with a potential range from -$45,421 to -$4,706).

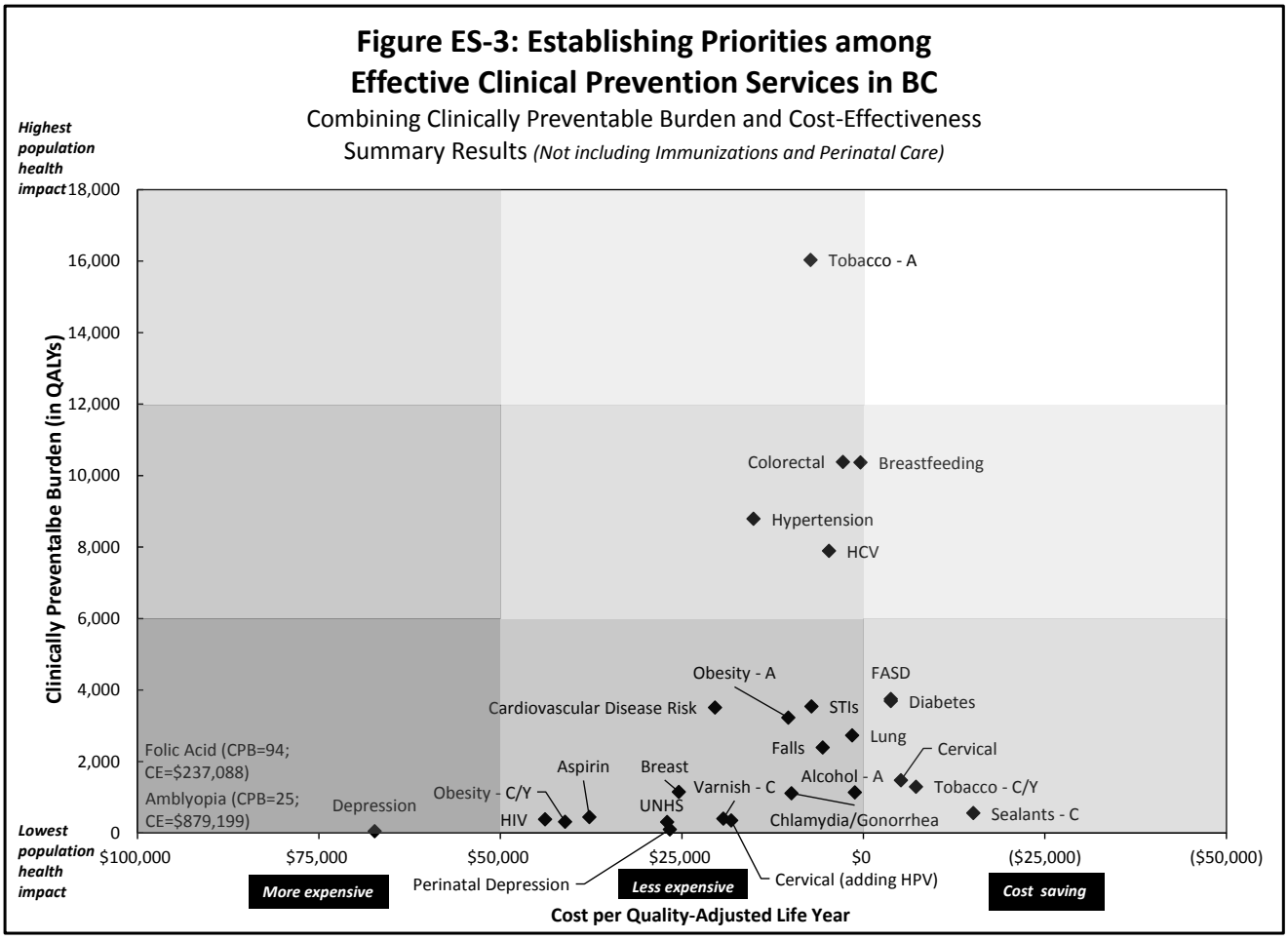


The base models include an estimate of costs associated with a person's time used in accessing the preventive service. The most significant effect of these inclusions/exclusions is seen in services that require frequent contact with health care providers. For example, the cost/QALY associated with screening for breast cancer is reduced from $25,412 to $13,859 if patient time costs are excluded. The cost/QALY associated with cytology-based screening for cervical cancer is reduced from $18,217 to $8,239, the cost/QALY associated with screening for HIV is reduced from $43,846 to $9,955, the cost/QALY associated with screening for hypertension is reduced from $15,131 to $8,400, the cost/QALY associated with screening and counselling to reduce alcohol misuse is reduced from $1,175 to *negative* $19,238 and the cost/QALY associated with applying fluoride varnish to primary teeth is reduced from $19,292 to $3,482.

The results for CPB and CE are combined in Figure ES-3. CPB is on the vertical axis, ranging from 0 to 18,000 QALYs. CE is on the horizontal axis, ranging from $100,000/QALY at the intersection of the x- and y-axis to -$50,000 at the far right of the x-axis. By arranging CPB and CE in this manner, the most positive results are on the upper

right of the chart and the least positive results are in the lower left of the chart. We also divided CPB into three equal segments as follows; 0 to 6,000 QALYs, 6,001 to 12,000 QALYs and 12,001 to 18,000 QALYs. CE was also divided into three equal segments as follows: $100,000 to $50,000 per QALY, $50,000 to $0 per QALY and $0 to -$50,000 per QALY.

The resulting nine equivalent segments are shown in Figure ES-3. Services in the upper right segment have the most favourable combination of CPB and CE while services in the lower left segment have the least favourable combination of CPB and CE.



In Figures ES-4 to ES-6, we have incorporated visual information on plausible ranges (based on one-way sensitivity analysis) with the point estimates for each service. To avoid overcrowding the above figure (ES-3), we have separated the services into three figures. Figure ES-4 includes services specific to children and youth, Figure ES-5 includes screening services and Figure ES-6 includes behavioural counselling, etc. services.

Figure ES-4: Establishing Priorities among Effective Clinical Prevention Services in BC

Combining CPB and CE

Summary Results and Plausible Ranges for Children/Youth

(Not including Immunizations and Perinatal Care)

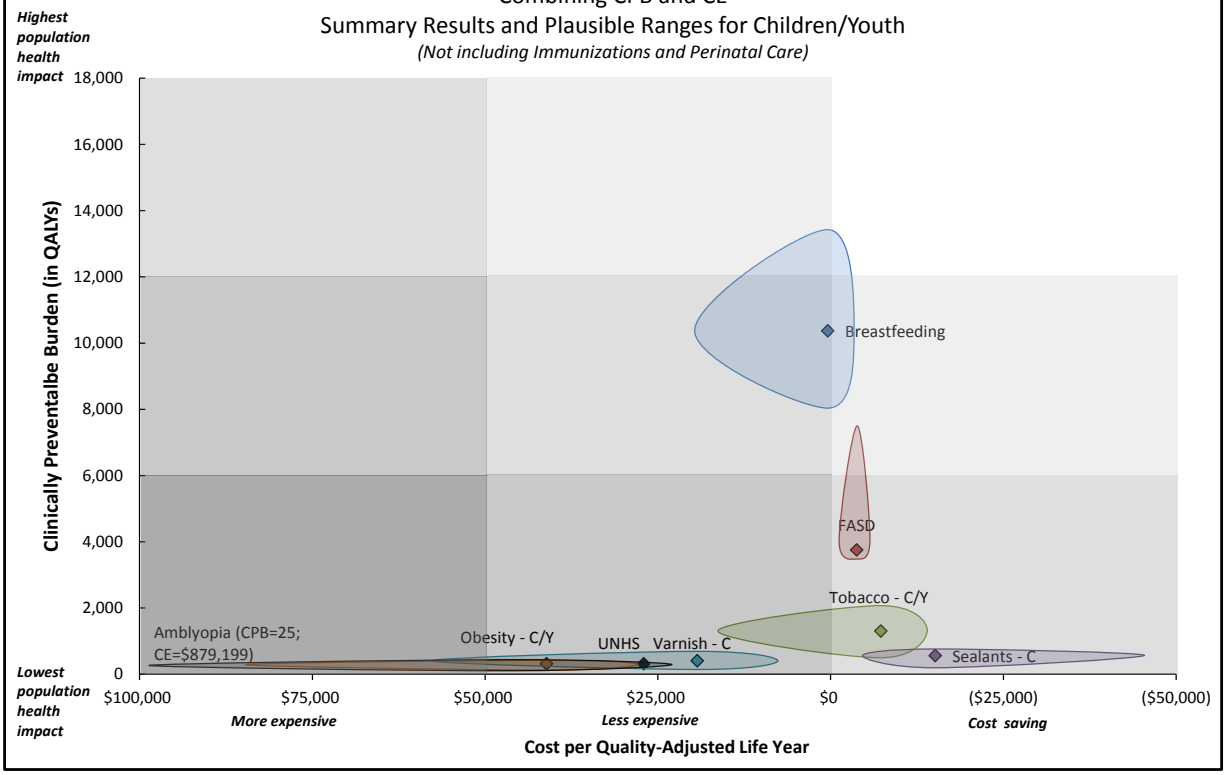


Figure ES-5: Establishing Priorities among Effective Clinical Prevention Services in BC

Combining CPB and CE

Summary Results and Plausible Ranges for Screening Maneuvers

(Not including Immunizations and Perinatal Care)

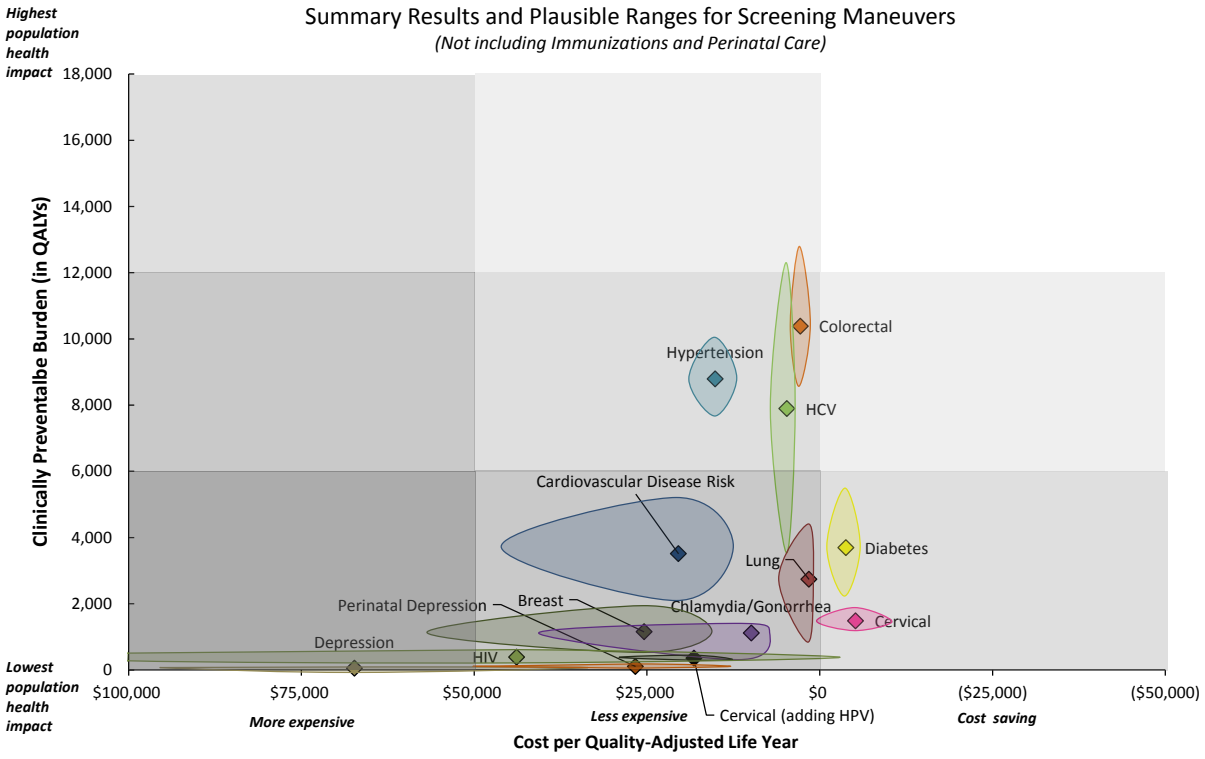
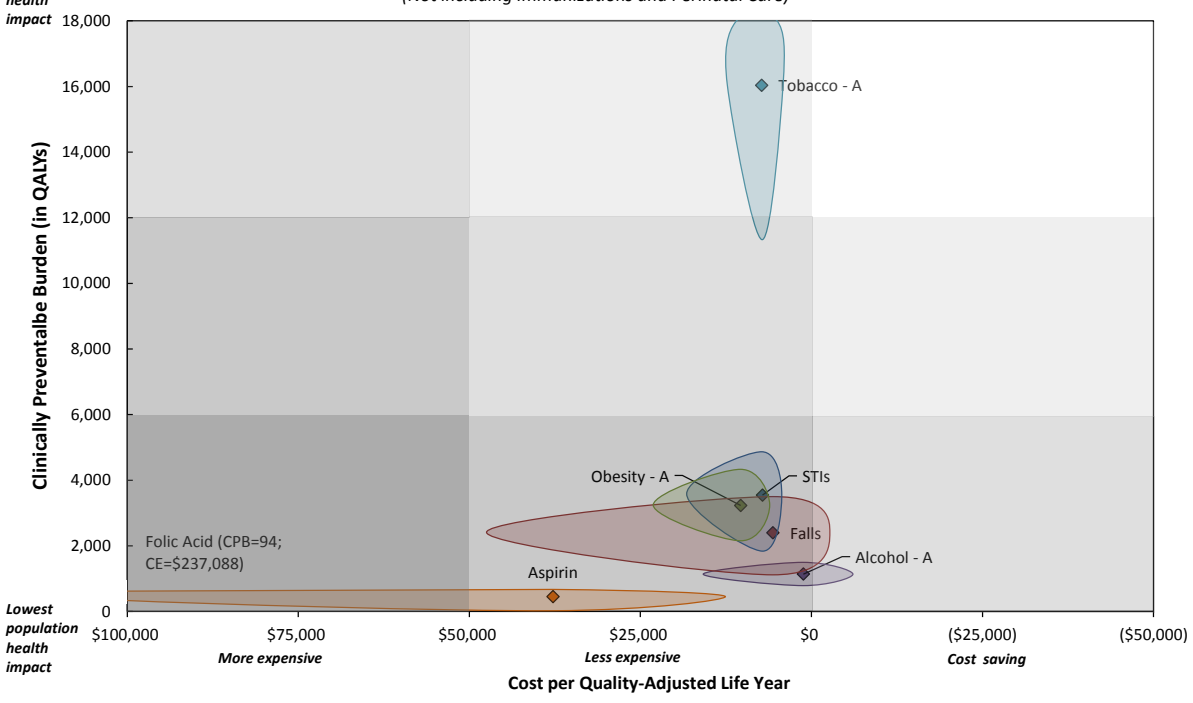


Figure ES-6: Establishing Priorities among Effective Clinical Prevention Services in BC

Combining CPB and CE

Summary Results and Plausible Ranges for Behavioural Counselling and Preventive Medicines

(Not including Immunizations and Perinatal Care)



Key Assumptions

The following key assumptions have been made throughout this project.

Duplication of Effort

In order not to duplicate evidence reviews, the Lifetime Prevention Schedule Expert Advisory Committee decided to refer any recommendations regarding immunizations to the BC Immunization Schedule and any recommendations regarding prenatal care, intrapartum care and immediate postpartum care to the Perinatal Services BC (PSBC) guidelines or to other agencies responsible for specific recommendations.

Delivery Mechanism(s)

The definition of clinical prevention is independent of delivery mechanism(s). In estimating cost-effectiveness, however, we had to make assumptions about delivery mechanisms in order to estimate the costs of providing the service. For purposes of consistency and comparability between the various preventive services, we chose to use a general physician's office as the delivery mechanism whenever appropriate. That is, if an established delivery mechanism is not in place, then we assumed, for costing purposes, that it would take place in a general physician's office. For example, no program currently exists in BC for screening and interventions to reduce falls in community-dwelling elderly so we assumed this would take place in a general physician's office. Determining which delivery mechanism would be most suitable for each service will be assessed in subsequent phases of the policy cycle.

Patient Costs

Clinical prevention services are offered to the asymptomatic general population. As such, people are being asked to give up some of their time for a service which has a (relatively small) chance of detecting a clinically relevant issue. Alternatively, they may be asked to give up some of their time for a behavioural counselling intervention that has a modest potential for success. As such, it is important to value this time in an assessment of the cost-effectiveness of the intervention. For the purposes of consistency and comparability, we have assessed this time by including travel time to and from the intervention as well as time during the intervention and then valued this total time based on average wage rates for the BC population. We have also identified the proportion of costs attributable to patient costs for each service.

Spillover Effects

The literature on 'spillover effects' (e.g. when the illness of a child or family member has an economic or quality of life impact on the broader family or caregiver(s) is nascent and further work is required before these effects can be relied upon with confidence.[3,4,5] These effects are not included in the base case analyses.

Discounting

In the economic appraisal of health programs or interventions, costs and benefits that are spread over time are usually weighted according to when they are experienced. The further in the future, the less heavily they are weighted or the more they are discounted. This can be particularly challenging for interventions in which costs are current and benefits are further in the future (e.g. prevention). The impact of discounting is most noticeable for preventive services in children and youth, given that costs are generally current, whereas benefits and potential costs avoided may stretch over the lifetime of the individual.[6,7,8,9]

From a health economics perspective, the usual approach is to discount both costs and benefits when calculating cost-effectiveness. However, discounting may fail to reflect a value we as a society might hold for the future of our children. The Netherlands, for example, require that a discount rate of 1.5% be applied to benefits while a discount rate of 4% be applied to costs.[10] It would thus be important to explicitly understand the impact of discounting in the current project. To do so, we will use both a 3% discount rate as well as a 0% discount rate. A 0% discount rate is equivalent to not discounting.

[3] Wittenberg E and Prosser L. Disutility of illness for caregivers and families: a systematic review of the literature. *Pharmacoeconomics*. 2013; 31(6): 489-500.
[4] Wittenberg E, Ritter G and Prosser L. Evidence of spillover of illness among household members EQ-5D scores from a US sample. *Medical Decision Making*. 2013; 33(2): 235-43.
[5] Tilford J and Payakachat N. Progress in measuring family spillover effects for economic evaluations. *Expert Review of Pharmacoeconomics & Outcomes Research*. 2015; 15(2): 195-8.
[6] Parsonage M and Neuburger H. Discounting and health benefits. *Health Economics*. 1992; 1(1): 71-6.
[7] Brouwer WB, Niessen LW, Postma MJ et al. Need for differential discounting of costs and health effects in cost effectiveness analyses. *British Medical Journal*. 2005; 331(7514): 446-8.
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[9] Gravelle H, Brouwer W, Niessen L et al. Discounting in economic evaluations: stepping forward towards optimal decision rules. *Health Economics*. 2007; 16(3): 307-17.
[10] Tan S, Bouwmans C, Rutten F et al. Update of the Dutch manual for costing in economic evaluations. *International Journal of Technology Assessment in Health Care*. 2012; 28(2): 152-8.

Incorporating Information on Current Coverage

A number of the preventive services assessed in this project have an established history in the province while others may only be provided in a limited, fairly random approach (as 'random acts of kind prevention'). With this in mind, we set out to assess CPB and CE from two perspectives. First, assuming that the service had no current coverage in the province (i.e. that the service had not yet been established in the province). Second, assessing the gap between current coverage in the province and what arguably could be considered the best possible coverage (based on information on 'best in the world' coverage for the service).

Incorporating Key Recent Evidence

The USPSTF is attempting to update their evidence review and recommendations every five years. It is possible that seminal research has been published during the interval between updates and that this research may alter recommendations. To take this into account, we reviewed evidence reviews from other organizations (e.g. the Cochrane Collaboration and the National Institute for Health and Clinical Excellence [NICE] in the UK) for any USPSTF or CTFPHC recommendations published more than four years ago.

Focus on the Best Available Evidence

An important assumption of this project is to focus on the highest level of available evidence. Given the limited capacity in the health care system, it is better to focus on a limited number of preventive interventions that are clearly proven to be effective, will have an important impact on the health of the entire population of BC and are likely to be cost-effective. The focus should be on achieving potential coverage and an effective dose for a limited number of preventive services rather than incomplete coverage of a larger number of preventive services.

List of Abbreviations

AABR – Automated Auditory Brainstem Response

ABR – Auditory Brainstem Response

ACC – American College of Cardiology

AHA – American Heart Association

ASA – Acetylsalicylic Acid

ASCVD – Atherosclerotic Cardiovascular Disease

AOAE – Automated Otoacoustic Emissions

AUD – Australian Dollars

BC – British Columbia

BiW – Best in the World

BCEHP – British Columbia Early Hearing Program

CAD – Canadian Dollars

CE – Cost-Effectiveness

CHD – Coronary Heart Disease

CI – Confidence Interval

CLEM – Cardiovascular Life Expectancy Model

CPB – Clinically Preventable Burden

CPS – Clinical Prevention Service

CRC – Colorectal Cancer

CSS – Canadian Cardiovascular Society

CTFPHC – Canadian Task Force on Preventive Health Care

CVD – Cardiovascular Disease

ES – Executive Summary

FASD – Fetal Alcohol Spectrum Disorder

FRS – Framingham Heart Study Risk Score

FTE – Full Time Equivalent

GI – Gastrointestinal

GP – General Practitioner

HDL-C – High-Density Lipoprotein Cholesterol

ICD – International Classification of Diseases

IR – Intermediate Risk

IQ – Intelligence Quotient

LDL – Low-Density Lipoprotein

LDL-C – Low-Density Lipoprotein Cholesterol

LPS – Lifetime Prevention Schedule

LPSEC – Lifetime Prevention Schedule Expert Committee

MEA – Middle Ear Analysis

MSP – Medical Service Plan

NICE – National Institute for Health and Clinical Excellence

NSAID – Nonsteroidal Anti-Inflammatory Drug

NTD – Neural Tube Defect

OME – Otitis Media with Effusion

OR – Odds Ratio

OAE – Otoacoustic Emissions

PCHI – Permanent Childhood Hearing Impairment

PCI – Percutaneous Coronary Intervention

PHSA – Provincial Health Services Authority

PSBC – Perinatal Services British Columbia

QALY – Quality-Adjusted Life-Year

QoL – Quality of life

RCT – Randomized Controlled Trial

RR – Relative Risk

TEOAE –Transient Evoked Otoacoustic Emissions

UK – United Kingdom

UNHS – Universal Newborn Hearing Screening

USD – United States Dollars

USPSTF – United States Preventive Services Task Force

WHO – World Health Organization

Clinical Prevention in Children and Youth

Screening for Asymptomatic Disease or Risk Factors

Screening for Hearing Loss in Newborn Infants

Universal newborn hearing screening (UNHS) programs tend to focus on "permanent sensory or conductive hearing loss averaging 30 to 40 dB or more in the frequency region important for speech recognition (~500 – 4000 Hz). The focus of UNHS is on congenital as opposed to acquired or progressive hearing loss that may not be detected in the newborn period."[11] The goal of most UNHS programs are to **identify** and **treat** the hearing loss by 6 months of age or prior to language development.

Screening for Hearing Loss in Preschool Children

Some have suggested that in addition to UNHS, universal screening should continue in preschool children to detect **acquired** hearing loss.[12,13] In BC, universal hearing screening at kindergarten entry is provided in four of five health authorities.[14] There is limited data on the effectiveness of universal hearing screening in preschool children. The most common cause of acquired hearing loss is otitis media with effusion (OME), which has a high rate of spontaneous resolution. A 2007 Cochrane Review set out to find evidence of the effect of screening and treating children with clinically important OME, on language and behavioural

[11] Nelson H, Bougatsos C and Nygren P. Universal newborn hearing screening: systematic review to update the 2001 US preventative services task force recommendation. *Pediatrics*. 2008; 122(1): e266-e76.

[12] Shisler L and Eiserman W. *Early Childhood Hearing Screening: Not Just for Newborns*. 2016. Utah State University National Center for Hearing Assessment and Management. Available at http://infanthearing.org/ehdi-ebook/2016_ebook/23%20Chapter23EarlyChildhood2016.pdf. Accessed January 2017.

[13] Hall J. Effective and efficient pre-school hearing screening: essential for successful early hearing detection and intervention (EHDI). *Journal of Early Hearing Detection and Intervention*. 2016; 1(1): 2-12.

[14] Melanie Foster, Senior Policy Analyst, Early Childhood Health, Public Health Services and Office of Aboriginal Health, Population and Public Health, Ministry of Health. Personal communication, January 11, 2017.

outcomes, in the first four years of their life. The Cochrane Review "found no evidence of a clinically important benefit in language development from screening and treating children with clinically important OME".[15]

For the purposes of establishing the effectiveness of an intervention, a Cochrane Review is considered to be a high-quality systematic review. Their finding that the effectiveness of screening for hearing loss in preschool children has not been established means that this intervention does not pass the first step in being considered for inclusion on the LPS.

Universal Newborn Hearing Screening

The 2008 statement from the USPSTF cited below focuses on screening for hearing loss in newborn infants. ***The remainder of this section is an evaluation of universal newborn hearing screening only.***

United States Preventive Services Task Force Recommendations (USPSTF; 2008)[16]

> *The USPSTF recommends screening for hearing loss in all newborn infants (Grade B recommendation).*
>
> *Screening programs should be conducted by using a 1-step or 2-step validated protocol. A frequently-used 2-step screening process involves otoacoustic emissions followed by auditory brain stem response in newborns who fail the first test. Infants with positive screening test results should receive appropriate audiologic evaluation and follow-up after discharge. Procedures for screening and follow-up should be in place for newborns delivered at home, birthing centers, or hospitals without hearing screening facilities.*
>
> *All infants should have hearing screening before 1 month of age. Infants who do not pass the newborn screening should undergo audiologic and medical evaluation before 3 months of age.*
>
> *Early intervention services for hearing-impaired infants should meet the individualized needs of the infant and family, including acquisition of communication competence, social skills, emotional well-being, and positive self-esteem. Early intervention comprises evaluation for amplification or sensory devices, surgical and medical evaluation, and communication assessment and therapy. Cochlear implants are usually considered for children with severe-to-profound hearing loss only after inadequate response to hearing aids.*

The USPSTF website notes that "the U.S. Preventive Services Task Force (USPSTF) has decided not to review the evidence and update its recommendations for this topic. The previous evidence review and recommendation may contain information that is outdated."[17] The procedure manual for the USPSTF indicates that a topic may be inactivated for one or more of the following reasons:

- "Topic is no longer relevant to clinical practice because of changes in technology, new understanding of disease etiology/natural history, or evolving natural history of the disease

[15] Simpson S, Thomas C, van der Linden M et al. Identification of children in the first four years of life for early treatment for otitis media with effusion. *Cochrane Database of Systematic Reviews.* 2007.
[16] US Preventive Services Task Force. Universal screening for hearing loss in newborns: US preventive services task force recommendation statement. *Pediatrics*. 2008; 122(1): 143-8.
[17] US Preventive Services Task Force. *Hearing Loss in Newborns: Screening*. 2008. Available at https://www.uspreventiveservicestaskforce.org/BrowseRec/InactiveTopic/218. Accessed December 2016.

- Topic is not relevant to primary care because the service is not implemented in a primary care setting or not referable by a primary care provider
- Topic has a low public health burden
- Topic is otherwise outside of the Task Force's scope"

If a topic is inactivated…the status on the task force web site continues to be listed as "active" for a minimum of 5 years from the date of the original recommendation, unless considerations arise beforehand to change the status. After this period, the status changes to "inactive."[18]

We were unable to find a specific reason for the inactive status of the 2008 USPSTF recommendations regarding screening for hearing loss in newborn infants.

Canadian Task Force on Preventive Health Care (CTFPHC; 1989)

In 1989, the CTFPHC (then known as the Canadian Task Force on the Periodic Health Examination) found that "there is insufficient evidence to recommend the inclusion or exclusion of screening for hearing impairment among preschool children."[19] No review has been completed since then.

Utilization of This Clinical Preventive Service

Currently in British Columbia

The BC Early Hearing Program (BCEHP) for healthy babies was initiated in October of 2007 with the roll-out completed by March 31, 2009.[20] The BCEHP provides screening for congenital hearing loss to all newborns in BC. Other services provided by BCEHP include ongoing monitoring for later-onset loss; medical and audiological assessment for confirmation of hearing status and early intervention supports, including centralized province-wide intake and support, parent-to-parent support, speech-language therapy, sign language instruction and hearing aid(s).

Hearing impairment in BC is currently defined as mild (26-40 dB loss, in better ear), moderate (41-55 dB loss, in better ear), moderate-severe (56-70 dB loss, in better ear), severe (71-90 dB loss, in better ear) and profound (≥91 dB loss, in better ear). The hearing aid funding policy of the BCEHP provides hearing aids to children who meet a 35 dB loss criteria in at least 2 of 4 speech frequencies in both ears. Funding for hearing aids will be considered, however, for children with hearing loss (including unilateral hearing loss) who do not meet this criteria, but have speech and language delays.[21]

The proportion of children 0-3 years of age who have had hearing screening in BC has increased from 94.1% in 2007/08 to 96.8% in 2012/13.[22] Program data for 2013/14 indicates that 42,223 of the 43,429 (97.2%) (Table 1-1, row b) babies eligible completed screening,

[18] US Preventive Services Task Force. *Procedure Manual*. December 2015. Available at https://www.uspreventiveservicestaskforce.org/Page/Name/methods-and-processes. Accessed March 2017.
[19] Canadian Task Force on the Periodic Health Examination. Periodic health examination, 1989 update: 3. preschool examination for developmental, visual and hearing problems. *Canadian Medical Association Journal*. 1989; 141: 1136-40.
[20] BC Early Hearing Program. *Information Update*. 2009. Provincial Health Services Authority. Available at http://www.phsa.ca/Documents/bcehp_physiciansinfofall09.pdf. Accessed December 2016.
[21] Diane Bremner. Director, BC Early Hearing Program. Personal communication, March 2017.
[22] Child Health BC & BC's Provincial Health Officer. *Is "Good", Good Enough? The Health & Well-being of Children and Youth in BC.* November 2016. Available at http://www2.gov.bc.ca/assets/gov/health/about-bc-s-health-care-system/office-of-the-provincial-health-officer/reports-publications/annual-reports/pho-annual-report-2016.pdf. Accessed March 2017.

with 658 (1.56%) having a positive screen. For the babies with a positive screen, 90% received their follow-up hearing assessment and 89 infants (0.21%) were confirmed with a permanent hearing loss.[23]

Best in the World

The 2012/13 results from the Newborn Hearing Screening Program in England indicate that 97.54% of newborns are screened by 4/5 weeks and 98.95% by three months in that country.[24]

We have assumed that BC's current screening rate of 97% is essentially equivalent to the best in the world.

Relevant British Columbia Population in 2013

A total of 43,991 live births were registered by residents in BC in 2011, the latest year for which this data is publically available.[25]

Modelling CPB and CE

In this section, we will calculate the CPB and CE associated with screening for hearing loss in newborn infants.

In estimating CPB, we made the following assumptions:

Definition and Prevalence of Congenital Hearing Loss

- The World Health Organization classifies hearing impairment as slight/mild (26-40 dB loss, in better ear), moderate (41-60 dB loss, in better ear), severe (61-80 dB loss, in better ear), and profound (≥81 dB loss, in better ear).[26] BY comparison, the current definition of hearing impairment in BC is mild (26-40 dB loss, in better ear), moderate (41-55 dB loss, in better ear), moderate-severe (56-70 dB loss, in better ear), severe (71-90 dB loss, in better ear) and profound (≥91 dB loss, in better ear).[27]
- The criteria for assessing severity are not consistent. For example, both Wake et al[28] and Ching et al[29] use the WHO criteria of >80dB hearing loss in defining "profound"

[23] Ministry of Children and Family Development. *British Columbia's Early Years Annual Report 2013/2015*. 2015. Available at http://www2.gov.bc.ca/assets/gov/family-and-social-supports/child-care/bc_early_years_annual_report.pdf. Accessed December 2016.
[24] Wood SA, Sutton GJ and Davis AC. Performance and characteristics of the newborn hearing screening programme in England: the first seven years. *International Journal of Audiology*. 2015; 54(6): 353-8.
[25] British Columbia Vital Statistics Agency. *Selected Vital Statistics and Health Status Indicators*. 2011. Available at http://www2.gov.bc.ca/assets/gov/birth-adoption-death-marriage-and-divorce/statistics-reports/annual-reports/2011/pdf/introduction.pdf. Accessed January 2017.
[26] World Health Organization. *Prevention of Blindness and Deafness: Grades of Hearing Impairment*. 2016. Available at http://www.who.int/pbd/deafness/hearing_impairment_grades/en/. Accessed December 2016.
[27] Diane Bremner. Director, BC Early Hearing Program. Personal communication, March 2017.
[28] Wake M, Poulakis Z, Hughes E et al. Hearing impairment: a population study of age at diagnosis, severity, and language outcomes at 7–8 years. *Archives of Disease in Childhood*. 2005; 90(3): 238-44.
[29] Ching TC, Dillon H, Marnane V et al. Outcomes of early-and late-identified children at 3 years of age: findings from a prospective population-based study. *Ear and hearing*. 2013; 34(5): 535-52.

hearing gloss. Korver et al[30], on the other hand use >90 dB loss while Pimperton et al[31] use ≥95dB loss.

- The prevalence of hearing impairment in childhood depends on what is included in the target disorder. Ideally the target disorder is described by impairment severity, frequency range, laterality (one or both ears), and permanence, as well as the site of the disorder in the auditory system and the associated categories of impairment type.[32]
- Between 1985 and 1993, the prevalence of congenital permanent childhood hearing impairment/loss (PCHI) of ≥40 dB in Trent, England was 112 (CI of 101 – 123) / 100,000. The rate for profound impairment was 24 (CI of 20 - 30) / 100,000. Prevalence was increased six-fold for children with a history of neonatal intensive care and 14-fold for children with a family history, compared with children with no risk factors.[33]
- Based on a birth cohort of 157,000 infants born in southern England between 1992 and 1997, the prevalence of bilateral congenital PCHI (≥40 dB hearing loss) is 107 per 100,000.[34]
- Based on a birth cohort of 570,386 born in the Netherlands between January 1, 2003 and December 31, 2005, 434 infants (76 per 100,000) were identified with bilateral congenital PCHI (a hearing loss of 40 dB or greater).[35] This population consists of 146 (49.2%) of 297 infants with moderate, 79 (26.6%) with severe and 72 (24.2%) with profound hearing loss. Their criteria for severe (61-90 dB hearing loss) and profound (>90 dB) vary from the WHO definition.
- Based on a birth cohort of 3,496,452 infants born in the US in 2004, 3,600 infants (103 per 100,000) were identified with "permanent childhood hearing loss" with the rate ranging from a low of 22 per 100,000 in North Dakota to a high of 361 per 100,000 in Hawaii.[36] The prevalence of hearing loss declines based on the hearing threshold and laterality.
    - Any impairment with threshold sensitivity of >25dB hearing loss or worse (unilateral or bilateral) – 310 per 100,000 ranging from 170 to 500.
    - Bilateral impairment with a sensitivity threshold of >25dB hearing loss or worse – 90 per 100,000 ranging from 40 to 170.
    - Bilateral impairment with a sensitivity threshold of >40dB hearing loss or worse – 30 per 100,000 ranging from 11 to 74.

[30] Korver A, Konings S, Dekker F et al. Newborn hearing screening vs later hearing screening and developmental outcomes in children with permanent childhood hearing impairment. *Journal of the American Medical Association*. 2010; 304(15): 1701-8.
[31] Pimperton H and Kennedy C. The impact of early identification of permanent childhood hearing impairment on speech and language outcomes. *Archives of Disease in Childhood*. 2016; 101(1): 9-15.
[32] Schopflocher D, Corabian P, Eng K et al. *IHE Report: Screening Newborns for Hearing*. 2007. Institute of Health Economics. Available at http://www.ihe.ca/download/screening_newborns_for_hearing.pdf. Accessed December 2016.
[33] Fortnum H and Davis A. Epidemiology of permanent childhood hearing impairment in Trent Region, 1985-1993. *British Journal of Audiology*. 1997; 31(6): 409-46.
[34] Kennedy C, McCann D, Campell M et al. Language ability after early detection of permanent childhood hearing impairment. *New England Journal of Medicine*. 2006; 354(20): 2131-41.
[35] Korver A, Konings S, Dekker F et al. Newborn hearing screening vs later hearing screening and developmental outcomes in children with permanent childhood hearing impairment. *Journal of the American Medical Association*. 2010; 304(15): 1701-8.
[36] Mehra S, Eavey R and Keamy D. The epidemiology of hearing impairment in the United States: newborns, children, and adolescents. *Otolaryngology – Head & Neck Surgery*. 2009; 140(4): 461-72.

- In BC, 89 of 42,233 infants screened in 2013/14 had a confirmed "permanent hearing loss".[37] This is a rate of 211 per 100,000, significantly higher than the rates observed in the studies noted above of 76 to 112 per 100,000, probably because a more inclusive definition of hearing impairment is used in BC.
- Based on WHO definitions of hearing loss severity, Wake et al found that 28 (43.1%) of 65 infants had moderate hearing loss, 17 (26.2%) had severe hearing loss and 20 (30.8%) had profound hearing loss.[38]
- Based on WHO definitions of hearing loss severity, Ching et al found that 149 (40.8%) of 365 infants had moderate hearing loss, 71 (19.5%) had severe hearing loss and 145 (39.7%) had profound hearing loss.[39]
- When using 40 to 69dB hearing loss as 'moderate', 70-94dB as 'severe' and ≥95dB as profound, Schroeder et al found that 65 (54.2%) of 120 infants had moderate hearing loss, 29 (24.2%) had severe hearing loss and 26 (21.7%) had profound hearing loss.[40]
- For modelling purposes we assumed a prevalence of bilateral congenital PCHI of at least 40dB in the better ear to be 0.092% (the midpoint of 76 and 112 / 100,000) with the sensitivity analysis ranging from 0.076% to 0.112% (Table 1-1, row d).
- For modelling purposes, we created weighted averages (based on the sample size in each study) from the studies by Wake et al and Ching et al as follows: 41.1% moderate (Table 1-1, row f), 20.5% severe (Table 1-1, row g) and 38.4% (Table 1-1, row h) profound.

Protocols for Hearing Screening and Diagnosis

- There are two approaches to screening infants for hearing loss: universal screening of all newborns or targeted screening of high risk newborns.
- At-risk populations (infants who have been in the neonatal intensive care unit, those with a family history of hearing impairment or those with craniofacial abnormalities) represent approximately 10% of the population and include 50% to 59% of those with congenital hearing loss.[41]
- The most common screening protocol is an automated transient evoked otoacoustic emissions (TEOAE) test followed by an automated auditory brainstem response (AABR) test for infants who did not pass the TEOAE. A positive AABR screen is followed by a diagnostic audiological evaluation.[42]
- The TEOAE uses "frequency-specific measurements of peripheral auditory sensitivity. A transducer placed in the ear delivers the stimuli and records OAE for

[37] Ministry of Children and Family Development. *British Columbia's Early Years Annual Report 2013/2015*. 2015. Available at http://www2.gov.bc.ca/assets/gov/family-and-social-supports/child-care/bc_early_years_annual_report.pdf. Accessed December 2016.
[38] Wake M, Poulakis Z, Hughes E et al. Hearing impairment: a population study of age at diagnosis, severity, and language outcomes at 7–8 years. *Archives of Disease in Childhood*. 2005; 90(3): 238-44.
[39] Ching TC, Dillon H, Marnane V et al. Outcomes of early-and late-identified children at 3 years of age: findings from a prospective population-based study. *Ear and hearing*. 2013; 34(5): 535-52.
[40] Schroeder L, Petrou S, Kennedy C et al. The economic costs of congenital bilateral permanent childhood hearing impairment. *Pediatrics*. 2006; 117(4): 1101-12.
[41] Kemper A and Downs S. A cost-effectiveness analysis of newborn hearing screening strategies. *Archives of Pediatrics and Adolescent Medicine*. 2000; 154(5): 484-88.
[42] Keren R, Helfand M, Homer C et al. Projected cost-effectiveness of statewide universal newborn hearing screening. *Pediatrics*. 2002; 110(5): 855-63.

immediate computer processing. Multiple responses are averaged to get a specific repeatable waveform and a pass/refer result."[43]

- AABR screening uses a device to deliver "a rapid series of low-intensity clicks (usually at about 35 dB hearing level) through an insert or supra-aural earphone and record electrical activity from the scalp via electrodes/sensors. Averaged electrical waveforms are computed and automated statistical response detection algorithms evaluate the presence or absence of the ABR. AABR systems compare an infant's waveform with that of a template developed from normative ABR infant data and a pass/refer result is determined."[44]
- Most screening tests produce false-positive (in this case, an infant is diagnosed as having hearing impairment when they do not have hearing impairment) and false-negative (the hearing impairment is missed by screening but eventually diagnosed by other means) results. In their review for the 2008 USPSTF, Nelson et al assumed a prevalence of 115 per 100,000 population. For every true positive case, screening resulted in 7.48 false positive results and 0.09 false negative results.[45]
- In BC in 2013/14, a total of 658 infants had a positive screen, with 89 confirmed with a permanent hearing loss.[46] For every true positive case, screening resulted in 6.39 false positive results.
- In a study based on a hypothetical birth cohort of 80,000 infants, Keren and colleagues estimated that there would be 128 (0.160%) deaf infants in the cohort.[47] A total of 1,314 (1.643%) infants would fail the initial screening test. Of these 1,314 infants, 116 (0.145%) would be true positives and 1,198 (1.498%) would be false positives. This is a rate of 10.33 false positives for every true positive. Of the 1,314 infants, 1,015 (1.269%) would receive a diagnostic evaluation. The diagnostic evaluation would be positive for 97 (0.121%) infants of which 89 (0.111%) are true positive and 8 (0.010%) are false positives. The 8 false positive (non-deaf) infants would go on to receive unnecessary interventions for hearing loss.
- For modelling purposes we have assumed a false positive rate of 6.94 per true positive (the midpoint between the false positive rate of 7.48 per true positive identified in the Nelson et al study for the USPSTF[48] and the rate of 6.39 calculated for BC in 2013/14 noted above), with a range between 6.39 and 7.48 used in the sensitivity analysis (Table 1-1, row l).
- Even the diagnostic audiological evaluation after a positive TEOAE and AABR test is not guaranteed. Keren et al estimated that for every true positive identified through the final screening step (the diagnostic audiological evaluation), 0.09 false positive

[43] Schopflocher D, Corabian P, Eng K et al. *IHE Report: Screening Newborns for Hearing*. 2007. Institute of Health Economics. Available at http://www.ihe.ca/download/screening_newborns_for_hearing.pdf. Accessed December 2016.

[44] Schopflocher D, Corabian P, Eng K et al. *IHE Report: Screening Newborns for Hearing*. 2007. Institute of Health Economics. Available at http://www.ihe.ca/download/screening_newborns_for_hearing.pdf. Accessed December 2016.

[45] Nelson H, Bougatsos C and Nygren P. Universal newborn hearing screening: systematic review to update the 2001 US preventative services task force recommendation. *Pediatrics*. 2008; 122(1): e266-e76.

[46] Ministry of Children and Family Development. *British Columbia's Early Years Annual Report 2013/2015*. 2015. Available at http://www2.gov.bc.ca/assets/gov/family-and-social-supports/child-care/bc_early_years_annual_report.pdf. Accessed December 2016.

[47] Keren R, Helfand M, Homer C et al. Projected cost-effectiveness of statewide universal newborn hearing screening. *Pediatrics*. 2002; 110(5): 855-63.

[48] Nelson H, Bougatsos C and Nygren P. Universal newborn hearing screening: systematic review to update the 2001 US preventative services task force recommendation. *Pediatrics*. 2008; 122(1): e266-e76.

results would remain. False positive tests may cause parental anxiety, result in unnecessary follow-up tests and occasionally unnecessary interventions.[49, 50, 51, 52, 53, 54]

Age of Diagnosis and Age of Treatment Onset

- The goal of most UNHS programs are to identify and treat the hearing loss by 6 months of age or prior to language development. The implementation of UNHS programs has resulted in earlier identification and treatment. In the Trent Health Region in the UK, the median age at referral, confirmation and fitting of hearing aids, respectively, was 10.4, 18.1 and 26.3 months for births in the period between 1985 and 1993.[55] By 2012/13, UNHS in England had led to a median age at screen completion of 9 days, entry into follow-up at 30 days, confirmation of hearing loss at 49 days, referral to early intervention at 50 days and hearing-aid fitting at 82 days (or 2.7 months).[56] The establishment of UNHS in this region has resulted in a decrease in the mean age of hearing aid fitting of 23.6 months (from 26.2 to 2.7 months).
- In California, newborn hearing screening versus no newborn hearing screening was associated with the hearing loss being identified 24.6 months earlier, fitting of hearing aids 23.5 months earlier and early intervention 20.0 months earlier.[57]
- In Austria, UNHS has led to the identification of 69% of hearing impaired infants by 6 months of age, compared with just 6% in unscreened infants.[58]In the Netherlands, the mean age of cochlear implantation in children under age 5 was reduced from 2.4 to 1.2 years of age following the implementation of UNHS. The percentage of early (prior to one year of age) implanted children rose from 9% to 37%.[59]
- For modelling purposes, we have assumed that both the fitting of hearing aids and cochlear implantation occur 24 months (2 years) earlier in the presence of UNHS than in the absence of UNHS (Table 1-1, row n).

Outcomes in Language, Academics and Behaviour

- The 2008 USPSTF recommendation statement notes that "children with hearing loss have increased difficulties with verbal and nonverbal communication skills, increased behavioral problems, decreased psychosocial well-being, and lower educational

[49] Keren R, Helfand M, Homer C et al. Projected cost-effectiveness of statewide universal newborn hearing screening. *Pediatrics*. 2002; 110(5): 855-63.
[50] Weichbold V, Nekahm-Heis D and Welzl-Mueller K. Ten-year outcome of newborn hearing screening in Austria. *International Journal of Pediatric Otorhinolaryngology*. 2006; 70(2): 235-40.
[51] Tueller S and White K. Maternal anxiety associated with newborn hearing screening. *Journal of Early Hearing Detection and Intervention*. 2016; 1(1): 87-92.
[52] Thompson D, McPhillips H, Davis R et al. Universal newborn hearing screening: summary of evidence. *Journal of the American Medical Association*. 2001; 286(16): 2000-10.
[53] Poulakis Z, Barker M and Wake M. Six month impact of false positives in an Australian infant hearing screening programme. *Archives of Disease in Childhood*. 2003; 88(1): 20-4.
[54] van der Ploeg C, Lanting C, Kauffman-de Boer M et al. Examination of long-lasting parental concern after false-positive results of neonatal hearing screening. *Archives of Disease in Childhood*. 2008; 93(6): 508-11.
[55] Fortnum H and Davis A. Epidemiology of permanent childhood hearing impairment in Trent Region, 1985-1993. *British Journal of Audiology*. 1997; 31(6): 409-46.
[56] Wood SA, Sutton GJ and Davis AC. Performance and characteristics of the newborn hearing screening programme in England: the first seven years. *International Journal of Audiology*. 2015; 54(6): 353-8.
[57] Sininger Y, Martinez A, Eisenberg L et al. Newborn hearing screening speeds diagnosis and access to intervention by 20-25 months. *Journal of the American Academy of Audiology*. 2009; 20(1): 49-57.
[58] Weichbold V, Nekahm-Heis D and Welzl-Mueller K. Ten-year outcome of newborn hearing screening in Austria. *International Journal of Pediatric Otorhinolaryngology*. 2006; 70(2): 235-40.
[59] Lammers MJ, Jansen TT, Grolman W et al. The influence of newborn hearing screening on the age at cochlear implantation in children. *The Laryngoscope*. 2015; 125(4): 985-90.

attainment compared with children with normal hearing" and that "good-quality evidence shows that early detection improves language outcomes."[60]

- **The key question is whether initiating treatment early (by 6 months of age or prior to language development) improves longer term language and communication outcomes and/or other developmental outcomes compared to initiating treatment later (by 24 months of age).** To address this question, the 2008 USPSTF leaned heavily on the research by Kennedy et al.[61] Kennedy and co-authors studied 120 children with bilateral permanent hearing impairment (≥40dB hearing loss) born between 1992 and 1997 in southern England. Confirmation of hearing impairment by 9 months of age was associated with significantly higher scores for receptive language[62] at 7.9 years of age but not with higher scores for expressive language.[63] Kennedy et al. conclude that "early detection of childhood hearing impairment was associated with higher scores for language but not for speech in mid childhood." The USPSTF review suggested that the results were equivalent to an increase of 10-12 points in verbal IQ.[64]
- The USPSTF review placed less emphasis on the results of the study by Wake et al in Australia.[65] In an assessment of 89 children aged 7 to 8 years fitted with hearing aids for congenital hearing loss by the age of 4.5 years, they found that diagnosis at less than 12 months (after adjusting for the severity of hearing loss and non-verbal IQ) was **not** associated with better language outcomes.
- Several relevant studies have been published since the 2008 USPSTF review.
- Korver and colleagues assessed all infants diagnosed with permanent childhood hearing impairment between 2003 and 2005 in the Netherlands (n=434).[66] Traditionally, hearing tests for infants were done by play audiometry, also referred to as the distraction method. This had to be done in a soundproof booth and required three adults. The audiologist would be behind a one-way mirror assessing the baby's ability to turn toward a sound emitted from a speaker in the room. The second adult would use a visually appealing toy to distract the baby from the sound and bring the baby's gaze back to the centre. The third adult, usually a parent, would hold the baby in a sitting position. This type of hearing assessment is not possible with newborns, because they can't sit and they don't localize to sound by head turning. With the advent of portable devices that measure otoacoustic emissions, it became possible to conduct newborn hearing screening quickly and easily. Because all regions within the Netherlands replaced distraction hearing screening with UNHS at different rates between 2002 and 2006, 263 of the infants were identified by UNHS and received amplification at a mean of 15.7 months while 171 of the infants were identified by distraction hearing and received amplification at a mean of 29.2 months. At 3 to 5 years of age, infants identified through UNHS had improved gross motor

[60] US Preventive Services Task Force. Universal screening for hearing loss in newborns: US preventive services task force recommendation statement. *Pediatrics*. 2008; 122(1): 143-8.
[61] Kennedy C, McCann D, Campell M et al. Language ability after early detection of permanent childhood hearing impairment. *New England Journal of Medicine*. 2006; 354(20): 2131-41.
[62] The ability to understand information.
[63] The ability to put thoughts into words and sentences, in a way that makes sense and is grammatically accurate.
[64] Nelson H, Bougatsos C and Nygren P. Universal newborn hearing screening: systematic review to update the 2001 US preventative services task force recommendation. *Pediatrics*. 2008; 122(1): e266-e76.
[65] Wake M, Poulakis Z, Hughes E et al. Hearing impairment: a population study of age at diagnosis, severity, and language outcomes at 7–8 years. *Archives of Disease in Childhood*. 2005; 90(3): 238-44.
[66] Korver A, Konings S, Dekker F et al. Newborn hearing screening vs later hearing screening and developmental outcomes in children with permanent childhood hearing impairment. *Journal of the American Medical Association*. 2010; 304(15): 1701-8.

development, social development and quality of life (as identified by the parents). From a language perspective, they used sign language less frequently but no statistically significant differences were observed in either expressive language or language comprehension.

- In reviewing the results of the three population based studies by Kennedy et al, Wake et al and Korver et al, Ching and colleagues noted that "two of the three population studies revealed no benefit of early detection, and one reported a weak benefit for receptive but not expressive spoken language. These findings do not lend support to the benefit of early detection in improving outcomes."[67]
- Ching et al further hypothesized that early auditory intervention (i.e. by 6 months of age) may be associated with better longer term language outcomes. They studied a population cohort of 451 infants born between May 2002 and August 2007 in three states in Australia. Of this cohort, 255 (57%) were fitted with hearing aids before 6 months of age. The cohort also included 134 children with cochlear implants, with the median age of implantation at 15 months. They found that early hearing-aid fitting was not significantly associated with improved receptive and expressive language, speech production, social development or auditory functional performance at three years of age. In contrast, the age at which the first cochlear implant was switched on, specifically before or after 12 months of age, was positively associated with improved receptive and expressive language, speech production, social development and auditory functional performance at three years of age. The authors of the study conclude that "this implies that UNHS and early auditory intervention are important for improving outcomes of children with severe or profound hearing loss."[68]
- Pimperton et al followed a cohort of infants with bilateral permanent childhood hearing impairment (PCHI) through an average of 17.1 years in southern England.[69] Being born during the time period with UNHS **was not associated** with improved reading comprehension while confirmation of PCHI by nine months of age **was associated** with a significant improvement in reading comprehension. The study suffers from poor retention (49%) and a narrow focus on reading comprehension.
- ***The preponderance of the better evidence currently available suggests that the long term benefits associated with early vs. later initiation of treatment for hearing loss may be restricted to infants with profound hearing loss eligible for cochlear implantation.***

Quality of Life Measures

- Cochlear implantation is a relatively safe procedure but both surgical and medical complications do occur. In a review of 322 consecutive paediatric cochlear implantations (mean age of 5.7 years) between June of 1989 and December of 2006 in France, Venail et al observed 47 complications (14.6%).[70] Of these complications, 24 (7.5%) required reimplantation; 2 (0.62%) due to infection and 22 (6.8%) due to device failure. An additional 10 (3.1%) children had revision surgery without reimplantation. In 3 (0.93%) of these children, an infection was related to a skin

[67] Ching TC, Dillon H, Marnane V et al. Outcomes of early-and late-identified children at 3 years of age: findings from a prospective population-based study. *Ear and hearing*. 2013; 34(5): 535-52.
[68] Ching TC, Dillon H, Marnane V et al. Outcomes of early-and late-identified children at 3 years of age: findings from a prospective population-based study. *Ear and hearing*. 2013; 34(5): 535-52.
[69] Pimperton H, Blythe H, Kreppner J et al. The impact of universal newborn hearing screening on long-term literacy outcomes: a prospective cohort study. *Archives of Disease in Childhood*. 2016; 101(1): 9-15.
[70] Venail F, Sicard M, Piron J et al. Reliability and complications of 500 consecutive cochlear implantations. *Archives of Otolaryngology – Head & Neck Surgery*. 2008; 134(12): 1276-81.

disease that "could not be resolved by drainage, receiver relocation, antiseptic irrigation, and intravenous antibiotics". The device was removed and not reimplanted. Finally, 13 (4.0%) children had complications that were treated successfully with "conservative medical treatment".

- In another study of 434 consecutive paediatric cochlear implantations (mean age of 4.7 years) between January 1, 1990 and April 30, 2008 in France, Loundon et al observed 43 complications (9.9%).[71] Major complications occurred in 24 (5.5%) children while minor complication occurred in 19 (4.4%) children. Major complications were defined as "the need for surgery or the occurrence of an ear-related medical condition requiring a new admission and/or an extended hospital stay."
- For modelling purposes, we assumed that 7.5% (Table 1-1, row q) of children with a cochlear implant would have a major complication requiring reimplantation of their device (based on the 7.5% of children requiring a reimplantation in the Venail et al study[72]). These children would lose their QoL gain (see below) for a six month period. A further 3.1% (Table 1-1, row r) of children with a cochlear implant would have a major complication requiring device removal without reimplantation (based on the 3.1% of children who had revision surgery without reimplantation in the Venail et al study[73]). These children would lose their QoL gain (see below) for the remainder of their lives.
- In the Netherlands, quality of life (QoL) (as identified by the parents) was higher at 3 to 5 years of age by 0.053 (95% CI of 0.011 to 0.171) for children whose hearing impairment was diagnosed via UNHS.[74]
- Based on an assessment by 90 profoundly hearing impaired adults (30 eligible for a cochlear implant, 30 with a unilateral and 30 with a bilateral implant), QoL improved by 0.18 to 0.29 with a cochlear implant, depending on the measure of QoL used.[75] No significant difference in QoL was observed between unilateral and bilateral implants.
- Parent-reported change in quality of life following a cochlear implant in their profoundly deaf children (average age 7.5 years) improved by 0.22 to 0.39, depending on the measure of QoL used.[76]
- For modelling purposes, we have assumed that infants with moderate to severe hearing loss diagnosed early through UNHS would receive a benefit from early intervention (the fitting and use of hearing aids) for a 2 year period (Table 1-1, row n). This benefit results in an improved QoL of 0.066 (with a sensitivity analysis from 0.021 to 0.111) (Table 1-1, row r) for that 2 year period.[77] Infants with profound

[71] Loundon N, Blanchard M, Roger G et al. Medical and surgical complications in pediatric cochlear implantation. *Archives of Otolaryngology – Head & Neck Surgery*. 2010; 136(1): 12-5.
[72] Venail F, Sicard M, Piron J et al. Reliability and complications of 500 consecutive cochlear implantations. *Archives of Otolaryngology – Head & Neck Surgery*. 2008; 134(12): 1276-81.
[73] Venail F, Sicard M, Piron J et al. Reliability and complications of 500 consecutive cochlear implantations. *Archives of Otolaryngology – Head & Neck Surgery*. 2008; 134(12): 1276-81.
[74] Korver A, Konings S, Dekker F et al. Newborn hearing screening vs later hearing screening and developmental outcomes in children with permanent childhood hearing impairment. *Journal of the American Medical Association*. 2010; 304(15): 1701-8.
[75] Kuthubutheen J, Mittmann N, Amoodi H et al. The effect of different utility measures on the cost-effectiveness of bilateral cochlear implantation. *Laryngoscope*. 2015; 125(2): 442-7.
[76] Cheng A, Rubin H, Powe N et al. Cost-utility analysis of the cochlear implant in children. *Journal of the American Medical Association*. 2000; 284(7): 850-6.
[77] Korver A, Konings S, Dekker F et al. Newborn hearing screening vs later hearing screening and developmental outcomes in children with permanent childhood hearing impairment. *Journal of the American Medical Association*. 2010; 304(15): 1701-8.

hearing loss diagnosed early through UNHS would receive a benefit from early intervention (cochlear implantation) for the remainder of their lives. This benefit results in an improved QoL of 0.285 (with a sensitivity analysis from 0.180 to 0.390) (Table 1-1, row s) for an average of 82 years (Table 1-1, row o). The 0.285 is based on the midpoint between the low and high estimates of 0.180[78] and 0.390[79] found in the literature. Note that there is no available evidence that the benefit from early intervention with a cochlear implant will last for a lifetime and we have reduced this to age 21 in the sensitivity analysis. Model results (see below) are highly sensitive to this assumption.

- The life expectancy of an infant born in BC of 82 years (Table 1-1, row o) is based on life tables for 2009 to 2011 for BC.[80]

Based on these assumptions, the CPB associated with hearing screening in newborn infants is 312 QALYs (see Table 1-1, row w). The CPB of 312 represents the gap between no coverage and the 97.2% currently being achieved in BC.

[78] Kuthubutheen J, Mittmann N, Amoodi H et al. The effect of different utility measures on the cost-effectiveness of bilateral cochlear implantation. *Laryngoscope*. 2015; 125(2): 442-7.
[79] Cheng A, Rubin H, Powe N et al. Cost-utility analysis of the cochlear implant in children. *Journal of the American Medical Association*. 2000; 284(7): 850-6.
[80] See http://www.statcan.gc.ca/pub/84-537-x/2013005/tbl-eng.htm. Accessed January 2017.

Table 1-1: CPB of Screening for Hearing Loss in Newborn Infants in a Birth Cohort of 40,000			
Row Label	**Variable**	**Base Case**	**Data Source**
a	Infants in birth cohort	40,000	
b	Proportion screened	97.2%	√
c	Number screened	38,880	= (a * b)
d	Proportion with moderate to profound bilateral congenital hearing loss (>40dB in better ear)	0.092%	√
e	Number with moderate to profound bilateral congenital hearing loss	35.6	= (c * d)
f	Proportion with moderate bilateral congenital hearing loss (41-60 dB loss, in better ear)	41.1%	√
g	Proportion with severe bilateral congenital hearing loss (61-80 dB loss, in better ear)	20.5%	√
h	Proportion with profound bilateral congenital hearing loss (>80 dB loss, in better ear)	38.4%	√
i	Number with **moderate** hearing loss	14.6	= (e * f)
j	Number with **severe** hearing loss	7.3	= (e * g)
k	Number with **profound** hearing loss	13.7	= (e * h)
l	False positive results per true positive result	6.94	√
m	# of false positive results	246.7	= (e * l)
n	Years of hearing gained with UNHS	2.0	√
o	Years of life expectancy of a newborn infant in BC	82.0	√
p	Proportion of children with cochlear implants with major complications requiring reimplantation.	7.5%	√
q	Proportion of children with cochlear implants with major complications and the device is removed and not reimplanted.	3.1%	√
r	QoL gained with hearing aids	0.066	√
s	QoL gained with cochlear implantation	0.285	√
	Benefits		
t	QALYs gained in infants with moderate to severe hearing loss	2.9	= (i + j) * n * r
u	QALYs gained in infants with profound hearing loss	319.3	= k * o * s
	Harms		
v	QALYs lost due to cochlear implant complications	-10.0	= -(k * o * s * 0.5)-(k * q * o * s)
w	**Potential QALYs gained, Intervention screening from 0% to 97%**	**312**	= t + u + v

√ = Estimates from the literature

For our sensitivity analysis, we modified a number of major assumptions and recalculated the CPB as follows:

- Assume that the proportion of the population with moderate to profound bilateral congenital hearing loss (>40dB in the better ear) is reduced from 0.092% to 0.076% (Table 1-1, row d): CPB = 259.
- Assume that the proportion of the population with moderate to profound bilateral congenital hearing loss (>40dB in the better ear) is increased from 0.092% to 0.107% (Table 1-1, row d): CPB = 365.
- Assume that the ratio of false positive to true positive screening results is reduced from 6.94 to 6.39 (Table 1-1, row l): CPB = 312.
- Assume that the ratio of false positive to true positive screening results is increased from 6.94 to 7.48 (Table 1-1, row l): CPB = 312.
- Assume that the QoL gained with the use of hearing aids is reduced from 0.066 to 0.021 (Table 1-1, row r) and QoL gained with the use of a cochlear implant is reduced from 0.285 to 0.180 (Table 1-1, row s): CPB = 196.

- Assume that the QoL gained with the use of hearing aids is increased from 0.066 to 0.110 (Table 1-1, row r) and QoL gained with the use of a cochlear implant is increased from 0.285 to 0.390 (Table 1-1, row s): CPB = 428.
- Assume that the benefit from early intervention with a cochlear implant only lasts to age 21, rather than a lifetime: CPB = 82.

In estimating CE, we made the following assumptions:

- An estimated 25% of infants in BC require a second screening test because the first screening did not show a clear response from one or both ears (Table 1-2, row d).[81]
- The automated otoacoustic emissions (AOAE) test takes 10-15 minutes per baby. The AABR test takes 15-20 minutes per baby.[82]
- AABR screening usually takes about 20 minutes if your baby is quiet or sleeping.[83]
- The document *A Sound Start* estimates screening costs of $40 per infant in BC (in 2003/04 Canadian Dollars) based on a screening program that existed on Vancouver Island at that time. No information is provide with respect to what costs are included or how they are calculated. The $40 is roughly equivalent to $45 CAD in 2013.[84]
- Burke et al estimated the cost per infant screened to be £12.69 (in 2010 UK £; $23.71 in 2013 CAD)[85] using the AOAE test and £19.66 ($36.73 in 2013 CAD using the AABR test. They include staffing (based on an estimated screen time of 10 minutes) and supplies but not equipment costs. Supply costs are £1.12 ($2.09 in 2013 CAD) for AOAE and £7.16 ($13.38 in 2013 CAD for AABR.[86]
- *A Sound Start* estimates that 100 OAE and 31 AABR units are required in BC at a unit cost of $15,000 (in 2003/04 dollars) for the OAE and $25,000 for the AABR units. Annual maintenance, warranty and replacement costs are estimated at 20% of equipment purchase costs. The estimated number of units are based on screening 38,135 infants.[87]
- Current technology allows for both ABR and OAE screening using the same unit. The GN Otometrics MADSEN AccuScreen Model 8-04-13904,[88] for example, has a price of $18,554 (2016 USD) or $22,395 in Canadian funds.[89]

[81] BC Early Hearing Program. *Information Update*. 2009. Provincial Health Services Authority. Available at http://www.phsa.ca/Documents/bcehp_physiciansinfofall09.pdf. Accessed December 2016.
[82] Patel H and Feldman M. Universal newborn hearing screening. *Paediatrics and Child Health*. 2011; 16(5): 301-5.
[83] Provincial Health Services Authority. *Hearing Screening*. Available at http://www.phsa.ca/our-services/programs-services/bc-early-hearing-program/hearing-test. Accessed December 2016.
[84] The Early Hearing Detection and Intervention BC Steering Committee. *Hearing Screening for Every Baby – A Sound Start: A British Columbia Initiative for Early Hearing Detection and Intervention* 2004. Available at http://www.health.gov.bc.ca/library/publications/year/2004/ehdi_strategy_draft_july30_2004.pdf. Accessed December 2016.
[85] Campbell and Cochrane Economics Methods Group. *CCEMG – EPPI-Centre Cost Converter*. 2016. Available at https://eppi.ioe.ac.uk/costconversion/. Accessed December 2016.
[86] Burke M, Shenton R and Taylor M. The economics of screening infants at risk of hearing impairment: an international analysis. *International Journal of Pediatric Otorhinolaryngology*. 2012; 76(2): 212-18.
[87] The Early Hearing Detection and Intervention BC Steering Committee. *Hearing Screening for Every Baby – A Sound Start: A British Columbia Initiative for Early Hearing Detection and Intervention* 2004. Available at http://www.health.gov.bc.ca/library/publications/year/2004/ehdi_strategy_draft_july30_2004.pdf. Accessed December 2016.
[88] Medex Supply. *GN Otometrics MADSEN AccuScreen Screener with ABR and TE*. Available at https://www.medexsupply.com/personal-care-eye-ear-care-ear-care-gn-otometrics-madsen-accuscreen-screener-with-abr-and-te-x_pid-61343.html. Accessed December 2016.

- Keren et al assume that 71 OAE and 106 AABR units would be required to screen a birth cohort of 80,000 in the US. We estimated that 89 units would be needed for a birth cohort of 40,000.[90]
- Diane Bremner, director of the BC Early Hearing Program, estimates infrastructure support for the BC UNHS program of 2.3 FTE regional co-ordinators and 0.6 FTE administrative support. The annual wage for the regional coordinators (including benefits) is $105,500 and $64,230 for the administrative support for a total annual infrastructure support cost of $281,880.[91]
- **Screening costs** - For modelling purposes we have assumed a labour and supply cost per screen of $45 (Table 1-2, row f). We have increased this to $65 in the sensitivity analysis due to uncertainty regarding the actual average time required for the screening and uncertainty about whether the $45 includes full costs (e.g. benefits, calculation for non-productive time, etc.). Equipment costs of $11.50 per infant (Table 1-2, row g) screened is calculated based on 100 units at an average cost of $22,395 per unit times 20% for annual maintenance, warranty and replacement costs. Infrastructure support costs per infant screened are estimated at $7.25 ($281,880 / 38,800) (Table 1-2, row h).
- Program data for 2013/14 in BC indicates that 658 of 42,223 (1.56%) infants screened had a positive screen and will require an audiological assessment (Table 1-2, row j).[92]
- In BC, the audiological assessment includes taking a full case history, an initial otoscopy, auditory brainstem response (ABR) and (time permitting while the infant is asleep and depending on the ABR test results) otoacoustic emissions (OAE) and middle ear analysis (MEA).[93] It is not uncommon to require several appointments to obtain complete results, as infants do not always sleep long enough during one appointment for complete results.[94] For modelling purposes we have assumed an average of 1.4 appointments per assessment (Table 1-2, row l) and that each appointment will be approximately 2.5 hours in length (Table 1-2, row m).[95]
- **Audiological assessment costs** - To calculate labour costs per audiological assessment we used the BC 2016 hourly wage for a Grade II Audiologist (grid level 12) with three years of experience ($36.05). [96] To this we added 26% for benefits

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[89] Campbell and Cochrane Economics Methods Group. *CCEMG – EPPI-Centre Cost Converter*. 2016. Available at https://eppi.ioe.ac.uk/costconversion/. Accessed December 2016.

[90] Keren R, Helfand M, Homer C et al. Projected cost-effectiveness of statewide universal newborn hearing screening. *Pediatrics*. 2002; 110(5): 855-63.

[91] Diane Bremner. Director, BC Early Hearing Program. Personal communication, March 2017.

[92] Ministry of Children and Family Development. *British Columbia's Early Years Annual Report 2013/2015*. 2015. Available at http://www2.gov.bc.ca/assets/gov/family-and-social-supports/child-care/bc_early_years_annual_report.pdf. Accessed December 2016.

[93] BC Early Hearing Program. *Audiology Assessment Protocol: Version 4.1*. 2012. Provincial Health Services Authority. Available at http://www.phsa.ca/Documents/bcehpaudiologyassessmentprotocol.pdf. Accessed December 2016.

[94] BC Early Hearing Program. *Information Update*. 2009. Provincial Health Services Authority. Available at http://www.phsa.ca/Documents/bcehp_physiciansinfofall09.pdf. Accessed December 2016.

[95] The Early Hearing Detection and Intervention BC Steering Committee. *Hearing Screening for Every Baby – A Sound Start: A British Columbia Initiative for Early Hearing Detection and Intervention* 2004. Available at http://www.health.gov.bc.ca/library/publications/year/2004/ehdi_strategy_draft_july30_2004.pdf. Accessed December 2016.

[96] Health Sciences Association. *Health Science Professionals Provincial Agreement 2014-2019 Wage Schedules*. Available at http://www.hsabc.org/sites/default/files/uploads/2016%20HSPBA%20Wage%20Schedules%20updated%20with%20ESD%20Feb%201.pdf. Accessed December 2016.

(e.g. dental, medical, long term disability, etc.) and 40% for paid non-productive time (e.g. statutory holidays, vacation, education leave, sick time, coffee breaks, etc.) for an estimated hourly cost of $63.59 (Table 1-2, row o). A range of hourly rates from $57.91 to $72.27 was used in the sensitivity analysis to reflect from one to six years of experience.

- **Referral to an otolaryngologist** - Infants with confirmed PCHI diagnosed during the audiological assessment in BC are referred to an otolaryngologist.[97] The purpose of the medical evaluation is to determine the etiology of the hearing loss, to identify related physical conditions, and to provide recommendations for medical/surgical treatment (if applicable) as well as referral for other services.[98] We assumed a MSP fee of $92.48 for an otolaryngologist (i.e. consultation with pure tone audiogram #02511) (Table 1-2, row r) based on MSP billing data for 2013/14.[99] BC program data for 2013/14 indicates that 89 of 42,223 (0.21%) infants screened were confirmed with a permanent hearing loss, each requiring a referral to an otolaryngologist (Table 1-2, row q).[100]

- **Patient time and travel costs** - For patient time and travel costs, we assumed an hourly wage of $24.39 (the BC average in 2013)[101] plus 18% benefits for an average cost per hour of $28.78 (Table 1-2, row v). We assumed that each audiological assessment would take 3.5 hours of a patient's time (2.5 hours for the assessment and 1 hour travel time) and that each otolaryngologist consultation would take 2 hours of a patient's time. Because the vast majority of screening sessions take place before the mother and infant are discharged from the hospital, we did not estimate additional patient costs for the screening.

- **Additional costs of early intervention** – We have assumed that two years of hearing are gained with UNHS versus no UNHS (see above and Table 1-1, row n). This means that infants with early audiologic intervention will, on average, require a hearing aid or cochlear implant for two years longer than those diagnosed later.

- A 2013 survey of hearing aid prices in the US found a range from $1,657 to $2,958 with a weighted average of $2,363 (or $2,916 in Canadian dollars),[102] depending on whether an economy, mid-level or premium device was purchased. The breakdown was 19% economy, 44% mid-level and 30% premium.[103] A 2001 survey of hearing

[97] BC Early Hearing Program. *Audiology Assessment Protocol: Version 4.1*. 2012. Provincial Health Services Authority. Available at http://www.phsa.ca/Documents/bcehpaudiologyassessmentprotocol.pdf. Accessed December 2016.
[98] BC Early Hearing Program. *Medical Management of Infants and Young Children with Sensorineural Hearing Loss*. 2007. Provincial Health Services Authority. Available at http://www.phsa.ca/bc-early-hearing/Documents/BCEHP-medical-management-guidelines.pdf. Accessed December 2016.
[99] British Columbia Ministry of Health. *MSP Fee-For-Service Payment Analysis 2011/2012 - 2015/2016*. 2016. Available at http://www2.gov.bc.ca/assets/gov/health/practitioner-pro/medical-services-plan/ffs_complete.pdf. Accessed January 2017.
[100] Ministry of Children and Family Development. *British Columbia's Early Years Annual Report 2013/2015*. 2015. Available at http://www2.gov.bc.ca/assets/gov/family-and-social-supports/child-care/bc_early_years_annual_report.pdf. Accessed December 2016.
[101] Statistics Canada. *Average Hourly Wages of Employees by Selected Characteristics and Occupation, Unadjusted Data, by Province (Monthly) (British Columbia)*. 2013. Available at http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/labr69k-eng.htm. Accessed December 2013.
[102] Campbell and Cochrane Economics Methods Group. *CCEMG – EPPI-Centre Cost Converter*. 2016. Available at https://eppi.ioe.ac.uk/costconversion/. Accessed December 2016.
[103] Strom KE. HR 2013 dispenser survey: dispensing in the age of internet and big box retailers. *Hearing Review*. 2014; 21(4): 22-8.

aid prices in Canada found an average price of $1,575.[104] We have assumed an average cost of $2,916 per hearing aid and that the useful lifetime of a hearing aid is 5 years, largely due to upgrades in technology.[105] The additional two years of wearing hearing aids would thus cost $1,166 ($2,916 / 5 * 2). This is applied to the 22 infants identified with moderate to severe hearing loss (Table 1-1, rows I & j) (Table 1-2, row x).

- Between 2005 and 2014, there have been an average of 58.8 cochlear implantations in BC annually at an estimated cost of $27,599 (95% CI of $26,761 to $28,437) between 2009 and 2012. This includes the costs of the surgery, the implant device and assuring the proper functioning of the device. Not included are surgical fees which are estimated at $955.16 per surgery in BC.[106]
- A review of cochlear implantation in 18 children (average age of implantation = 6.7 years) in an Ontario hospital estimated assessment costs of $3,074 (in 2004 $), implantation costs of $33,584 (including device costs of $28,525), follow-up programming and assessment costs of $3,473 in year one, $1,390 in year two and $988 in year three. Rehabilitation costs, primarily for auditory-verbal therapy sessions, during the first three years post-implantation were $21,662.[107]
- In the UK, the ongoing routine maintenance costs for a paediatric cochlear implant are estimated at £4,716 in year 1, £3,640 in year 2 and £1,897 in each subsequent year (in 2005/06 UK £).[108] The ongoing costs of £1,897 per year translates into $3,945 in 2013 CAD.[109]
- We have assumed ongoing annual costs associated with cochlear implantation of $3,945. The additional two years of cochlear implantation would thus cost $7,890 ($3,945 * 2). This is applied to the 14 infants identified with profound hearing loss (Table 1-1, rows k) (Table 1-2, row y).
- The mean annual costs for health and social service use by 7-9 year old children with PCHI was £14,093 (in 2003 UK £ sterling) compared to £4,209 in children without hearing loss, a difference of £9,886. Exposure to a newborn screening program was associated with a decrease in total costs in the preceding year of £2,213 but this reduction is not statistically significant (95% CI: -£6,458 to £2,032; P = 0.30). Confirmation of PCHI by 9 months of age (vs. confirmation after 9 months of age) was also **not associated** with a significant decrease in annual costs (difference of £371; 95% CI: -£3,884 to £4,626; P = 0.86).[110]
- Discount rate of 3%.

[104] Children Youth and Social Developments Directorate. *Price Survey of Assistive Devices and Supports for Persons with Disabilities: Final Report*. 2003. Human Resources Development Canada. Available at http://publications.gc.ca/collections/Collection/RH63-1-585-11-03E.pdf. Accessed January 2017.

[105] Bond M, Mealing S, Anderson R et al. The effectiveness and cost-effectiveness of cochlear implants for severe to profound deafness in children and adults: a systematic review and economic model. *Health Technology Assessment*. 2009; 13(44): 1-330.

[106] Crowson MG, Chen JM and Tucci D. Provincial variation of cochlear implantation surgical volumes and cost in Canada. *Otolaryngology – Head & Neck Surgery*. 2016:

[107] Fitzpatrick E, Durieux-Smith A, Angus D et al. Economic evaluation of cochlear implants in children. *Journal of Speech-Language Pathology and Audiology*. 2006; 30(4): 215-23.

[108] Bond M, Mealing S, Anderson R et al. The effectiveness and cost-effectiveness of cochlear implants for severe to profound deafness in children and adults: a systematic review and economic model. *Health Technology Assessment*. 2009; 13(44): 1-330.

[109] Campbell and Cochrane Economics Methods Group. *CCEMG – EPPI-Centre Cost Converter*. 2016. Available at https://eppi.ioe.ac.uk/costconversion/. Accessed December 2016.

[110] Schroeder L, Petrou S, Kennedy C et al. The economic costs of congenital bilateral permanent childhood hearing impairment. *Pediatrics*. 2006; 117(4): 1101-12.

Based on these assumptions, the CE associated with hearing screening in newborn infants is $27,159 / QALY (Table 1-2, row ae).

Table 1-2: CE of Screening for Hearing Loss in Newborn Infants in a Birth Cohort of 40,000

Row Label	Variable	Base Case	Data Source
a	Infants in birth cohort	40,000	
b	Proportion screened	97.2%	Table 1-1, row b
c	Number screened	38,880	= a * b
d	Screens per infant	1.25	√
e	Total # of screens	48,600	= c * d
f	Labour and supply cost per screen	$45.00	√
g	Equipment cost per infant screened	$11.50	√
h	Infrastructure support costs per infant screened	$7.25	√
i	Estimated cost of screening	$2,916,000	= (e * f) + (g * c) + (h * c)
j	Proportion of 'positive' screens each requiring an audiological assessment	1.56%	√
k	Number of 'positive' screens each requiring an audiological assessment	607	= c * j
l	Hours required per audiological assessment	2.5	√
m	Number of sessions required per audiological assessment	1.4	√
n	Total audiologist hours required	2,123	= m * l * k
o	Cost per hour of an audiologist	$63.59	√
p	Cost of audiological assessments	$134,992	= n * o
q	Proportion of screened infants with a confirmed hearing loss	0.21%	√
r	Cost per otolaryngologist consultation	$92.48	√
s	Cost of otolaryngologist consultations	$7,579	= n * o
t	**Estimated cost of screening**	**$3,058,571**	= s + p + i
u	Patient time required (hours)	3,136	= (k * m * 3.5) + (c * q * 2)
v	Value of patient time (per hour)	$28.78	√
w	**Value of patient time and travel for intervention**	**$90,251**	= u * v
x	Additional costs of early intervention - hearing aids	$1,166	√
y	Additional costs of early intervention - cochlear implantation	$7,890	√
z	**Additional costs of early intervention**	**$133,336**	
	CE Calculation		
aa	Cost of intervention over lifetime of birth cohort	$3,282,158	= t + w + z
ab	QALYs saved	312	Table 1-1, row z
ac	Cost of intervention over lifetime of birth cohort (3% discount)	$3,282,158	Calculated
ad	QALYs saved (3% discount)	121	Calculated
ae	**CE ($/QALY saved)**	**$27,159**	= ac / ad

√ = Estimates from the literature

For our sensitivity analysis, we modified a number of major assumptions and recalculated the CE as follows:

- Assume that the proportion of the population with moderate to profound bilateral congenital hearing loss (>40dB in the better ear) is reduced from 0.092% to 0.076% (Table 1-1, row d): CE = $32,473.
- Assume that the proportion of the population with moderate to profound bilateral congenital hearing loss (>40dB in the better ear) is increased from 0.092% to 0.107% (Table 1-1, row d): CE = $23,385.

- Assume that the QoL gained with the use of hearing aids is reduced from 0.066 to 0.021 (Table 1-1, row s) and QoL gained with the use of a cochlear implant is reduced from 0.285 to 0.180 (Table 1-1, row t): CE = $43,511.
- Assume that the QoL gained with the use of hearing aids is increased from 0.066 to 0.110 (Table 1-1, row s) and QoL gained with the use of a cochlear implant is increased from 0.285 to 0.390 (Table 1-1, row t): CE = $19,746.
- Assume that the benefit from early intervention with a cochlear implant only lasts to age 21, rather than a lifetime: CE = $99,374.
- Assume that the labour and supply cost per screen is increased from $45 to $65 (Table 1-2, row f): CE = $35,202.
- Assume that the cost per hour for an audiologist is reduced from $63.59 to $57.91 (Table 1-2, row o): CE = $27,059.
- Assume that the cost per hour for an audiologist is increased from $63.59 to $72.27 (Table 1-2, row o): CE = $27,312.

Summary

Table 1-3: Screening for Hearing Loss in Newborn Infants in a Birth Cohort of 40,000
Summary

	Base Case	Range	
CPB (Potential QALYs Gained)			
Assume No Current Service			
3% Discount Rate	121	33	166
0% Discount Rate	312	82	428
CE ($/QALY) **including** patient* time costs			
3% Discount Rate	$27,159	$19,746	$99,374
0% Discount Rate	$10,516	$7,669	$40,040
CE ($/QALY) **excluding** patient time costs			
3% Discount Rate	$26,412	$19,203	$96,642
0% Discount Rate	$10,227	$7,459	$38,939

** In this model, patient time costs include the mother / infant pair. We have assumed no time costs for the original screening as the majority of this screening takes place in hospital shortly after birth. Time costs are included for follow-up audiological assessments to confirm a positive test result.*

Screening for Developmental Delay in Children

Canadian Task Force on Preventive Health Care (CTFPHC; 2016)[111]

We recommend against screening for developmental delay using standardized tools in children aged one to four years with no apparent signs of developmental delay and whose

[111] Canadian Task Force on Preventive Health Care. Recommendations on screening for developmental delay. *Canadian Medical Association Journal*. 2016; 188(8): 579-87.

parents and clinicians have no concerns about development (strong recommendation, low-quality evidence).

This recommendation applies to children aged one to four years without recognized signs of possible developmental delay and whose parents or clinicians have no concerns about development. These are children whose age-appropriate developmental milestones have been sequentially acquired for gross and fine motor, social, emotional, language and cognitive domains. Milestone ages should be based on the oldest age by which the skill should have been achieved.

This recommendation does not apply to children who present with signs, symptoms or parental concern that could indicate delayed development or to whose development is being closely monitored because of identified risk factors, such as premature birth or low birth weight.

The recommendation of the Lifetime Prevention Schedule Expert Committee with respect to screening for developmental delay in children is as follows:

"Do not screen the general population for developmental delay using standardized screening tests. However we support ongoing developmental surveillance as part of routine clinical practice. Developmental surveillance should include monitoring for problems in the 5 domains of developmental delay, eliciting parental concerns, considering risk factors and doing a follow-up evaluation of those who may be at increased risk."

See the following glossary for a definition of key terms.

Glossary

Clinical surveillance (for all services): ongoing monitoring by a knowledgeable professional using skilled observation, history and patient concerns as part of standard clinical practice.

Developmental surveillance is the ongoing monitoring of development, identification of risk factors and elicitation of parental concerns,[112] using the five domains (gross motor, fine motor [including self-care], communication [speech, language and nonverbal], cognitive and social-emotional) as part of good clinical practice.

Monitoring development is the same as developmental surveillance.

Surveillance may result in going to case finding.

Case finding is the identification of potential conditions in clients that are at increased risk of the condition. Within the clinical judgement of the clinician, it may involve assessment and the use of standardized tools.

Screening is the use of standardized tools to search for clinical conditions that do not show any apparent signs, and patients are not considered high risk.

Screening for developmental delay is the use of standardized tools to search for developmental delay among children that do not show any apparent signs of developmental delay, are not considered to be at high risk for having developmental delay, and whose caregivers or clinicians have no concerns about development.

[112] Canadian Task Force on Preventive Health Care. Recommendations on screening for developmental delay. *Canadian Medical Association Journal*. 2016; 188(8): 579-87.

Screening for Asymptomatic Disease or Risk Factors

Screening for Cardiovascular Disease Risk and Treatment with Statins

United States Preventive Services Task Force Recommendations (USPSTF; 2016)[113]

The USPSTF recommends initiating use of low- to moderate-dose statins in adults aged 40 to 75 years without a history of CVD who have 1 or more CVD risk factors (dyslipidemia, diabetes, hypertension, or smoking) and a calculated 10-year CVD event risk of 10% or greater. (B recommendation)

Identification of dyslipidemia and calculation of 10-year CVD event risk requires universal lipids screening in adults aged 40-74 years.

The USPSTF recommends using the ACC/AHA Pooled Cohort Equations to calculate the 10-year risk of CVD events. The calculator derived from these equations takes into account age, sex, race, cholesterol levels, blood pressure level, antihypertension treatment, presence of diabetes, and smoking status as risk factors.

Canadian Task Force on Preventive Health Care (CTFPHC; 1993)[114]

In 1993, the CTFPHC (then known as the Canadian Task Force on the Periodic Health Examination) concluded the following:

There is insufficient evidence for the inclusion or exclusion of universal screening for hyper-cholesterolemia in a periodic health examination. Nonetheless, case-finding through repeated measurements of the nonfasting blood total cholesterol level should be considered in men 30 to 59 years of age… (with) individual clinical judgement being exercised in all other circumstances. This selective form of case-finding stresses the importance of the link between the detection of hypercholesterolemia and the favourable effect of lowering the cholesterol level on the incidence rate of coronary heart disease (CHD) in this group. Cholesterol testing should be considered when other CHD risk factors are present such as smoking, hypertension, or diabetes mellitus, or when there is a strong family history of hypercholesterolemia or premature CHD.

The CTFPHC has not completed a recent update due to the review completed by the Canadian Cardiovascular Society (CCS) in 2016.[115] A number of the CCS recommendations, particularly those associated with screening and primary prevention, are highlighted below.

[113] Bibbins-Domingo K, Grossman D, Curry S et al. Statin use for the primary prevention of cardiovascular disease in adults: US Preventive Services Task Force recommendation statement. *Journal of the American Medical Association*. 2016; 316(19): 1997-2007.
[114] Canadian Task Force on the Periodic Health Examination. Periodic health examination, 1993 update: 2. lowering the blood total cholesterol level to prevent coronary heart disease. *Canadian Medical Association Journal*. 1993; 148(4): 521-37.
[115] Dr. Richard Birtwhistle, Member, Canadian Task Force on Preventive Health Care. Personal communication, January 25, 2017.

Canadian Cardiovascular Society (CCS; 2016)[116]

Screening

We recommend that a CV risk assessment be completed every 5 years for men and women aged 40 to 75 years using the modified FRS (Framingham Heart Study Risk Score) or CLEM (Cardiovascular Life Expectancy Model) to guide therapy to reduce major CV events. A risk assessment might also be completed whenever a patient's expected risk status changes. (Strong Recommendation; High Quality Evidence).

We recommend sharing the results of the risk assessment with the patient to support shared decision making and improve the likelihood that patients will reach lipid targets. (Strong Recommendation; High Quality Evidence).

Primary Prevention

We recommend management that does not include statin therapy for individuals at low risk (modified FRS < 10%) to decrease the risk of CVD events. (Strong Recommendation; High-Quality Evidence).

We recommend management that includes statin therapy for individuals at high risk (modified FRS ≥ 20%) to decrease the risk of CVD events. (Strong Recommendation; High-Quality Evidence).

We recommend management that includes statin therapy for individuals at IR (intermediate risk: modified FRS 10%-19%) with LDL-C ≥ 3.5 mmol/L to decrease the risk of CVD events. Statin therapy should also be considered for IR persons with LDL-C < 3.5 mmol/L but with apoB ≥ 1.2 g/L or non-HDL-C ≥ 4.3 mmol/L or in men 50 years of age and older and women 60 years of age and older with ≥ 1 CV risk factor. (Strong Recommendation; High-Quality Evidence).

Utilization of This Clinical Preventive Service

Currently in British Columbia

In 2013, a total of 2,089,025 individuals between the ages of 40 and 75 were living in BC (see Table 2-1).[117]

In 2006 (the latest year for which we were able to find this data), the proportion of BC's population using statins was as follows:[118]

- Ages 20-29 – 0.1%
- Ages 30-39 – 0.7%
- Ages 40-49 – 3.3%
- Ages 50-59 – 10.4%
- Ages 60-69 – 22.0%
- Ages 70-79 – 31.1%

It is important to try and determine how many of these statin users were receiving this treatment as a preventive maneuver.

[116] Anderson T, Gregiore J, Pearson G et al. 2016 Canadian Cardiovascular Society guidelines for the management of dyslipidemia for the prevention of cardiovascular disease in then adult. *Canadian Journal of Cardiology.* 2016; 32: 1263-82.

[117] See http://www.bcstats.gov.bc.ca/StatisticsBySubject/Demography/PopulationEstimates.aspx. Accessed January 2017.

[118] Morgan S, Cunningham C, Hanley G et al. *The British Columbia Rx Atlas, 2nd Edition (The British Columbia Prescription Drug Atlas)*. 2009. UBC Centre for Health Services and Policy Research. Available at https://open.library.ubc.ca/cIRcle/collections/47136/items/1.0048292. Accessed January 2017.

Recent research in Canada suggests that the majority of statin use is for individuals with pre-existing conditions such as diabetes that places them at a high risk of a CVD event.[119] Fortunately, this research by Hennessy and colleagues grouped Canadians into those at low risk (defined as a mean 10-year risk of a CVD event of less than 10%), intermediate risk (mean 10-year risk of a CVD event of 10%-19%) and high risk of CVD (pre-existing heart disease, diabetes, high-risk hypertension, chronic kidney disease). Based on this approach, 73.3% of Canadians ages 20-79 are at a low risk of CVD with an average 10-year risk of a CVD event of 2.9%. Of these individuals, 2.1% are receiving statin treatment. A further 9.0% of Canadians ages 20-79 are at an intermediate risk of CVD with an average 10-year risk of a CVD event of 14.0%. Of these individuals, just 14.9% are receiving statin treatment. Finally, 19.7% are at a high risk of CVD with an average 10-year risk of a CVD event of 27.9%. Of these individuals, 44.4% are receiving statin treatment.

We used this Canadian data to group the BC population ages 20-79 by CVD risk status. We then estimated the proportion of each age group by risk status using statins based on the estimated Canadian statin usage adjusted for actual BC statin usage (see above). Finally, we included only those ages 40-75 to reflect the age recommendations of the USPSTF (see Table 2-1).

In summary, of the 2,089,025 British Columbians between the ages of 40 and 75 in 2013, 14.3% (or 299,630) are estimated to be at an intermediate risk (mean 10-year risk of a CVD event of 10%-19%) while 30.9% (or 645,341) are estimated to be at a high risk (mean 10-year risk of a CVD event of ≥20%). This is the population eligible to use statins as a primary prevention maneuver. Of the eligible population at intermediate risk, an estimated 30,426 (or 10.2%) are currently using statins. Of the eligible population at high risk, an estimated 198,459 (or 30.8%) are currently using statins (see Table 2-1). An estimated total of 24.2% of intermediate to high risk individuals are currently using statins in BC.

Table 2-1: Estimated Number of BC Adults Ages 40-75 By CVD Risk Status and Statin Usage in 2013

Age Group	BC Pop in 2013	% Using Statins	# Using Statins	Estimated % by CVD Risk Status in Canada			Estimated # by CVD Risk Status in BC				Estimated # Taking Statins by CVD Risk Status in BC			
				Low	Int.	High	Low	Int.	High	Total	Low	Int.	High	Total
20-29	622,969	0.1%	623	51.9%	0.2%	1.8%	1,266,101	616	12,132	1,278,849	106	69	448	623
30-39	606,620	0.7%	4,246								722	468	3,056	4,246
40-49	651,889	3.3%	21,512	42.2%	46.8%	34.2%	1,029,469	144,112	230,517	1,404,099	3,659	2,373	15,480	21,512
50-59	694,199	10.4%	72,197								12,281	7,965	51,951	72,197
60-69	538,046	22.0%	118,370	5.9%	53.0%	64.0%	143,931	163,204	431,378	738,512	20,135	13,059	85,176	118,370
70-79	307,737	31.1%	95,706								16,280	10,558	68,868	95,706
Total	**3,421,460**	**9.1%**	**312,655**				**2,439,501**	**307,931**	**674,028**	**3,421,460**	**53,184**	**34,492**	**224,979**	**312,655**
40-75	2,089,025	13.2%	275,800				1,144,054	**299,630**	**645,341**	2,089,025	46,915	**30,426**	**198,459**	275,800
							54.8%	14.3%	30.9%	100.0%				

Best in the World

Statin usage has increased dramatically since the late 1990s. Based on data from 14 European countries, statin usage between 1997 and 2002 increased from 11 to 42 defined daily doses / 1,000 population, an average increase of 31% per year.[120,121] In Finland, the number of

[119] Hennessy D, Tanuseputro P, Tuna M et al. Population health impact of statin treatment in Canada. *Health Reports*. 2016; 27(1): 20-8.
[120] Walley T, Folino-Gallo P, Stephens P et al. Trends in prescribing and utilization of statins and other lipid lowering drugs across Europe 1997–2003. *British Journal of Clinical Pharmacology*. 2005; 60(5): 543-51.
[121] Walley T, Folino-Gallo P, Schwabe U et al. Variations and increase in use of statins across Europe: data from administrative databases. *British Medical Journal*. 2004; (7436): 385-6.

ongoing users of statins increased 4.6-fold between 1999 and 2008.[122] The proportion of the population age 40+ using statins in Denmark increased from 9.1% in 2005 to 18.7% in 2010.[123] In Canada, statin usage increased from 12,187 to 72,067 prescriptions / 100,000 population (+491%) from 1996 to 2006. Expenditures on statins per capita averaged $61.88 in Canada in 2006. BC had one of the lowest costs per capita ($44.53), second only to Saskatchewan ($36.17).[124]

While substantial data exists on trends in statin utilization, it is more challenging to find information on the proportion of individuals at intermediate risk (i.e. with a mean 10-year risk of a CVD event of 10%-19%) who use statins for primary prevention. In BC, we have estimated that 24.2% of individuals between the ages of 40 and 75 who are at intermediate or high risk are using statins, although we do not know what proportion are using them for primary prevention purposes (see Table 2-1). While not directly comparable, 17.7% of those using statins in Finland in 2008 had no clinical indication of CVD or diabetes.[125] In Denmark in 2010, asymptomatic users accounted for 33.5% of all statin users.[126]

A further challenge is the issue of long-term persistence with statin therapy. While individuals within clinical trials tend to have 90% adherence after one year, 85% after two years and 80% after three years, real world adherence is much lower at 60%, 45% and 40% after years one, two and three. After three years, rates of adherence tend to stabilize.[127,128,129,130]

For modelling purposes, after taking into account long-term persistence and rates in countries such as Denmark, we have assumed that as many as 30% of intermediate and high risk individuals may be willing to take statins over the longer term for primary prevention purposes (Table 2-3, row al). We have used a range of 25% to 40% in the sensitivity analysis.

Relevant British Columbia Population in 2013

There were an estimated 2,089,025 individuals between the ages of 40 and 75 living in BC in 2013. All of these individuals would have been eligible for screening to determine their 10-year CVD event risk. Of these 2,089,025 individuals, an estimated 944,971 (45.2%) were at an intermediate or high risk and would thus would have been eligible for using statins as a preventive maneuver (see Table 2-1).

[122] Rikala M, Huupponen R, Helin-Salmivaara A et al. Channelling of statin use towards low-risk population and patients with diabetes. *Basic & Clinical Pharmacology & Toxicology*. 2013; 113(3): 173-8.
[123] Kildemoes HW, Vass M, Hendriksen C et al. Statin utilization according to indication and age: a Danish cohort study on changing prescribing and purchasing behaviour. *Health Policy*. 2012; 108(2): 216-27.
[124] Jackevicius CA, Cox JL, Carreon D et al. Long-term trends in use of and expenditures for cardiovascular medications in Canada. *Canadian Medical Association Journal*. 2009; 181(1-2): E19-E28.
[125] Rikala M, Huupponen R, Helin-Salmivaara A et al. Channelling of statin use towards low-risk population and patients with diabetes. *Basic & Clinical Pharmacology & Toxicology*. 2013; 113(3): 173-8.
[126] Kildemoes HW, Vass M, Hendriksen C et al. Statin utilization according to indication and age: a Danish cohort study on changing prescribing and purchasing behaviour. *Health Policy*. 2012; 108(2): 216-27.
[127] Avorn J, Monette J, Lacour A et al. Persistence of use of lipid-lowering medications: a cross-national study. *Journal of the American Medical Association*. 1998; 279(18): 1458-62.
[128] Perreault S, Blais L, Dragomir A et al. Persistence and determinants of statin therapy among middle-aged patients free of cardiovascular disease. *European Journal of Clinical Pharmacology*. 2005; 61(9): 667-74.
[129] Helin-Salmivaara A, Lavikainen P, Korhonen M et al. Long-term persistence with statin therapy: a nationwide register study in Finland. *Clinical Therapeutics*. 2008; 30(1): 2228-40.
[130] Greving J, Visseren F, De Wit G et al. Statin treatment for primary prevention of vascular disease: whom to treat? cost-effectiveness analysis. *British Medical Journal*. 2011; 342(1): d1672.

Modelling CPB and CE

In this section, we will calculate the CPB and CE associated with universal screening for and initiating use of low- to moderate-dose statins in adults aged 40 to 75 years without a history of CVD, who have 1 or more CVD risk factors, and a calculated 10-year CVD event risk of 10% or greater.

In estimating CPB, we made the following assumptions:

- Based on BC life tables for 2009 to 2011,[131] there are a total of 1,289,887 life years lived between the ages of 40 and 74 in a BC birth cohort of 40,000 (see Table 2-2 and Table 2-3, row a), with 583,029 (45.2%) of these life years lived at an intermediate or high risk of CVD (see Table 2-1 and Table 2-3, row b). Of the 583,029 life years, an estimated 141,093 (24.2%) life years are intermediate or high risk years during which the individual is taking statins (see Table 2-1 and Table 2-3, row d).

Table 2-2: Deaths and Years of Life Lived and Lost Between the Ages of 40 and 74
in a British Columbia Birth Cohort of 40,000

Age Group	*Mean Survival Rate*		*Individuals in Birth Cohort*			*Life Years Lived*	*Deaths in Birth Cohort*		*Deaths due to* Cardiovascular Disease		*Deaths due to* Cerebrovascular Disease		*Life Years Lost*			
	Males	Females	Males	Females	Total		%	#	%	#	%	#	Life Expectancy	All Deaths	Cardio	Cerebro
35-39	0.977	0.987	19,548	19,744	39,293											
40-44	0.971	0.983	19,410	19,665	39,075	195,375	0.6%	218	5.9%	13	3.1%	7	42	9,061	535	281
45-49	0.961	0.977	19,218	19,547	38,765	193,826	0.8%	310	11.8%	37	3.8%	12	37	11,445	1,351	435
50-54	0.947	0.969	18,938	19,372	38,310	191,551	1.2%	455	11.8%	54	3.8%	17	32	14,707	1,735	559
55-59	0.926	0.955	18,519	19,108	37,627	188,136	1.8%	683	11.8%	81	3.8%	26	28	19,005	2,243	722
60-64	0.894	0.935	17,887	18,704	36,591	182,955	2.8%	1,036	11.8%	122	3.8%	39	24	24,353	2,874	925
65-69	0.847	0.904	16,935	18,074	35,009	175,045	4.5%	1,582	16.7%	264	6.7%	106	19	30,675	5,123	2,055
70-74	0.776	0.854	15,514	17,086	32,600	162,999	7.4%	2,409	16.7%	402	6.7%	161	16	37,485	6,260	2,512
Total						**1,289,887**		**6,693**	**14.5%**	**972**	**5.5%**	**369**		**146,730**	**20,119**	**7,489**

- Based on BC life tables for 2009 to 2011, a total of 6,693 deaths would be expected between the ages of 40 and 74 in a BC birth cohort of 40,000 (Table 2-3, row f).[132]
- Based on BC vital statistics data, 59 of 993 (5.9%) deaths in 25-44 year olds in 2011 were due to cardiovascular disease (ICD-10 codes I00-I51) and 31 of 993 (3.1%) deaths were due to cerebrovascular disease (ICD-10 codes I60-I69). In 45-64 year olds, 601 of 5,076 (11.8%) deaths were due to cardiovascular disease, and 191 of 5,076 (3.8%) deaths were due to cerebrovascular disease. In 65-84 year olds, 2,248 of 13,481 (16.7%) deaths were due to cardiovascular disease while 905 of 13,481 (6.7%) deaths were due to cerebrovascular disease.[133] This data was used to estimate that approximately 972 of the 6,693 deaths in the birth cohort would be due to cardiovascular disease and 369 due to cerebrovascular disease (see Table 2-2 and Table 2-3, rows g & h).
- In 2010 in the US, there were an estimated 720,000 new and recurrent heart attacks and 122,071 deaths from heart attack.[134] We assumed that 15% of the 720,000 heart

[131] See http://www.statcan.gc.ca/pub/84-537-x/2013005/tbl-eng.htm. Accessed January 2017.
[132] See http://www.statcan.gc.ca/pub/84-537-x/2013005/tbl-eng.htm. Accessed January 2017.
[133] British Columbia Vital Statistics Agency. *Selected Vital Statistics and Health Status Indicators: One Hundred and Fortieth Annual Report*. 2011. British Columbmia Ministry of Health. Available at http://www2.gov.bc.ca/assets/gov/birth-adoption-death-marriage-and-divorce/statistics-reports/annual-reports/2011/pdf/ann2011.pdf. Accessed January 2017.
[134] Go A, Mozaffarian D, Roger V et al. American Heart Association Statistical Update. *Circulation*. 2014; 129: 399-410.

attacks were recurrent heart attacks and calculated that there are 5.01 (612,000 / 122,071) nonfatal heart attacks per fatal heart attack in the US (Table 2-3, row k).

- In 2010 in the US, there were an estimated 795,000 new and recurrent strokes and 129,476 deaths from stroke.[135] We assumed that 15%[136] of the 795,000 strokes were recurrent strokes and calculated that there are 5.22 (675,750 / 129,476) nonfatal strokes per fatal stroke in the US (Table 2-3, row q).
- In Canada, an average of 16.8% of patients with an incident ischemic stroke die in hospital. This increases to 40.4% for patients with an incident haemorrhagic stroke. Eighty-two percent of incident strokes are ischemic and 18% are hemorrhagic.[137] We used this data to estimate that there are 4.55 nonfatal cerebrovascular events per fatal cerebrovascular event occurring.
- For modelling purposes, we assumed a ratio of 5.01 nonfatal cardiovascular events per fatal event (Table 2-3, row k) and a ratio of 5.22 nonfatal cerebrovascular events per fatal event (Table 2-3, row q).
- In the US, the mean age for a non-fatal heart attack is 65.0 (Table 2-3, row m), for a non-fatal ischemic stroke it is 68.4 and for a non-fatal haemorrhagic stroke it is 59.8 (the mean for all stroke is 67.1, Table 2-3, row s).[138]
- Based on BC life tables for 2009 to 2011, an individual aged 65 would be expected to live another 21.0 years (Table 2-3, row n) while an individual aged 67.1 years would be expected to live another 19.3 years (Table 2-3, row t).[139]
- Based on a survey of 39,751 individuals in the US, a heart attack reduces QoL by a mean of 16.9% (95% CI of 16.6% to 17.2%) (Table 2-3, row o) while a stroke reduces QoL by a mean of 20.4% (95% CI of 20.0% to 20.8%) (Table 2-3, row u).[140]
- In a systematic review for the USPSTF, Chou et al included 19 randomized control trials (RCTs) with 71,344 participants with a mean age between 51 and 66 years and an average of 4.1 years of follow-up. They conclude that statin therapy is associated with a decreased risk of the following: [141]
    - All-cause mortality (risk ratio [RR], 0.86 [95%CI, 0.80 to 0.93]) (Table 2-3, row y)
    - Cardiovascular mortality (RR, 0.69 [95%CI, 0.54 to 0.88])
    - Myocardial infarction (RR, 0.64 [95%CI, 0.57 to 0.71]) (Table 2-3, row ab)
    - Stroke (RR, 0.71 [95%CI, 0.62 to 0.82]) (Table 2-3, row ae)

[135] Go A, Mozaffarian D, Roger V et al. American Heart Association Statistical Update. *Circulation*. 2014; 129: 399-410.
[136] Krueger H, Lindsay P, Cote R et al. Cost avoidance associated with optimal stroke care in Canada. *Stroke*. 2012; 43(8): 2198-206.
[137] Krueger H, Lindsay P, Cote R et al. Cost avoidance associated with optimal stroke care in Canada. *Stroke*. 2012; 43(8): 2198-206.
[138] O'Sullivan A, Rubin J, Nyambose J et al. Cost estimation of cardiovascular disease events in the US. *PharmacoEconomics*. 2011; 29(8): 693-704.
[139] See http://www.statcan.gc.ca/pub/84-537-x/2013005/tbl-eng.htm. Accessed January 2017.
[140] Nyman J, Barleen N, Dowd B et al. Quality-of-life weights for the US population: self-reported health status and priority health conditions, by demographic characteristics. *Medical Care*. 2007; 45(7): 618-28.
[141] Chou R, Dana T, Blazina I et al. Statins for prevention of cardiovascular disease in adults: evidence report and systematic review for the US Preventive Services Task Force. *Journal of the American Medical Association*. 2016; 316(19): 2008-24.

- Based on the review for the USPSTF, statin therapy (when compared with a placebo) is not associated with an increased risk of withdrawal due to adverse events, serious adverse events, any cancer, fatal cancer, myalgias or elevated aminotransferase levels, rhabdomyolysis or myopathy, renal dysfunction, cognitive harms or new-onset diabetes following initiation of statin therapy.[142]
- The disutility of taking statins for cardiovascular prevention is estimated at 0.24% (95% CI of 0.17% to 0.33%) (Table 2-3, row ai).[143, 144, 145] The studies by Hutchins and colleagues also found that a significant proportion of respondents (9.5% using the willingness-to-pay approach, 57.5% using the standard gamble approach and 87% using the time trade-off approach) identified no disutility associated with taking one pill daily. In the sensitivity analysis, we therefore ranged the disutility from 0% to 0.33%.
- The review for the USPSTF by Chou et al has been criticized on several fronts. Redberg and Katz note that the review did not exclude studies that included patients taking statins for secondary prevention.[146] A 2010 review by Ray and colleagues, which included only studies of patients receiving statins for primary prevention, did not find a benefit of statin use and all-cause mortality (RR, 0.91; 95%CI of 0.83 to 1.01).[147] In addition, Redberg and Katz note that the most commonly reported side effect of muscle weakness and pain is not included in the review by Chou et al. Clinical trials suggest that statin myopathy occurs in 1-5% of patients while it may range as high as 20-30% based on observations in clinical practice.[148,149]
- In a 2016 review of the available evidence on the safety of statin therapy, Collins and colleagues note that "(t)he only serious adverse events that have been shown to be caused by long-term statin therapy - i.e., adverse effects of the statin are myopathy (defined as muscle pain or weakness combined with large increases in blood concentrations of creatine kinase), new-onset diabetes mellitus, and, probably, haemorrhagic stroke. Typically, treatment of 10 000 patients for 5 years with an effective regimen (e.g., atorvastatin 40 mg daily) would cause about 5 cases of myopathy (one of which might progress, if the statin therapy is not stopped, to the more severe condition of rhabdomyolysis), 50–100 new cases of diabetes, and 5–10 haemorrhagic strokes. However, any adverse impact of these side-effects on major vascular events has already been taken into account in the estimates of the absolute benefits. Statin therapy may cause symptomatic adverse events (e.g., muscle pain or weakness) in up to about 50–100 patients (i.e., 0·5–1·0% absolute harm) per 10 000

[142] Chou R, Dana T, Blazina I et al. Statins for prevention of cardiovascular disease in adults: evidence report and systematic review for the US Preventive Services Task Force. *Journal of the American Medical Association*. 2016; 316(19): 2008-24.
[143] Thompson A, Guthrie B and Payne K. Do pills have no ills? capturing the impact of direct treatment disutility. *PharmacoEconomics*. 2016; 34(4): 333-6.
[144] Hutchins R, Pignone M, Sheridan S et al. Quantifying the utility of taking pills for preventing adverse health outcomes: a cross-sectional survey. *British Medical Journal Open*. 2015; 5(e006505): 1-9.
[145] Hutchins R, Viera AJ, Sheridan SL et al. Quantifying the utility of taking pills for cardiovascular prevention. *Circulation: Cardiovascular Quality and Outcomes*. 2015; 8(2): 155-63.
[146] Redberg R and Katz M. Statins for primary prevention: the debate is intense, but the data are weak. *Journal of the American Medical Association*. 2016; 316(19): 1979-81.
[147] Ray K, Seshasai S, Erqou S et al. Statins and all-cause mortality in high-risk primary prevention: a meta-analysis of 11 randomized controlled trials involving 65 229 participants. *Archives of Internal Medicine*. 2010; 170(12): 1024-31.
[148] Magni P, Macchi C, Morlotti B et al. Risk identification and possible countermeasures for muscle adverse effects during statin therapy. *European Journal of Internal Medicine*. 2015; 26(2): 82-8.
[149] Thompson P. What to believe and do about statin-associated adverse effects. *Journal of the American Medical Association*. 2016; 316(19): 1969-70.

treated for 5 years. However, placebo-controlled randomised trials have shown definitively that almost all of the symptomatic adverse events that are attributed to statin therapy in routine practice are not actually caused by it (i.e., they represent misattribution)….It is, therefore, of concern that exaggerated claims about side-effect rates with statin therapy may be responsible for its under-use among individuals at increased risk of cardiovascular events. For, whereas the rare cases of myopathy and any muscle-related symptoms that are attributed to statin therapy generally resolve rapidly when treatment is stopped, the heart attacks or strokes that may occur if statin therapy is stopped unnecessarily can be devastating."[150]

- The controversy over side-effects continues, especially regarding muscle problems, as evidenced by the series of letters in the March 18, 2017 issue of *The Lancet* responding to the Collins et al review. In our sensitivity analysis, we have included an assumption that 5%[151,152] of patients taking statins would develop muscle problems and that their QoL would be reduced by 53%[153] during the estimated 3 months it would take for the statin withdrawal and rechallenge process[154,155] to determine that the muscle problem is associated with the use of statins.

Based on these assumptions, the CPB associated with universal screening for and initiating use of low- to moderate-dose statins in adults aged 40 to 75 years without a history of CVD who have 1 or more CVD risk factors and a calculated 10-year CVD event risk of 10% or greater is 3,510 QALYs (see Table 2-3, row as). This is based on the assumption of moving from no statin use in this intermediate or high risk cohort to 30% of this cohort initiating and sustaining statin use. If we assume that 15% of this cohort are currently using statins in BC, the difference between the 15% and 30% would translate into 1,755 QALYs.

[150] Collins R, Reith C, Emberson J et al. Interpretation of the evidence for the efficacy and safety of statin therapy. *The Lancet*. 2016; 388(10059): 2532-61.
[151] Parker B, Capizzi J, Grimaldi A et al. The effect of statins on skeletal muscle function. *Circulation*. 2013; 127(1): 96-103.
[152] Ganga H, Slim H and Thompson P. A systematic review of statin-induced muscle problems in clinical trials. *American Heart Journal*. 2014; 168(1): 6-15.
[153] Cham S, Evans M, Denenberg J et al. Statin-associated muscle-related adverse effects: a case series of 354 patients. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*. 2010; 30(6): 541-53.
[154] Jacobson T. Toward "pain-free" statin prescribing: clinical algorithm for diagnosis and management of myalgia. *Mayo Clinic Proceedings*. 2008; 83(6): 687-700.
[155] Ahmad Z. Statin intolerance. *American Journal of Cardiology*. 2014; 113(10): 1765-71.

Table 2-3: CPB of Universal Screening for and Initiating Use of Statins in Adults Aged 40 to 75 Years with an Intermediate or High Risk of CVD in a Birth Cohort of 40,000			
Label	**Variable**	**Base Case**	**Data Source**
	Estimated current status		
a	# of life years lived between the ages of 40-74 in birth cohort	1,289,887	Table 2-2
b	% of life years at intermediate or high risk	45.2%	Table 2-1
c	# of life years at intermediate or high risk	583,481	= (a * b)
d	% of life years at intermediate or high risk on statins	24.2%	√
e	# of life years at intermediate or high risk on statins	141,327	= (c * d)
f	Total deaths in birth cohort between the ages of 40-74	6,693	Table 2-2
g	Cardiovascular deaths in birth cohort between the ages of 40-74	972	Table 2-2
h	Cerebrovascular deaths in birth cohort between the ages of 40-74	369	Table 2-2
i	Life years lost due to total deaths	146,730	Table 2-2
j	Life years lost per death	21.9	= (i / f)
k	# of nonfatal cardiovascular events per fatal event	5.01	√
l	# of nonfatal cardiovascular events	4,872	= (g * k)
m	Average age of individual with a cardiovascular event	65.0	√
n	Life years lived with a nonfatal cardiovascular event	21.0	√
o	QoL reduction living with a nonfatal cardiovascular event	0.169	√
p	QALYs lost due to nonfatal cardiovascular events	17,291	= (l * n * o)
q	Ratio of nonfatal cerebrovascular events per fatal event	5.22	√
r	# of nonfatal cerebrovascular events	1,924	= (q * h)
s	Average age of individual with a cerebrovascular event	67.1	√
t	Life years lived with a nonfatal cerebrovascular event	19.3	√
u	QoL reduction living with a nonfatal cerebrovascular event	0.204	√
v	QALYs lost due to nonfatal cerebrovascular events	7,574	= (l * n * o)
	If 100% of intermediate or high risk individuals were on statins		
w	% of life years at intermediate or high risk on statins	100%	Assumed
x	# of life years at intermediate or high risk on statins	583,481	= (w * c)
y	% reduction in all cause mortality associated with statin use	14%	√
z	Deaths avoided with 100% statin usage	424	= (b * y * f)
aa	Life years gained with 100% statin usage	9,292	= (z * j)
ab	% reduction in cardiovascular events associated with statin use	36%	√
ac	Cardiovascular events avoided with 100% statin usage	793	= (b * ab * l)
ad	QALYs gained due to a reduction in nonfatal cardiovascular events associated with statin use	2,816	= (ac * n * o)
ae	% reduction in cerebrovascular events associated with statin use	29%	√
af	Cerebrovascular events avoided with 100% statin usage	252	= (b * ae * r)
ag	QALYs gained due to a reduction in nonfatal cerebrovascular events associated with statin use	994	= (af * t * u)
ah	Total QALYs gained if 100% of intermediate or high risk individuals were on statins	13,102	= (aa + ad + ag)
ai	Disutility per year associated with taking pills for cardiovascular prevention	-0.0024	√
aj	Disutility associated with taking pills for cardiovascular prevention	-1,400	= (x * ai)
ak	Proportion of individuals taking statins who experience muscle problems	0.0%	√
al	Length of time for muscle problems to be indentified and resolved (in years)	0.00	√
am	Disutilty per years associated with muscle problems	0.00	√
an	Disutility associated with muscle problems	0	Table 2-2 * b * ak * al * am
ao	Net QALYs gained if 100% of intermediate risk individuals were on statins	11,701	= (ah + aj + an)
	If 30% of intermediate risk individuals were on statins		
ap	% of life years at intermediate or high risk on statins	30%	√
	Benefits		
aq	QALYs gained if intermediate or high risk individuals were on statins	3,931	= (ah * ap)
	Harms		
ar	QALYs lost if intermediate or high risk individuals were on statins	-420	= (aj + an) * ap
as	**Potential QALYs gained, Screening & Intervention from 0% to 30%**	**3,510**	= (aq + ar)

√ = Estimates from the literature

For our sensitivity analysis, we modified a number of major assumptions and recalculated the CPB as follows:

- Assume that the QoL reduction associated with a stroke is reduced from 0.169 to 0.166 and the QoL reduction associated with a heart attack is reduced from 0.204 to 0.200 (Table 2-3, row o & u): CPB = 3,490.
- Assume that the QoL reduction associated with a stroke is increased from 0.169 to 0.172 and the QoL reduction associated with a heart attack is increased from 0.204 to 0.208 (Table 2-3, row o & u): CPB = 3,531.
- Assume that decreased risk of all-cause mortality associated with statin therapy is reduced from 14% to 7% (Table 2-3, row y), the decreased risk of a myocardial infarction is reduced from 36% to 29% (Table 2-3, row ab) and the decreased risk of stroke is reduced from 29% to 18% (Table 2-3, row ae): CPB = 1,839.
- Assume that decreased risk of all-cause mortality associated with statin therapy is increased from 14% to 20% (Table 2-3, row y), the decreased risk of a myocardial infarction is increased from 36% to 43% (Table 2-3, row ab) and the decreased risk of stroke is increased from 29% to 38% (Table 2-3, row ae): CPB = 4,962.
- Assume that the disutility per year associated with taking pills for cardiovascular prevention is reduced from -0.0024 to 0.0 (Table 2-3, row ai): CPB = 3,931.
- Assume that the disutility per year associated with taking pills for cardiovascular prevention is increased from -0.0024 to -0.0033 (Table 2-3, row ai): CPB = 3,353.
- Assume that the percent of life years at intermediate risk on statins is reduced from 30% to 25% (Table 2-3, row ap): CPB = 2,925.
- Assume that the percent of life years at intermediate risk on statins is increased from 30% to 40% (Table 2-3, row ap): CPB = 4,681.
- Assume that statin use is associated with muscle problems in 5% of users (Table 2-3, row ak): CPB = 3,477.

In estimating CE, we made the following assumptions:

Cost of Screening for CVD Risk

- The USPSTF recommends using the ACC/AHA Pooled Cohort Equations to calculate the 10-year risk of CVD events.[156]
- The *2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk* indicate that "it is reasonable to …estimate 10-year ASCVD risk every 4-6 years in adults 40-79 years of age who are free from ASCVD."[157]
- The ACC-AHA-ASCVD score, however, overestimates the 10-year ASCVD risk. The USPSTF recognizes this. "The reasons for this possible overestimation are still unclear. The Pooled Cohort Equations were derived from prospective cohorts of volunteers from studies conducted in the 1990s and may not be generalizable to a

[156] Bibbins-Domingo K, Grossman D, Curry S et al. Statin use for the primary prevention of cardiovascular disease in adults: US Preventive Services Task Force recommendation statement. *Journal of the American Medical Association*. 2016; 316(19): 1997-2007.

[157] Goff D, Lloyd-Jones D, Bennett G et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. *Circulation*. 2014; 135(2): S49-S74.

more contemporary and diverse patient population seen in current clinical practice."[158]

- Cook and Ridker, using the Women's Health Study, found that the ACC-AHA-ASCVD score overestimated the actual 10-year ASCVD risk in women by 43% to 90% in women, depending on their baseline risk.[159] DeFilippis and colleagues compared the performance of five risk assessment tools in a community-based, sex-balanced, multiethnic cohort. The ACC-AHA-ASCVD score overestimated the 10-year ASCVD risk by 78%. They found that the best risk assessment tool was the Reynolds Risk Score.[160] Rana and co-authors used a large contemporary, multi-ethnic population to assess the ACC-AHA-ASCVD score. They found that the ACC-AHA-ASCVD score substantially overestimated the actual 5-year ASCVD risk and that this overestimation was similar in both males and females and in four major ethnic groups (black, Asian/Pacific Islander, Hispanic and white).[161] In a commentary, Nissen notes that "the extent of miscalibration is substantial…. This is not a trivial problem…. Overestimation by the guideline risk equations would likely add millions of Americans to the roles of patients for whom statins are recommended."[162]
- The USPSTF notes that "because the Pooled Cohort Equations lack precision, the risk estimation tool should be used as a starting point to discuss with patients their desire for lifelong statin therapy."[163]
- For screening purposes, we have assumed that 54.8% of the BC population ages 40-75 is at a low risk for CVD (Table 2-4, row b), 14.3% is at an intermediate risk (Table 2-4, row d) and 30.9% is at a high risk (Table 2-4, row f) (see also Table 2-1).
- We have assumed that 70% of physicians would screen patients (Table 2-4, row j).
- We have assumed that the CVD screening would take place once every five years and modified this to once every two years in the sensitivity analysis (Table 2-4, row h).
- Completion of a risk assessment includes a clinician visit and a full lipid profile (total cholesterol [TC]; high density lipoprotein cholesterol [HDL-C]; low-density lipoprotein cholesterol [LDL-C], non-HDL-C; and triglycerides [TG]). The full lipid profile costs $21.31 (Table 2-4, row p).[164]

[158] Bibbins-Domingo K, Grossman D, Curry S et al. Statin use for the primary prevention of cardiovascular disease in adults: US Preventive Services Task Force recommendation statement. *Journal of the American Medical Association*. 2016; 316(19): 1997-2007.
[159] Cook NR and Ridker PM. Further insight into the cardiovascular risk calculator: the roles of statins, revascularizations, and underascertainment in the Women's Health Study. *Journal of the American Medical Association Internal Medicine*. 2014; 174(12): 1964-71.
[160] DeFilippis A, Young R, Carrubba C et al. An analysis of calibration and discrimination among multiple cardiovascular risk scores in a modern multiethnic cohort. *Annals of Internal Medicine*. 2015; 162(4): 266-75.
[161] Rana J, Tabada G, Solomon M et al. Accuracy of the atherosclerotic cardiovascular risk equation in a large contemporary, multiethnic population. *Journal of the American College of Cardiology*. 2016; 67(18): 2118-30.
[162] Nissen SE. Prevention guidelines: bad process, bad outcome. *Journal of the American Medical Association Internal Medicine*. 2014; 174(12): 1972-3.
[163] Bibbins-Domingo K, Grossman D, Curry S et al. Statin use for the primary prevention of cardiovascular disease in adults: US Preventive Services Task Force recommendation statement. *Journal of the American Medical Association*. 2016; 316(19): 1997-2007.
[164] Ministry of Health. *Cardiovascular Disease – Primary Prevention* 2014. Available at http://www2.gov.bc.ca/assets/gov/health/practitioner-pro/bc-guidelines/cvd.pdf. Accessed January 2017.

- We estimated the average cost of a visit to a General Practitioner to be $34.00 (Table 2-4, row n).[165] A follow-up phone call or email correspondence would be $15.00 (MSP fee G14079 - GP Telephone/Email Management Fee) (Table 2-4, row o).
- We assumed that a 10-minute office visit would be required for the initial screening. If the results indicate a low risk of CVD, then the follow-up would consist of a phone call to the patient. If the results indicate an intermediate or high risk of CVD, then a follow-up visit would be required to discuss the results and the possibility of taking statins (Table 2-4, row m).
- For patient time and travel costs, we assumed an hourly wage of $24.39 (the BC average in 2013)[166] plus 18% benefits for a cost per hour of $28.78 (Table 2-4, row t) applied to the estimated two hours of patient time required for a cost per clinician visit (Table 2-4, row s).

Costs of the Intervention

- We noted earlier that adherence with statin therapy in the real world is relatively poor, plateauing at about 40% after 3 years. Benner and colleagues found that early and frequent follow-up by physicians (including cholesterol retesting) improves long-term adherence by approximately 45% (OR 1.45; 95% CI of 1.34 – 1.55).[167]
- Brookhart et al., in a study based on BC data, found that a return to adherence after a period of nonadherence was associated with a return visit to the physician who initially prescribed the statin and a retest of cholesterol. "Our results suggest that continuity of care combined with increased follow-up and cholesterol testing could promote long-term adherence."[168]
- Pandya and colleagues estimated one additional physician visit per year for individuals in a disease-free state taking statins (i.e., for primary prevention).[169]
- The BC Guidelines for the primary prevention of cardiovascular disease suggest a follow-up physician visit 4-6 months after the initiation of statin which includes the measuring of lipid levels with a non-HDL-C or an apolipoprotein B (apoB) test, to assess patient adherence to statin therapy and any response to statin therapy, with further follow-ups as clinically indicated. The cost of a non-HDL-C test is $12.20 while that of an apoB test is $16.60.[170] For modelling purposes, we used the midpoint cost of these two tests (Table 2-4, row ac).
- For modelling purposes, we have assumed that 30% of intermediate and high risk patients would adhere to long-term statin therapy and modified this from 25% to 40% in the sensitivity analysis (Table 2-3, row al and Table 2-4, row v). We further

[165] Medical Services Commission. *Payment Schedule: Section 7 General Practice*. 2013. Available at http://www.health.gov.bc.ca/msp/infoprac/physbilling/payschedule/pdf/7-general-practice.pdf. Accessed December 2013.
[166] Statistics Canada. *Average Hourly Wages of Employees by Selected Characteristics and Occupation, Unadjusted Data, by Province (Monthly) (British Columbia)*. 2013. Available at http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/labr69k-eng.htm. Accessed December 2013.
[167] Benner J, Tierce J, Ballantyne C et al. Follow-up lipid tests and physician visits are associated with improved adherence to statin therapy. *PharmacoEconomics*. 2004; 22(3): 13-23.
[168] Brookhart M, Patrick A, Schneeweiss S et al. Physician follow-up and provider continuity are associated with long-term medication adherence: a study of the dynamics of statin use. *Archives of Internal Medicine*. 2007; 167(8): 847-52.
[169] Pandya A, Sy S, Cho S et al. Cost-effectiveness of 10-year risk thresholds for initiation of statin therapy for primary prevention of cardiovascular disease. *Journal of the American Medical Association*. 2015; 314(2): 142-50.
[170] Ministry of Health. *Cardiovascular Disease – Primary Prevention* 2014. Available at http://www2.gov.bc.ca/assets/gov/health/practitioner-pro/bc-guidelines/cvd.pdf. Accessed January 2017.

assumed that one annual follow-up office visit per year (Table 2-4, row z) is required for patients on statin therapy, that 100% of this office visit (Table 2-4, row aa) is allocated to discussing the statin therapy and that a follow-up lipid test (non-HDL-C or apoB) would be required once every five years (Table 2-4, row ab).

- In 2006, the average British Columbian using statins did so for approximately 290 days of the year at an estimated cost of $1.88 per day.[171]
- The estimated cost per day of treatment for cholesterol-lowering drugs in Canada (in 2012/13) is $0.96 for females and $0.85 for males.[172]
- The BC Reference Drug Pricing program fully covers the costs of two statins, atorvastatin and rosuvastatin.[173] The cost of 10mg rosuvastatin, taken by the majority of patients, is $95 plus four dispensing fees of $10 each, for an annual cost of $135 (Table 2-4, row x). The cost of 80mg atorvastatin is $206 plus four dispensing fees of $10 each, for an annual cost of $246. We have used this higher cost in the sensitivity analysis.

Costs Avoided due to the Intervention

- In the US, the cost estimates for the acute phase of a **fatal** myocardial infarction and a **fatal** stroke are $17,259 and $10,647 (in 2013 US$), respectively. We have converted these costs to equivalent Canadian health care costs by reducing costs by 29% to reflect excess health care prices in the US.[174,175] This value was then adjusted to 2013 Canadian dollars ($12,254 and $7,559) based on differences in the value of the two currencies that year.[176]
- For modelling purposes, we assumed that the acute care costs avoided per death avoided would be $10,962 (Table 2-4, row ai). This is based on the mix of cardiovascular and cerebrovascular deaths in the cohort (73% and 27%, respectively) (see Table 2-2) and the estimated cost of the acute care phase associated with a fatal myocardial infarction ($12,254) and a fatal stroke ($7,559).
- Dehmer and colleagues estimated the first year costs associated with a myocardial infarct to be $37,095 (in 2012 USD).[177] We have converted these costs to equivalent Canadian health care costs by reducing costs by 29% to reflect excess health care prices in the US.[178,179] This value was then adjusted to 2013 CAD based on

[171] Morgan S, Cunningham C, Hanley G et al. *The British Columbia Rx Atlas, 2nd Edition (The British Columbia Prescription Drug Atlas)*. 2009. UBC Centre for Health Services and Policy Research. Available at https://open.library.ubc.ca/cIRcle/collections/47136/items/1.0048292. Accessed January 2017.

[172] Morgan S, Smolina K, Mooney D et al. *The Canadian Rx Atlas, 3rd Edition (The Canadian Prescription Drug Atlas)*. 2013. UBC Centre for Health Services and Policy Research. Available at https://open.library.ubc.ca/media/stream/pdf/47136/1.0048514/1. Accessed December 2016.

[173] See BC *Reference Drug Program*. Available online at http://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/pharmacare/prescribers/reference-drug-program. Accessed March 2017.

[174] Anderson GF, Reinhardt UE, Hussey PS et al. It's the prices, stupid: why the United States is so different from other countries. *Health Affairs*. 2003; 22(3): 89-105.

[175] Reinhardt U. *Why Does US Health Care Cost So Much? (Part I)*. 2008. Available at https://economix.blogs.nytimes.com/2008/11/14/why-does-us-health-care-cost-so-much-part-i/. Accessed January 2017.

[176] The US and Canadian dollars were roughly on par during 2013. See http://www.bankofcanada.ca/rates/exchange/10-year-converter/. Accessed January, 2017.

[177] Dehmer S, Maciosek M, LaFrance A et al. Health benefits and cost-effectiveness of asymptomatic screening for hypertension and high cholesterol and aspirin counseling for primary prevention. *The Annals of Family Medicine*. 2017; 15(1): 23-36.

[178] Anderson GF, Reinhardt UE, Hussey PS et al. It's the prices, stupid: why the United States is so different from other countries. *Health Affairs*. 2003; 22(3): 89-105.

differences in the value of the two currencies that year (see below) for an estimated cost of $26,337 (Table 2-4, row aj).[180]

- Dehmer and colleagues estimated the first year costs associated with a stroke to be $18,192 (in 2012 USD).[181] We have converted these costs to equivalent Canadian health care costs by reducing costs by 29% to reflect excess health care prices in the US.[182,183] This value was then adjusted to 2013 CAD based on differences in the value of the two currencies that year (see below) for an estimated cost of $12,196.[184]
- Gloede and coauthors in Australia estimated the first year costs associated with an ischemic stroke to be $30,110 (in 2010 AUD) while costs associated with a haemorrhagic stroke were $17,767.[185] Based on a mix of 85% ischemic strokes,[186] the weighted cost would be $28,258. We converted this cost to 2013 CAD ($24,947).[187]
- For modelling purposes, we used the midpoint between $12,196 and $24,947 in the base case ($18,571, Table 2-4, row ak) and the extremes in the sensitivity analysis.
- Dehmer and colleagues estimated the ongoing annual costs following a myocardial infarct to be $2,490 (in 2012 USD).[188] We have converted these costs to equivalent Canadian health care costs by reducing costs by 29% to reflect excess health care prices in the US.[189,190] This value was then adjusted to 2013 CAD based on differences in the value of the two currencies that year (see below) for an estimated cost of $1,768 (Table 2-4, row am).[191]

[179] Reinhardt U. *Why Does US Health Care Cost So Much? (Part I)*. 2008. Available at https://economix.blogs.nytimes.com/2008/11/14/why-does-us-health-care-cost-so-much-part-i/. Accessed January 2017.
[180] The US and Canadian dollars were roughly on par during 2012. See http://www.bankofcanada.ca/rates/exchange/10-year-converter/. Accessed January, 2017.
[181] Dehmer S, Maciosek M, LaFrance A et al. Health benefits and cost-effectiveness of asymptomatic screening for hypertension and high cholesterol and aspirin counseling for primary prevention. *The Annals of Family Medicine*. 2017; 15(1): 23-36.
[182] Anderson GF, Reinhardt UE, Hussey PS et al. It's the prices, stupid: why the United States is so different from other countries. *Health Affairs*. 2003; 22(3): 89-105.
[183] Reinhardt U. *Why Does US Health Care Cost So Much? (Part I)*. 2008. Available at https://economix.blogs.nytimes.com/2008/11/14/why-does-us-health-care-cost-so-much-part-i/. Accessed January 2017.
[184] The US and Canadian dollars were roughly on par during 2012. See http://www.bankofcanada.ca/rates/exchange/10-year-converter/. Accessed January, 2017.
[185] Gloede T, Halbach S, Thrift A et al. Long-term costs of stroke using 10-year longitudinal data from the North East Melbourne Stroke Incidence Study. *Stroke*. 2014: 1-8.
[186] Krueger H, Lindsay P, Cote R et al. Cost avoidance associated with optimal stroke care in Canada. *Stroke*. 2012; 43(8): 2198-206.
[187] Campbell and Cochrane Economics Methods Group. *CCEMG – EPPI-Centre Cost Converter*. 2016. Available at https://eppi.ioe.ac.uk/costconversion/. Accessed December 2016.
[188] Dehmer S, Maciosek M, LaFrance A et al. Health benefits and cost-effectiveness of asymptomatic screening for hypertension and high cholesterol and aspirin counseling for primary prevention. *The Annals of Family Medicine*. 2017; 15(1): 23-36.
[189] Anderson GF, Reinhardt UE, Hussey PS et al. It's the prices, stupid: why the United States is so different from other countries. *Health Affairs*. 2003; 22(3): 89-105.
[190] Reinhardt U. *Why Does US Health Care Cost So Much? (Part I)*. 2008. Available at https://economix.blogs.nytimes.com/2008/11/14/why-does-us-health-care-cost-so-much-part-i/. Accessed January 2017.
[191] The US and Canadian dollars were roughly on par during 2012. See http://www.bankofcanada.ca/rates/exchange/10-year-converter/. Accessed January, 2017.

- Dehmer and colleagues estimated the ongoing annual costs following a stroke to be $5,389 (in 2012 USD).[192] We have converted these costs to equivalent Canadian health care costs by reducing costs by 29% to reflect excess health care prices in the US.[193,194] This value was then adjusted to 2013 CAD based on differences in the value of the two currencies that year (see below) for an estimated cost of $3,826.[195]
- Gloede and coauthors in Australia estimated the ongoing annual costs (including informal care and out-of-pocket costs) associated with an ischemic stroke to be $7,996 (in 2010 AUD) while costs associated with a haemorrhagic stroke were $10,251.[196] Based on a mix of 85% ischemic strokes,[197] the weighted cost would be $8,335. We converted this cost to 2013 CAD ($7,358).[198]
- For modelling purposes, we used the midpoint between $3,826 and $7,358 in the base case ($5,592, Table 2-4, row an) and the extremes in the sensitivity analysis.
- Discount rate of 3%.

Based on these assumptions, the CE associated with universal screening for and initiating use of low- to moderate-dose statins in adults aged 40 to 75 years without a history of CVD, who have 1 or more CVD risk factors, and a calculated 10-year CVD event risk of 10% or greater is $20,440 / QALY (Table 2-4, row ax).

[192] Dehmer S, Maciosek M, LaFrance A et al. Health benefits and cost-effectiveness of asymptomatic screening for hypertension and high cholesterol and aspirin counseling for primary prevention. *The Annals of Family Medicine*. 2017; 15(1): 23-36.
[193] Anderson GF, Reinhardt UE, Hussey PS et al. It's the prices, stupid: why the United States is so different from other countries. *Health Affairs*. 2003; 22(3): 89-105.
[194] Reinhardt U. *Why Does US Health Care Cost So Much? (Part I)*. 2008. Available at https://economix.blogs.nytimes.com/2008/11/14/why-does-us-health-care-cost-so-much-part-i/. Accessed January 2017.
[195] The US and Canadian dollars were roughly on par during 2012. See http://www.bankofcanada.ca/rates/exchange/10-year-converter/. Accessed January, 2017.
[196] Gloede T, Halbach S, Thrift A et al. Long-term costs of stroke using 10-year longitudinal data from the North East Melbourne Stroke Incidence Study. *Stroke*. 2014: 1-8.
[197] Krueger H, Lindsay P, Cote R et al. Cost avoidance associated with optimal stroke care in Canada. *Stroke*. 2012; 43(8): 2198-206.
[198] Campbell and Cochrane Economics Methods Group. *CCEMG – EPPI-Centre Cost Converter*. 2016. Available at https://eppi.ioe.ac.uk/costconversion/. Accessed December 2016.

Table 2-4: CE of Universal Screening for and Initiating Use of Statins in Adults Aged 40 to 75 Years with an Intermediate or High Risk of CVD in a Birth Cohort of 40,000			
Row Label	**Variable**	**Base Case**	**Data Source**
a	# of life years lived between the ages of 40-74 in birth cohort	1,289,887	Table 2-2
b	% of life years at low risk	54.8%	Table 2-1
c	# of life years at low risk	706,406	= (a * b)
d	% of life years at intermediate risk	14.3%	Table 2-1
e	# of life years at intermediate risk	185,009	= (a * d)
f	% of life years at high risk	30.9%	Table 2-1
g	# of life years at high risk	398,472	= (a * f)
h	Annual frequency of screening	0.20	√
i	Potential screens with 100% adherence	257,977	= (c + g) * h
j	Adherence with offers to receive screening	70%	Assumed
k	Total # of screens in birth cohort	180,584	= (i * j)
	Estimated cost of screening		
l	Number of office visits associated with screening - low risk	1.0	Assumed
m	Number of office visits associated with screening - medium or high risk	2.0	Assumed
n	Cost of 10-minute office visit	$34.00	√
o	Cost of a follow-up phone call	$15.00	√
p	Cost to measure cholesterol	$21.31	√
q	Health care costs of screening - low risk	$6,953,441	= (k * b) * l * (n + o + p)
r	Health care costs of screening - intermediate and high risk	$7,295,495	= ((d + f) * k * m)*(n + (p/2))
s	Patient time required / office visit (hours)	2.0	√
t	Value of patient time (per hour)	$28.78	√
u	Value of patient time and travel for screening	$10,394,425	
	Estimated cost of intervention		
v	Adherence with long-term statin therapy in intermediate and high risk cohort	30%	Table 2-3, row al
w	Years on statin therapy	175,044	= (e + g) * v
x	Cost of statin therapy / year	$135.00	√
y	Cost of statin therapy	$23,630,975	= (w * x)
z	# of follow-up office visits per year re: statin therapy	1.0	√
aa	Portion of 10-minute office visit for follow-up re: statin therapy	100%	Assumed
ab	# of lab tests (non-HDL-C or apoB) per year re: statin therapy	0.2	Assumed
ac	Cost per lab test	$14.40	√
ad	Follow-up costs	$6,455,632	= (w * z * aa * p) + (w * ab * ac)
ae	Value of patient time and travel for intervention	$10,075,547	= (w * z * m * l)
	Estimated costs avoided due to intervention		
af	# of deaths avoided	127.2	Table 2-3, row z * v
ag	# of nonfatal cardiovascular events avoided	238.0	Table 2-3, row ac * v
ah	# of nonfatal cerebrovascular events avoided	75.7	Table 2-3, row af * v
ai	Acute care costs avoided per avoided death	-$10,962	√
aj	First year costs avoided per nonfatal cardiovascular event avoided	-$26,337	√
ak	First year costs avoided per nonfatal cerebrovascular events avoided	-$18,571	√
al	Acute care costs avoided	-$9,068,634	= (af * ai) + (ag * aj) + (ah * ak)
am	Post-first-year annual costs avoided for nonfatal cardiovascular events avoided	-$1,768	√
an	Post-first-year annual costs avoided for nonfatal cerebrovascular events avoided	-$5,592	√
ao	Post-first-year costs avoided for nonfatal cardiovascular events avoided	-$8,837,233	= ag * Table 2-3, row n * am
ap	Post-first-year costs avoided for nonfatal cerebrovascular events avoided	-$8,171,072	= ah * Table 2-3, row t * an
aq	Costs avoided due to intervention	-$26,076,939	= al + ao + ap
	CE Calculation		
ar	Cost of intervention over lifetime of birth cohort	$64,805,516	= q + r + u + y + ad + ae
as	Costs avoided due to intervention over lifetime of birth cohort	-$26,076,939	= aq
at	QALYs saved	3,510	Table 2-3, row ao
au	Cost of intervention over lifetime of birth cohort (3% discount)	$40,480,441	Calculated
av	Costs avoided due to intervention over lifetime of birth cohort (3% discount)	-$10,790,348	Calculated
aw	QALYs saved (3% discount)	1,453	Calculated
ax	**CE ($/QALY saved)**	**$20,440**	= (au + av) / aw

√ = Estimates from the literature

For our sensitivity analysis, we modified a number of major assumptions and recalculated the CE as follows:

- Assume that decreased risk of all-cause mortality associated with statin therapy is reduced from 14% to 7% (Table 2-3, row y), the decreased risk of a myocardial infarction is reduced from 36% to 29% (Table 2-3, row ab) and the decreased risk of stroke is reduced from 29% to 18% (Table 2-3, row ae): CE = $42,963.
- Assume that decreased risk of all-cause mortality associated with statin therapy is increased from 14% to 20% (Table 2-3, row y), the decreased risk of a myocardial infarction is increased from 36% to 43% (Table 2-3, row ab) and the decreased risk of stroke is increased from 29% to 38% (Table 2-3, row ae): CE = $13,149.
- Assume that the disutility per year associated with taking pills for cardiovascular prevention is reduced from -0.0024 to 0.0 (Table 2-3, row ai): CE = $18,255.
- Assume that the disutility per year associated with taking pills for cardiovascular prevention is increased from -0.0024 to -0.0033 (Table 2-3, row ai): CE = $21,400.
- Assume that the percent of life years at intermediate or high risk on statins is reduced from 30% to 25% (Table 2-3, row ap): CE = $22,559.
- Assume that the percent of life years at intermediate or high risk on statins is increased from 30% to 40% (Table 2-3, row ap): CE = $17,790.
- Assume that statin use is associated with muscle problems in 5% of users (Table 2-3, row ak): CE = $20,635.
- Assume that the annual frequency of screening is increased from once every five years to once every two years (Table 2-4, row h): CE = $36,336.
- Assume that the cost of statin therapy in increased from $135 per year to $246 per year (Table 2-4, row x): CE = $28,795.
- Assume that the first-year costs avoided following a nonfatal cerebrovascular are decreased from $18,571 to $12,196 (Table 2-4, row ak): CE = $20,577.
- Assume that the first-year costs avoided following a nonfatal cerebrovascular are increased from $18,571 to $24,947 (Table 2-4, row ak): CE = $20,302.
- Assume that the post-first-year annual costs avoided for nonfatal cerebrovascular events avoided are decreased from $5,592 to $3,826 (Table 2-4, row an): CE = $21,175.
- Assume that the post-first-year annual costs avoided for nonfatal cerebrovascular events avoided are increased from $5,592 to $7,358 (Table 2-4, row an): CE = $19,705.

Summary

Table 2-5: Universal Screening for and Initiating Use of Statins in Adults aged 40 to 75 years with an Intermediate or High Risk of CVD in a Birth Cohort of 40,000

Summary

	Base Case	Range	
CPB (Potential QALYs Gained)			
Gap between No Service and 'Best in the World' (30%)			
3% Discount Rate	1,453	761	2,053
0% Discount Rate	3,510	1,839	4,962
Gap between B.C. Current (15%) and 'Best in the World' (30%)			
3% Discount Rate	727	381	1,027
0% Discount Rate	1,755	920	2,481
CE ($/QALY) **including** patient time costs			
3% Discount Rate	$20,440	$13,149	$42,963
0% Discount Rate	$11,033	$6,494	$25,008
CE ($/QALY) **excluding** patient time costs			
3% Discount Rate	$11,637	$6,922	$26,162
0% Discount Rate	$5,201	$2,368	$13,878

Preventive Medication / Devices

Routine Aspirin Use for the Prevention of Cardiovascular Disease and Colorectal Cancer

Background

In 2007, the USPSTF recommended "against the routine use of aspirin… to prevent colorectal cancer in individuals at average risk for colorectal cancer" with a D recommendation.[199] In 2009, the USPSTF recommended "the use of aspirin for men age 45 to 79 years when the potential benefit due to a reduction in myocardial infarctions outweighs the potential harm due to an increase in gastrointestinal hemorrhage". The USPSTF also recommended "the use of aspirin for women age 55 to 79 years when the potential benefit of a reduction in ischemic strokes outweighs the potential harm of an increase in gastrointestinal hemorrhage". Both of these 2009 recommendations were given an 'A'.[200]

In a 2014 update of the BC LPS, members of the Lifetime Prevention Schedule Expert Committee (LPSEC) reviewed key research that had been published since the 2009 USPSTF recommendations[201,202,203] calling into question the clinical effectiveness of low-dose aspirin in primary prevention.[204,205,206] A major concern of this new research was that the evidence used for the 2009 USPSTF recommendations appeared to overestimate the benefits of the use of aspirin in primary prevention (e.g. a reduction in cardiovascular disease) and to underestimate the harms (e.g. gastrointestinal bleeding and hemorrhagic stroke). Based on this updated evidence on clinical effectiveness, the LPSEC found that the routine use of low-dose aspirin in primary prevention no longer passed the initial test for inclusion on the BC LPS, namely that the maneuver is not clinically effective (i.e. benefits do not significantly outweigh harms).[207]

In the process of updating both their 2007 and 2009 recommendation on the routine use of aspirin to prevent colorectal cancer and cardiovascular diseases, the USPSTF commissioned three systematic evidence reviews[208,209,210] and one decision analysis using simulation modelling.[211]

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[199] U.S. Preventive Services Task Force. Routine aspirin or nonsteroidal anti-inflammatory drugs for the primary prevention of colorectal cancer. *Annals of Internal Medicine*. 2007; 146(5): 361-4.

[200] U.S. Preventive Services Task Force. Aspirin for the prevention of cardiovascular disease: U.S. Preventive Services Task Force recommendation statement. *Annals of Internal Medicine*. 2009; 150(6): 396-404.

[201] Baigent C, Blackwell L, Collins R et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *The Lancet*. 2009; 373(9678): 1849-60.

[202] Seshasai SR, Wijesuriya S, Sivakumaran R et al. Effect of aspirin on vascular and nonvascular outcomes: meta-analysis of randomized controlled trials. *Archives of Internal Medicine*. 2012; 172(3): 209-16.

[203] Sutcliffe P, Connock M, Gurung T et al. Aspirin for prophylactic use in the primary prevention of cardiovascular disease and cancer: a systematic review and overview of reviews. *Health Technology Assessment*. 2013; 17(43): 1-253.

[204] Selak V, Elley CR, Wells S et al. Aspirin for primary prevention: yes or no? *Journal of Primary Health Care*. 2010; 2(2): 92-9.

[205] Raju NC and Eikelboom JW. The aspirin controversy in primary prevention. *Current Opinion in Cardiology*. 2012; 27(5): 499-507.

[206] Patrono C. Low-dose aspirin in primary prevention: cardioprotection, chemoprevention, both, or neither? *European Heart Journal*. 2013; 34(44): 3403-11.

[207] H. Krueger & Associates Inc. *Establishing Priorities among Effective Clinical Prevention Services in British Columbia: Summary and Technical Report*. July 16, 2014.

[208] Guirguis-Blake J, Evans C, Senger C et al. Aspirin for the primary prevention of cardiovascular events: a systematic evidence review for the U.S. Preventive Services Task Force. *Annals of Internal Medicine*. 2016; 164(12): 804-13.

The systematic review by Guirguis-Blake and colleagues noted that very-low dose aspirin use (≤100mg daily) for primary prevention reduced the risk of nonfatal myocardial infarction by 17% (RR of 0.83, 95% CI of 0.74 – 0.94) and nonfatal stroke by 14% (RR of 0.86, 95% CI of 0.76 – 0.98) but they found no reduction in all-cause or cardiovascular mortality.[212]

The systematic review by Chubak and co-authors noted that using aspirin (in dosages ranging from 50 to 500mg daily) for primary prevention reduced the incidence of colorectal cancer by 40% (RR of 0.60, 95% CI of 0.47 – 0.76) but only in secondary studies which followed individuals for at least 10 years. In addition, the use of aspirin for approximately 5 years reduced the risk of death from CRC about 20 years later by 33% (RR of 0.67, 95% CI of 0.52 – 0.86). Aspirin's effect on ***total cancer*** mortality and incidence was not clearly established.[213]

The systematic review by Whitlock et al. found that very-low dose aspirin use (≤100mg daily or every other day) increased the risk of major gastrointestinal bleeding by 58% (RR of 1.58, 95% CI of 1.29 – 1.95) and the risk of haemorrhagic stroke by 27% (RR of 1.27, 95% CI of 0.96 – 1.68).[214]

To help disentangle the "uncertain relationship between the benefits and harms of long-term aspirin use", the USPSTF commissioned the decision analysis by Dehmer and colleagues.[215] The decision analysis found that the results of net gains (as measured by QALYs) were quite sensitive to all assumptions about the relative risks of both benefits and harms, including baseline risks for GI bleeding. In addition, the results are highly sensitive to assumptions made about the potential disutility associated with regular aspirin use. Their base-case scenario assumed no disutility associated with regular aspirin use.

The collation of this evidence resulted in the following recommendation by the USPSTF.

United States Preventive Services Task Force Recommendations (USPSTF; 2016)[216]

> *The USPSTF recommends initiating low dose aspirin use for the primary prevention of CVD and CRC in adults aged 50 to 59 years who have a 10% or greater 10-year*

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[209] Chubak J, Whitlock E, Williams S et al. Aspirin for the prevention of cancer incidence and mortality: systematic evidence reviews for the U.S. Preventive Services Task Force. *Annals of Internal Medicine*. 2016; 164(12): 814-25.

[210] Whitlock E, Burda B, Williams S et al. Bleeding risks with aspirin use for primary prevention in adults: a systematic review for the U.S. Preventive Services Task Force. *Annals of Internal Medicine*. 2016; 164(12): 826-35.

[211] Dehmer S, Maciosek M, Flottemesch T et al. Aspirin for the primary prevention of cardiovascular disease and colorectal cancer: a decision analysis for the US Preventive Services Task Force. *Annals of Internal Medicine*. 2016; 164(12): 777-86.

[212] Guirguis-Blake J, Evans C, Senger C et al. Aspirin for the primary prevention of cardiovascular events: a systematic evidence review for the U.S. Preventive Services Task Force. *Annals of Internal Medicine*. 2016; 164(12): 804-13.

[213] Chubak J, Whitlock E, Williams S et al. Aspirin for the prevention of cancer incidence and mortality: systematic evidence reviews for the U.S. Preventive Services Task Force. *Annals of Internal Medicine*. 2016; 164(12): 814-25.

[214] Whitlock E, Burda B, Williams S et al. Bleeding risks with aspirin use for primary prevention in adults: a systematic review for the U.S. Preventive Services Task Force. *Annals of Internal Medicine*. 2016; 164(12): 826-35.

[215] Dehmer S, Maciosek M, Flottemesch T et al. Aspirin for the primary prevention of cardiovascular disease and colorectal cancer: a decision analysis for the US Preventive Services Task Force. *Annals of Internal Medicine*. 2016; 164(12): 777-86.

[216] Bibbins-Domingo K. Aspirin use for the primary prevention of cardiovascular disease and colorectal cancer: US Preventive Services Task Force recommendation statement. *Annals of Internal Medicine*. 2016; 164(12): 836-45.

CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years. (B recommendation)

The decision to initiate low-dose aspirin use for the primary prevention of CVD and CRC in adults aged 60 to 69 years who have a 10% or greater 10-year CVD risk should be an individual one. Persons who are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years are more likely to benefit. Persons who place a higher value on the potential benefits than the potential harms may choose to initiate low-dose aspirin. (C recommendation)

Risk factors for gastrointestinal (GI) bleeding with aspirin use include higher dose and longer duration of use, history of GI ulcers or upper GI pain, bleeding disorders, renal failure, severe liver disease, and thrombocytopenia. Other factors that increase risk for GI or intracranial bleeding with low-dose aspirin use include concurrent anticoagulation or nonsteroidal anti-inflammatory drug (NSAID) use, uncontrolled hypertension, male sex, and older age.

Canadian Task Force on Preventive Health Care (CTFPHC; 1991) [217]

In 1991, the CTFPHC (then known as the Canadian Task Force on the Periodic Health Examination) found that

Given the available information there is no clear evidence that routine use of ASA in asymptomatic men leads to a reduction in the rates of death from all causes, from cardiovascular disease or from myocardial infarction (when sudden deaths are taken into account). The benefit of ASA therapy observed in the decreased incidence of myocardial infarction needs to be balanced against the potential adverse effects, particularly disabling stroke, that may be related to hemorrhagic properties of ASA.

The evidence is not strong enough to support a recommendation that routine ASA therapy be used or not be used for the primary prevention of cardiovascular disease in asymptomatic men. The decision on whether to prescribe ASA should be made on an individual basis after the benefits of decreased risk of ischemic cardiovascular events have been balanced against the potential risks associated with prolonged ASA use.

No review has been completed by the CTFPHC since 1991.

The remainder of this section is an evaluation of initiating low dose aspirin use for the primary prevention of CVD and CRC in adults starting anywhere between the ages of 50 and 59 for those who have a 10% or greater 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years.

[217] Goldbloom R, Battista R, Anderson G et al. Periodic health examination, 1991 update: 6. acetylsalicylic acid and the primary prevention of cardiovascular disease. *Canadian Medical Association Journal*. 1991; 145(9): 1091-5.

Utilization of This Clinical Preventive Service

Currently in British Columbia

We were unable to find specific data on low-dose aspirin use for primary prevention purposes in BC in individuals ages 50-69. In a survey of 807 family practice patients with an average age of 62.6 years in Alberta, 16.2% used ASA for primary cardiovascular prevention.[218]

For modeling purposes, we have assumed that 15% of adults ages 50-69 in BC who have a 10% or greater 10-year CVD risk, are not at increased risk for bleeding and have a life expectancy of at least 10 years are currently taking low-dose aspirin daily for primary prevention purposes.

Best in the World

In the United States, the use of aspirin for primary prevention has increased significantly between 1980 and 2010.[219] By 2010, an estimated 25% to 45% of US adults ages 50-59 were regular users of aspirin for the primary prevention of CVD.[220,221] A study by Maious and colleagues found that 32% of adults over the age of 40 with no previously diagnosed CVD and a 10-year CHD risk of >10% were regular users of aspirin in 2011/12.[222] The US tends to have higher rates of aspirin utilization for the primary prevention of CVD than European countries,[223,224] although there is evidence of aspirin *under*- and *over*-utilization in the US.[225,226] Since 2010, the prevalence of aspirin use for primary prevention in the US may have declined. In examining the time frame from 2012 to 2015, Stuntz and colleagues found that only 24% of the US population aged 50-64 were using aspirin for primary prevention of CVD.[227]

For modelling purposes, we have assumed a 'best in the world' rate of 30% of adults ages 50-69 who have a 10% or greater 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years and are willing to take low-dose aspirin daily for at least 10 years.

[218] Kolber M, Sharif N, Marceau R et al. Family practice patients' use of acetylsalicylic acid for cardiovascular disease prevention. *Canadian Family Physician*. 2013; 59(1): 55-61.
[219] Luepker R, Steffen L, Duval S et al. Population trends in aspirin use for cardiovascular disease prevention 1980–2009: the Minnesota heart survey. *Journal of the American Heart Association*. 2015; 4(12): 1-7.
[220] Zhou Y, Boudreau D and Freedman A. Trends in the use of aspirin and nonsteroidal anti-inflammatory drugs in the general U.S. population. *Pharmacoepidemiology and Drug Safety*. 2014; 23(1): 43-50.
[221] Williams C, Chan A, Elman M et al. Aspirin use among adults in the US: results of a national survey. *American Journal of Preventive Medicine*. 2015; 48(5): 501-8.
[222] Mainous A, Tanner R, Shorr R et al. Use of aspirin for primary and secondary cardiovascular disease prevention in the United States, 2011-2012. *Journal of the American Heart Association*. 2014; doi:10.1161/JAHA.114.000989.
[223] Filippi A, Bianchi C, Parazzini F et al. A national survey on aspirin patterns of use and persistence in community outpatients in Italy. *European Journal of Cardiovascular Prevention & Rehabilitation*. 2011; 18(5): 695-703.
[224] Rodondi N, Cornuz J, Marques-Vidal P et al. Aspirin use for the primary prevention of coronary heart disease: a population-based study in Switzerland. *Preventive Medicine*. 2008; 46(2): 137-44.
[225] VanWormer J, Miller A and Rezkalla S. Aspirin overutilization for the primary prevention of cardiovascular disease. *Clinical Epidemiology*. 2014; 6(1): 433.
[226] VanWormer J, Greenlee R, McBride P et al. Aspirin for primary prevention of CVD: are the right people using it? *Journal of Family Practice*. 2012; 61(9): 525-33.
[227] Stuntz M and Bernstein B. Recent trends in the prevalence of low-dose aspirin use for primary and secondary prevention of cardiovascular disease in the United States, 2012–2015. *Preventive Medicine Reports*. 2017; 5: 183-6.

Relevant British Columbia Population in 2013

In 2013, a total of 693,914 individuals between the ages of 50 and 59 were living in BC.[228]

Hennessy and colleagues grouped Canadians ages 20-79 into those at low risk (defined as a mean 10-year risk of a CVD event of less than 10%), intermediate risk (mean 10-year risk of a CVD event of 10%-19%) and high risk of CVD (pre-existing heart disease, diabetes, high-risk hypertension, chronic kidney disease).[229] Of these Canadians ages 20-79, 70.3% are at low risk, 9.0% are at intermediate risk and 19.7% are at high risk. We used their data by age group to estimate that 466,271 of the 693,914 (67.2%) 50-59 year-olds living in BC are at low risk, 84,369 (12.2%) are at medium risk and 143,274 (20.6%) are at high risk of CVD.

Modelling CPB and CE

In this section, we will calculate the CPB and CE associated with initiating low dose aspirin use for the primary prevention of CVD and CRC in adults between the ages of 50 and 59 years who have a 10% or greater 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years.

In estimating CPB, we made the following assumptions:

- Based on BC life tables for 2009 to 2011,[230] there are a total of 379,687 life years lived between the ages of 50 and 59 in a BC birth cohort of 40,000 (see Table 3-1 and Table 3-2, row a), with 255,128 (67.2%, Table 3-2, row b & e) of these life years lived at a low risk, 46,164 (12.2%, Table 3-2, row c & f) at intermediate risk and 78,395 (20.6%, Table 3-2, row d & g) at high risk of cardiovascular disease.
- Based on BC life tables for 2009 to 2011, a total of 1,138 deaths would be expected between the ages of 50-59, a further 2,618 deaths between the ages of 60-69 and 6,017 deaths between the ages of 70-79 in a BC birth cohort of 40,000 (see Table 3-1 and Table 3-2, rows h, k & m).[231]
- Based on BC vital statistics data, 601 of 5,076 (11.8%) deaths in 45-64 year olds in 2011 were due to cardiovascular disease (ICD-10 codes I00-I51) and 191 of 5,076 (3.8%) deaths were due to cerebrovascular disease (ICD-10 codes I60-I69).[232] This data was used to estimate that approximately 203 of the 1,719 (11.8%) deaths between the ages of 55-64 in the birth cohort would be due to cardiovascular disease and 65 (3.8%) due to cerebrovascular disease (see Table 3-1 and Table 3-2, rows i & j).
- Based on BC Cancer Agency data, there were 3,021[233] new cases of colorectal cancers (CRC) in BC in 2012 and 1,099[234] deaths due to CRC that same year, for a

[228] See http://www.bcstats.gov.bc.ca/StatisticsBySubject/Demography/PopulationEstimates.aspx. Accessed January 2017.
[229] Hennessy D, Tanuseputro P, Tuna M et al. Population health impact of statin treatment in Canada. *Health Reports*. 2016; 27(1): 20-8.
[230] See http://www.statcan.gc.ca/pub/84-537-x/2013005/tbl-eng.htm. Accessed January 2017.
[231] See http://www.statcan.gc.ca/pub/84-537-x/2013005/tbl-eng.htm. Accessed January 2017.
[232] British Columbia Vital Statistics Agency. *Selected Vital Statistics and Health Status Indicators: One Hundred and Fortieth Annual Report*. 2011. British Colubmia Ministry of Health. Available at http://www2.gov.bc.ca/assets/gov/birth-adoption-death-marriage-and-divorce/statistics-reports/annual-reports/2011/pdf/ann2011.pdf. Accessed January 2017.
[233] BC Cancer Agency. *New Cancer Diagnoses for 2012 by Cancer Type, Age at Diagnosis and Gender*. 2012. Provincial Health Services Authority,. Available at http://www.bccancer.bc.ca/statistics-and-reports-site/Documents/Cancer_Incidence_Counts_2012.pdf. Accessed February 2017.

ratio of 2.75 new cases per death (Table 3-2, row aa). An estimated 19.9%[235] of deaths (or 219 in BC in 2012) from CRC are in individuals between the ages of 60-69. Since the effectiveness of aspirin on reducing the incidence of CRC only appears after approximately ten years, the age range of 65-74 is being used in the modelling when considering CRC ***incidence***. Similarly, the age range of 75-84 is being used in the modelling when considering CRC ***mortality*** due to the 20-year lag time observed for this outcome in the research.[236] An estimated 26.9%[237] of deaths (or 296 in BC in 2012) from CRC are in individuals between the ages of 70-79.

- Based on BC vital statistics data, there were 31,776 deaths in BC in 2011.[238] An estimated 12.5% of these deaths (or 3,972) are in individuals between the ages of 60-69 and 22.2% (or 7,065) in individuals between the ages of 70-79.[239] The 219 deaths from CRC between the ages of 60-69 therefore represents approximately 5.3% of all deaths in this age cohort. In the birth cohort of 40,000, 5.3% of deaths between the ages of 60-69 represents 139 deaths due to CRC (see Table 3-1 and Table 3-2, row l). The 296 deaths from CRC represents approximately 4.2% of all deaths in this age cohort. In the birth cohort of 40,000, 4.2% of deaths between the ages of 70-79 represents 253 deaths due to CRC (see Table 3-1 and Table 3-2, row n).

Table 3-1: Deaths and Selected Causes of Death Between the Ages of 50 and 79
in a British Columbia Birth Cohort of 40,000

Age Group	*Mean Survival Rate*		*Individuals in Birth Cohort*			*Life Years Lived*	*Deaths in Birth Cohort*		*Deaths due to* Cardiovascular Disease		*Deaths due to* Cerebrovascular Disease		Colorectal Cancer	
	Males	Females	Males	Females	Total		%	#	%	#	%	#	%	#
45-49	0.961	0.977	19,218	19,547	38,765									
50-54	0.947	0.969	18,938	19,372	38,310	191,551	1.2%	455	11.8%	54	3.8%	17		
55-59	0.926	0.955	18,519	19,108	37,627	188,136	1.8%	683	11.8%	81	3.8%	26		
60-64	0.894	0.935	17,887	18,704	36,591	182,955	2.8%	1,036	11.8%	122	3.8%	39	5.3%	55
65-69	0.847	0.904	16,935	18,074	35,009	175,045	4.5%	1,582	11.8%	187	3.8%	60	5.3%	84
70-74	0.776	0.854	15,514	17,086	32,600	162,999	7.4%	2,409					4.2%	101
75-79	0.673	0.777	13,453	15,540	28,992	144,961	12.4%	3,608					4.2%	152
Total						**1,045,647**		**9,773**		**443**		**143**		**391**

- In 2010 in the US, there were an estimated 720,000 new and recurrent heart attacks and 122,071 deaths from heart attack.[240] We assumed that 15% of the 720,000 heart

[234] BC Cancer Agency. *Cancer Deaths in British Columbia, 2012 by Cancer Type, Age at Death and Gender*. 2012. Provincial Health Services Authority,. Available at http://www.bccancer.bc.ca/statistics-and-reports-site/Documents/Cancer_Mortality_Counts_2013.pdf. Accessed February 2017.
[235] Canadian Cancer Society's Advisory Committee on Cancer Statistics. *Canadian Cancer Statistics 2016, Special Topic: HPV-Associated Cancers*. 2016. Canadian Cancer Society. Available at http://www.colorectal-cancer.ca/IMG/pdf/Canadian-Cancer-Statistics-2016-EN.pdf. Accessed February 2017.
[236] Chubak J, Whitlock E, Williams S et al. Aspirin for the prevention of cancer incidence and mortality: systematic evidence reviews for the U.S. Preventive Services Task Force. *Annals of Internal Medicine*. 2016; 164(12): 814-25.
[237] Canadian Cancer Society's Advisory Committee on Cancer Statistics. *Canadian Cancer Statistics 2016, Special Topic: HPV-Associated Cancers*. 2016. Canadian Cancer Society. Available at http://www.colorectal-cancer.ca/IMG/pdf/Canadian-Cancer-Statistics-2016-EN.pdf. Accessed February 2017.
[238] British Columbia Vital Statistics Agency. *Selected Vital Statistics and Health Status Indicators: One Hundred and Fortieth Annual Report*. 2011. British Columbia Ministry of Health. Available at http://www2.gov.bc.ca/assets/gov/birth-adoption-death-marriage-and-divorce/statistics-reports/annual-reports/2011/pdf/ann2011.pdf. Accessed January 2017.
[239] Jayaraman J and Joseph K. Determinants of place of death: a population-based retrospective cohort study. *BioMed Central Palliative Care*. 2013; 12(19): 1-9.
[240] Go A, Mozaffarian D, Roger V et al. American Heart Association Statistical Update. *Circulation*. 2014; 129: 399-410.

attacks were recurrent heart attacks and calculated that there are 5.01 (612,000 / 122,071) nonfatal heart attacks per fatal heart attack in the US (Table 3-2, row o).

- In 2010 in the US, there were an estimated 795,000 new and recurrent strokes and 129,476 deaths from stroke.[241] We assumed that 15%[242] of the 795,000 strokes were recurrent strokes and calculated that there are 5.22 (675,750 / 129,476) nonfatal strokes per fatal stroke in the US (Table 3-2, row u).
- We assumed that the average age at which a cardiovascular or cerebrovascular event was prevented due to the use of aspirin would be 60 (Table 3-2, rows q&w). For the prevention of a CRC event, this would be 70 (Table 3-2, row ac). For the prevention of a death due to CRC, this would be 80 (Table 3-2, row af). Based on BC life tables for 2009 to 2011, the average life expectancy of a 60 year old is 25.2 years (Table 3-2, row r & x), that of a 70 year old is 17.0 years (Table 3-2, row ad) and that of an 80 year old is 10.1 years (Table 3-2, row ag).[243]
- Based on a survey of 39,751 individuals in the US, a heart attack reduces QoL by a mean of 16.9% (95% CI of 16.6% to 17.2%) (Table 3-2, row s) while a stroke reduces QoL by a mean of 20.4% (95% CI of 20.0% to 20.8%) (Table 3-2, row y).[244]
- Colorectal cancer reduces QoL in survivors by a mean of 15.0% (95% CI of 6.0% to 23.0%) (Table 3-2, row ae).[245,246]
- Very-low dose aspirin use (≤100mg daily) for primary prevention reduces the risk of nonfatal myocardial infarction by 17% (RR of 0.83, 95% CI of 0.74 – 0.94) (Table 3-2, row al) and nonfatal stroke by 14% (RR of 0.86, 95% CI of 0.76 – 0.98) (Table 3-2, row ao), but does not reduce all-cause or cardiovascular mortality.[247]
- Use of aspirin (in dosages ranging from 50 to 500mg daily) for primary prevention reduces the incidence of colorectal cancer by 40% (RR of 0.60, 95% CI of 0.47 – 0.76) (Table 3-2, row ar) but only in secondary studies which followed individuals for at least 10 years.[248]
- The use of aspirin for approximately 5 years reduces the risk of death from CRC about 20 years later by 33% (RR of 0.67, 95% CI of 0.52 – 0.86) (Table 3-2, row au).[249]

[241] Go A, Mozaffarian D, Roger V et al. American Heart Association Statistical Update. *Circulation*. 2014; 129: 399-410.
[242] Krueger H, Lindsay P, Cote R et al. Cost avoidance associated with optimal stroke care in Canada. *Stroke*. 2012; 43(8): 2198-206.
[243] See http://www.statcan.gc.ca/pub/84-537-x/2013005/tbl-eng.htm. Accessed January 2017.
[244] Nyman J, Barleen N, Dowd B et al. Quality-of-life weights for the US population: self-reported health status and priority health conditions, by demographic characteristics. *Medical Care*. 2007; 45(7): 618-28.
[245] Ramsey S, Andersen M, Etzioni R et al. Quality of life in survivors of colorectal carcinoma. *Cancer*. 2000; 88(6): 1294-303.
[246] Ramsey S, Berry K, Moinpour C et al. Quality of life in long term survivors of colorectal cancer. *American Journal of Gastroenterology*. 2002; 97(5): 1228-34.
[247] Guirguis-Blake J, Evans C, Senger C et al. Aspirin for the primary prevention of cardiovascular events: a systematic evidence review for the U.S. Preventive Services Task Force. *Annals of Internal Medicine*. 2016; 164(12): 804-13.
[248] Chubak J, Whitlock E, Williams S et al. Aspirin for the prevention of cancer incidence and mortality: systematic evidence reviews for the U.S. Preventive Services Task Force. *Annals of Internal Medicine*. 2016; 164(12): 814-25.
[249] Chubak J, Whitlock E, Williams S et al. Aspirin for the prevention of cancer incidence and mortality: systematic evidence reviews for the U.S. Preventive Services Task Force. *Annals of Internal Medicine*. 2016; 164(12): 814-25.

- The disutility of taking aspirin daily is estimated at 0.24% (95% CI of 0.17% to 0.33%) (Table 3-2, row ax).[250, 251, 252] The studies by Hutchins and colleagues also found that a significant proportion of respondents (9.5% using the willingness-to-pay approach, 57.5% using the standard gamble approach and 87% using the time trade-off approach) identified no disutility associated with taking one pill daily. In the sensitivity analysis, we therefore ranged the disutility from 0% to 0.33%.
- The rate of a major bleeding event in a 50-69 year old not taking aspirin is 1.99 per 1,000 person-years (95% CI 1.82 to 2.18) (Table 3-2, row az). The rate of a major bleeding event in a 50-69 year old who is taking aspirin increases to 3.21 per 1,000 person-years (95% CI 2.93 to 3.53) (Table 3-2, row ba). Sixty-five percent of bleeding events are episodes of gastrointestinal bleeding (Table 3-2, row bc) while 35% are episodes of intracranial hemorrhage (Table 3-2, row bd).[253]
- In a study of 936 patients with acute upper gastrointestinal bleeding (AUGIB) in the UK, 42 (4.5%) had died by day 28 following the bleeding episode (Table 3-2, row bg). The mean QoL score at 28 days for surviving patients was 0.735 compared to 0.86 for the general UK population, a disutility of 14.5% (Table 3-2, row bk). We have assumed that this disutility lasts for a one-year period[254]
- An estimated 40% of patients die within 28 days after a haemorrhagic stroke (Table 4-2, row bh).[255]

Based on these assumptions, the CPB associated with screening for and initiating use of low-dose aspirin for the primary prevention of CVD and CRC in adults aged 50 to 59 years who have a 10% or greater 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years is 448 QALYs (see Table 3-2, row bv).

This is based on the assumption of moving from no aspirin use in this intermediate to high risk cohort to 30% of this cohort initiating and sustaining aspirin use. If we assume that 15% of this cohort are currently using aspirin in BC, the difference between the 15% and 30% would translate into 224 QALYs.

[250] Thompson A, Guthrie B and Payne K. Do pills have no ills? capturing the impact of direct treatment disutility. *PharmacoEconomics*. 2016; 34(4): 333-6.
[251] Hutchins R, Pignone M, Sheridan S et al. Quantifying the utility of taking pills for preventing adverse health outcomes: a cross-sectional survey. *British Medical Journal Open*. 2015; 5(e006505): 1-9.
[252] Hutchins R, Viera AJ, Sheridan SL et al. Quantifying the utility of taking pills for cardiovascular prevention. *Circulation: Cardiovascular Quality and Outcomes*. 2015; 8(2): 155-63.
[253] De Berardis G, Lucisano G, D'ettorre A et al. Association of aspirin use with major bleeding in patients with and without diabetes. *Journal of American Medical Association*. 2012; 307(21): 2286-94.
[254] Campbell H, Stokes E, Bargo D et al. Costs and quality of life associated with acute upper gastrointestinal bleeding in the UK: cohort analysis of patients in a cluster randomised trial. *British Medical Journal Open*. 2015; 5(4): e007230.
[255] Krueger H, Lindsay P, Cote R et al. Cost avoidance associated with optimal stroke care in Canada. *Stroke*. 2012; 43(8): 2198-206.

Table 3-2: CPB of Screening for and Initiating Use of Aspirin in Adults Between the Ages of 50 and 59 Years with an Intermediate or Higher Risk of CVD in a Birth Cohort of 40,000			
Label	**Variable**	**Base Case**	**Data Source**
	Estimated current status		
a	# of life years lived between the ages of 55-64 in birth cohort	371,091	Table 3-1
b	% of life years at low risk of CVD	67.2%	√
c	% of life years at intermediate risk of CVD	12.2%	√
d	% of life years at high risk of CVD	20.6%	√
e	# of life years at low risk	249,352	= (a * b)
f	# of life years at intermediate risk	45,119	= (a * c)
g	# of life years at high risk	76,620	= (a * d)
h	Total deaths in birth cohort between the ages of 55-64	1,719	Table 3-1
i	Cardiovascular deaths in birth cohort between the ages of 55-64	203	Table 3-1
j	Cerebrovascular deaths in birth cohort between the ages of 55-64	65	Table 3-1
k	Total deaths in birth cohort between the ages of 65-74	3,991	Table 3-1
l	Colorectal cancer deaths in birth cohort between the ages of 65-74	185	Table 3-1
m	Total deaths in birth cohort between the ages of 75-84	8,791	Table 3-1
n	Colorectal cancer deaths in birth cohort between the ages of 75-84	369	Table 3-1
o	# of nonfatal ***cardiovascular*** events per fatal event	5.01	√
p	# of nonfatal cardiovascular events	1,016	= (i * o)
q	Average age of individual with a cardiovascular event	60	√
r	Life years lived with a nonfatal cardiovascular event	25.2	√
s	QoL reduction living with a nonfatal cardiovascular event	0.169	√
t	QALYs lost due to nonfatal cardiovascular events	4,328	= (p * r * s)
u	Ratio of nonfatal ***cerebrovascular*** events per fatal event	5.22	√
v	# of nonfatal cerebrovascular events	341	= (j * u)
w	Average age of individual with a cerebrovascular event	60	√
x	Life years lived with a nonfatal cerebrovascular event	25.2	√
y	QoL reduction living with a nonfatal cerebrovascular event	0.204	√
z	QALYs lost due to nonfatal cerebrovascular events	1,753	= (v * x * y)
aa	Ratio of nonfatal ***colorectal cancer*** events per fatal event	2.75	√
ab	# of nonfatal colorectal cancer events, ages 65-74	509	= (l * aa)
ac	Average age of individual with colorectal cancer	70	√
ad	Life years lived with colorectal cancer	17.0	√
ae	QoL reduction living with a nonfatal colorectal cancer event	0.150	√
af	Average age of individual dying from colorectal cancer	80	√
ag	Life expectancy of a 80 year old in BC	10.1	√
ah	QALYs lost due to nonfatal colorectal cancer events	1,298	= (ab * ad * ae)
ai	QALYs lost due to deaths from colorectal cancer	3,729	= (n * ag)

Table 3-2 (continued): CPB of Screening for and Initiating Use of Aspirin in Adults Between the Ages of 50 and 59 Years with an Intermediate or Higher Risk of CVD in a Birth Cohort of 40,000			
Label	**Variable**	**Base Case**	**Data Source**
	If 100% of intermediate & high risk individuals were on aspirin		
	Benefits		
aj	% of life years at intermediate or high risk on aspirin	100%	Assumed
ak	# of life years at intermediate or high risk on aspirin	121,739	= (f + g)
al	% reduction in risk of ***cardiovascular*** disease associated with aspirin use	17%	√
am	Cardiovascular disease events avoided with 100% aspirin usage	173	= (al * p)
an	QALYs gained with 100% aspirin usage	736	= (p * q * am)
ao	% reduction in ***cerebrovascular*** events associated with aspirin use	14%	√
ap	Cerebrovascular events avoided with 100% aspirin usage	48	= (ao * v)
aq	QALYs gained due to a reduction in nonfatal cerebrovascular events associated with aspirin use	245	= (x * y * ap)
ar	% reduction in ***colorectal cancer*** events associated with aspirin use, ages 60-69	40%	√
as	Colorectal cancer events avoided with 100% aspirin usage	204	= (ar * ab)
at	QALYs gained due to a reduction in nonfatal colorectal cancer events associated with aspirin use	519	= (ad * ae* as)
au	% reduction in colorectal cancer deaths associated with aspirin use, ages 70-79	33%	√
av	QALYs gained due to a reduction in colorectal cancer deaths associated with aspirin use	1,231	= (ai * au)
aw	***Total QALYs gained*** if 100% of intermediate & high risk individuals were on aspirin	2,731	= (an + aq + at + av)
	Harms		
ax	Disutility per year associated with taking pills for cardiovascular prevention	-0.0024	√
ay	Disutility associated with taking pills for cardiovascular prevention	-292	= (ak * ax)
az	Risk of major bleeding event in age group 50-69 per 1,000 person-years, no aspirin	1.99	√
ba	Risk of major bleeding event in age group 50-69 per 1,000 person-years, with aspirin	3.21	√
bb	Major bleeding events in cohort due to aspirin	149	=((ak/1000)*ba)-((ak/1000)*az)
bc	Proportion of major bleeding events - gastrointestinal bleeding	0.65	√
bd	Proportion of major bleeding events - haemorrhagic stroke	0.35	√
be	Gastrointestinal bleeding events attributable to aspirin use	97	= (bb * bc)
bf	Haemorrhagic strokes attributable to aspirin use	52	= (bb * bc)
bg	Death rate following a gastrointestinal bleeding event	0.045	√
bh	Death rate following a haemorrhagic stroke	0.40	√
bi	Deaths due to a gastrointestinal bleeding event	4.3	= (be * bg)
bj	Deaths due to a haemorrhagic stroke	20.8	= (bf * bh)
bk	QoL reduction living with a gastrointestinal bleed (1 year only)	-0.145	√
bl	QoL reduction living with a haemorrhagic stroke (lifetime)	-0.204	=-y
bm	Average age of individual with a major bleeding event	55	√
bn	Life years lived following a non-fatal bleeding event	29.6	√
bo	QALYs lost due to gastrointestinal bleeding	-142	=(-bi*bn)+((be-bi)*bk)
bp	QALYs lost due to haemorrhagic stroke	-804	=(-bj*bn)+((bf-bj)*bn*bl)
bq	***Total QALYs lost*** if 100% of intermediate & high risk individuals were on aspirin	-1,238	= ay + bo + bp
br	***Net QALYs gained*** if 100% of intermediate & high risk individuals were on aspirin	1,493	= aw + bq
	If 30% of intermediate & high risk individuals were on aspirin		
bs	% of life years at intermediate & high risk on aspirin	30.0%	Table 3-3, row s
	Benefits		
bt	QALYs gained if intermediate & high risk individuals were on aspirin	819	= (aw * bs)
	Harms		
bu	QALYs lost if intermediate & high risk individuals were on aspirin	-371	= (bq * bs)
bv	**Potential QALYs gained, Screening & Intervention from 0% to 30%**	**448**	= bt + bu

√ = Estimates from the literature

For our sensitivity analysis, we modified a number of major assumptions and recalculated the CPB as follows:

- Assume that decreased risk of cardiovascular disease events associated with aspirin use is reduced from 17% to 6% (Table 3-2, row al), the decreased risk of cerebrovascular disease events is reduced from 14% to 2% (Table 3-2, row ao), the decreased risk of incident CRC is reduced from 40% to 24% (Table 3-2, row ar) and the decreased risk of mortality due to CRC is reduced from 33% to 14% (Table 3-2, row au): CPB = -33.
- Assume that decreased risk of cardiovascular disease events associated with aspirin use is increased 17% to 26% (Table 3-2, row al), the decreased risk of

cerebrovascular disease events is increased from 14% to 24% (Table 3-2, row ao), the decreased risk of incident CRC is increased from 40% to 53% (Table 3-2, row ar) and the decreased risk of mortality due to CRC is increased from 33% to 48% (Table 3-2, row au): CPB = 836.

- Assume that the disutility per year associated with taking pills for cardiovascular prevention is reduced from -0.0024 to -0.000 (Table 3-2, row ax): CPB = 536.
- Assume that the disutility per year associated with taking pills for cardiovascular prevention is increased from -0.0024 to -0.0033 (Table 3-2, row ax): CPB = 415.
- Assume that the rate of a major bleeding event in a 50-69 year old not taking aspirin is reduced from 1.99 to 1.82 per 1,000 person-years (Table 3-2, row az) while the rate of a major bleeding event in a 50-69 year old who is taking aspirin is reduced from 3.21 to 2.93 per 1,000 person-years (Table 3-2, row ba): CPB = 473.
- Assume that the rate of a major bleeding event in a 50-69 year old not taking aspirin is increased from 1.99 to 2.18 per 1,000 person-years (Table 3-2, row az) while the rate of a major bleeding event in a 50-69 year old who is taking aspirin is increased from 3.21 to 3.53 per 1,000 person-years (Table 3-2, row ba): CPB = 418.

In estimating CE, we made the following assumptions:

- **Screening for CVD risk** - The USPSTF notes that it used the ACC/AHA Pooled Cohort Equations to calculate the 10-year risk of CVD events in their analysis and identified key risk factors for GI bleeding: higher doses and longer duration of aspirin use, GI ulcers or upper GI pain, bleeding disorders, renal failure, severe liver disease, thrombocytopenia, concurrent anticoagulation or nonsteroidal anti-inflammatory drug use, uncontrolled hypertension, male sex and older age. [256]
- The need to concurrently screen for CVD risk, bleeding risk and willingness to take low-dose aspirin daily for at least 10 years has recently led to the development of a clinical decision support tool called the Aspirin Guide.[257,258]
- For screening purposes, we have assumed that 32.8% of the BC population ages 50-59 is at an intermediate or high risk of CVD (Table 3-3, row c).
- We have assumed that the CVD screening and bleeding risk assessment would take place three times between the ages of 50 and 59 (beginning, mid-point and end of this age range). This would involve screening individuals to determine their risk status and whether or not aspirin would be recommended as well as for follow-up purposes for individuals taking aspirin for primary prevention purposes (Table 3-3, row e).
- We have assumed that 70% of patients would adhere with offers to receive screening (Table 3-3, row g).
- Completion of a CVD risk assessment includes a physician visit and a full lipid profile (total cholesterol [TC]; high density lipoprotein cholesterol [HDL-C]; low-density lipoprotein cholesterol [LDL-C], non-HDL-C; and triglycerides [TG]). The

[256] Bibbins-Domingo K. Aspirin use for the primary prevention of cardiovascular disease and colorectal cancer: US Preventive Services Task Force recommendation statement. *Annals of Internal Medicine*. 2016; 164(12): 836-45.
[257] Mora S and Manson J. Aspirin for primary prevention of atherosclerotic cardiovascular disease: advances in diagnosis and treatment. *Journal of the American Medical Association Internal Medicine*. 2016; 176(8): 1195-204.
[258] Mora S, Ames J and Manson J. Low-dose aspirin in the primary prevention of cardiovascular disease: shared decision making in clinical practice. *Journal of the American Medical Association*. 2016; 316(7): 709-10.

full lipid profile costs $21.31 (Table 3-3, row m).[259] Note that a CVD risk assessment is required when considering both statins (see previous modelling section) and aspirin for the primary prevention of CVD.

- **Cost of an office visit** - We estimated the average cost of a visit to a General Practitioner to be $34.00 (Table 3-3, row k).[260] A follow-up phone call or email correspondence would be $15.00 (MSP fee G14079 - GP Telephone/Email Management Fee) (Table 3-3, row l).
- We assumed that a 10-minute office visit would be required for the initial screening (Table 3-3, row i). If the results indicate a low risk of CVD, then the follow-up would consist of a phone call to the patient. If the results indicate an intermediate or high risk of CVD, then a follow-up visit would be required to discuss the results and the possibility of taking aspirin (Table 3-3, row j).
- **Patient time and travel costs** - For patient time and travel costs, we assumed an hourly wage of $24.39 (the BC average in 2013)[261] plus 18% benefits for a cost per hour of $28.78 (Table 3-3, row q) applied to the estimated two hours of patient time required for a physician visit (Table 3-3, row p).
- We assumed that primary care providers would recommend aspirin therapy to 54% of their patients at intermediate or high risk of CVD (Table 3-3, row s). The strongest independent predictor of regular aspirin use for preventive purposes is having discussed aspirin therapy with a provider (OR=23.79, 95% CI of 17.8 to 31.5).[262] In 2011/12, 79% (95% CI of 71% to 85%) (Table 3-3, row t) of US adults ages 50-59 adhered to a medical recommendation to take aspirin for primary prevention purposes.[263,264,265,266] These assumptions, together with the assumption that 70% of patients would adhere to the recommendation to receive screening (Table 3-3, row g), results in overall long-term adherence to aspirin therapy in 30% of individuals ages 50-59 at intermediate or high risk of CVD (Table 3-3, row u) (1*70%*54%*79%).
- **Cost of aspirin therapy** – The cost of 100 – 81mg aspirin tablets at London Drugs is $14.99.[267] We assumed an annual cost of $54.70 (Table 3-3, row w).
- We assumed an annual follow-up visit with a clinician for patients taking aspirin for preventative purposes (Table 3-3, row y) and modified this to once every two years in the sensitivity analysis.

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[259] Ministry of Health. *Cardiovascular Disease – Primary Prevention* 2014. Available at http://www2.gov.bc.ca/assets/gov/health/practitioner-pro/bc-guidelines/cvd.pdf. Accessed January 2017.

[260] Medical Services Commission. *Payment Schedule: Section 7 General Practice*. 2013. Available at http://www.health.gov.bc.ca/msp/infoprac/physbilling/payschedule/pdf/7-general-practice.pdf. Accessed December 2013.

[261] Statistics Canada. *Average Hourly Wages of Employees by Selected Characteristics and Occupation, Unadjusted Data, by Province (Monthly) (British Columbia)*. 2013. Available at http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/labr69k-eng.htm. Accessed December 2013.

[262] Williams C, Chan A, Elman M et al. Aspirin use among adults in the US: results of a national survey. *American Journal of Preventive Medicine*. 2015; 48(5): 501-8.

[263] Gu Q, Dillon C, Eberhardt M et al. Preventive aspirin and other antiplatelet medication use among US adults aged≥ 40 years: data from the National Health and Nutrition Examination Survey, 2011–2012. *Public Health Reports*. 2015; 130(6): 643-54.

[264] Mainous A, Tanner R, Shorr R et al. Use of aspirin for primary and secondary cardiovascular disease prevention in the United States, 2011–2012. *Journal of the American Heart Association*. 2014; 3(4): 1-9.

[265] Malayala S and Raza A. Compliance with USPSTF recommendations on aspirin for prevention of cardiovascular disease in men. *International Journal of Clinical Practice*. 2016; 70(11): 898-906.

[266] Mainous A, Tanner R, Shorr R et al. Use of aspirin for primary and secondary cardiovascular disease prevention in the United States, 2011–2012. *Journal of the American Heart Association*. 2014; 3(4): 1-9.

[267] See http://www.londondrugs.com/. Accessed February 2017.

- **Costs avoided** – According to the Canadian Institute for Health Information's *Patient Cost Estimator*, the average cost for the acute care phase of a percutaneous coronary intervention (PCI) (CMG 175) / coronary artery bypass (CABG) (CMGs 166 to 172) in a 60-79 year-old in BC in 2013 was $9,547 and $25,157, respectively. Fifty-eight percent of treatments are PCI and 42% CABG with a weighted average cost of $16,051.[268]
- Dehmer and colleagues estimated the first year costs associated with a myocardial infarct to be $37,095 (in 2012 USD).[269] We have converted these costs to equivalent Canadian health care costs by reducing costs by 29% to reflect excess health care prices in the US.[270,271] This value was then adjusted to 2013 CAD based on differences in the value of the two currencies that year (see below) for an estimated cost of $26,337 (Table 3-3, row ah).[272]
- According to the Canadian Institute for Health Information's *Patient Cost Estimator*, the average cost for the acute care phase of a haemorrhagic (case-mix group [CMG] 025) / ischemic stroke (CMG 026) in a 60-79 year-old in BC in 2013 was $10,498 and $7,531, respectively. Sixteen percent of strokes in this age group are haemorrhagic and 84% ischemic with a weighted average cost of $8,002.[273]
- Dehmer and colleagues estimated the first year costs associated with a stroke to be $18,192 (in 2012 US$).[274] We have converted these costs to equivalent Canadian health care costs by reducing costs by 29% to reflect excess health care prices in the US.[275,276] This value was then adjusted to 2013 CAD based on differences in the value of the two currencies that year (see below) for an estimated cost of $12,196.[277]
- Gloede and coauthors in Australia estimated the first year costs associated with an ischemic stroke to be $30,110 (in 2010 AUD) while costs associated with a haemorrhagic stroke were $17,767.[278] Based on a mix of 85% ischemic strokes,[279] the weighted cost would be $28,258. We converted this cost to 2013 CAD ($24,947).[280]

[268] Canadian Institute for Health Information. *Patient Cost Estimator*. Available online at https://www.cihi.ca/en/spending-and-health-workforce/spending/patient-cost-estimator. Accessed January 2017

[269] Dehmer S, Maciosek M, LaFrance A et al. Health benefits and cost-effectiveness of asymptomatic screening for hypertension and high cholesterol and aspirin counseling for primary prevention. *The Annals of Family Medicine*. 2017; 15(1): 23-36.

[270] Anderson GF, Reinhardt UE, Hussey PS et al. It's the prices, stupid: why the United States is so different from other countries. *Health Affairs*. 2003; 22(3): 89-105.

[271] Reinhardt U. *Why Does US Health Care Cost So Much? (Part I)*. 2008. Available at https://economix.blogs.nytimes.com/2008/11/14/why-does-us-health-care-cost-so-much-part-i/. Accessed January 2017.

[272] The US and Canadian dollars were roughly on par during 2012. See http://www.bankofcanada.ca/rates/exchange/10-year-converter/. Accessed January, 2017.

[273] Canadian Institute for Health Information. *Patient Cost Estimator*. Available online at https://www.cihi.ca/en/spending-and-health-workforce/spending/patient-cost-estimator. Accessed January 2017.

[274] Dehmer S, Maciosek M, LaFrance A et al. Health benefits and cost-effectiveness of asymptomatic screening for hypertension and high cholesterol and aspirin counseling for primary prevention. *The Annals of Family Medicine*. 2017; 15(1): 23-36.

[275] Anderson GF, Reinhardt UE, Hussey PS et al. It's the prices, stupid: why the United States is so different from other countries. *Health Affairs*. 2003; 22(3): 89-105.

[276] Reinhardt U. *Why Does US Health Care Cost So Much? (Part I)*. 2008. Available at https://economix.blogs.nytimes.com/2008/11/14/why-does-us-health-care-cost-so-much-part-i/. Accessed January 2017.

[277] The US and Canadian dollars were roughly on par during 2012. See http://www.bankofcanada.ca/rates/exchange/10-year-converter/. Accessed January, 2017.

[278] Gloede T, Halbach S, Thrift A et al. Long-term costs of stroke using 10-year longitudinal data from the North East Melbourne Stroke Incidence Study. *Stroke*. 2014: 1-8.

- For modelling purposes, we used the midpoint between $12,196 and $24,947 in the base case ($18,571, Table 4-3, row ai) and the extremes in the sensitivity analysis.
- In estimating the costs of colorectal cancer, de Oliveira and coauthors examined the 3 month pre-diagnosis phase and the year following diagnosis in Ontario. Patients who survived at least one year used $37,945 (Table 3-3, row aj) in resources while those who died within the first year used $46,703 (Table 3-3, row ak).[281]
- Dehmer and colleagues estimated the ongoing annual costs following a myocardial infarct to be $2,490 (in 2012 USD).[282] We have converted these costs to equivalent Canadian health care costs by reducing costs by 29% to reflect excess health care prices in the US.[283,284] This value was then adjusted to 2013 CAD based on differences in the value of the two currencies that year (see below) for an estimated cost of $1,768 (Table 3-3, row am).[285]
- Dehmer and colleagues estimated the ongoing annual costs following a stroke to be $5,389 (in 2012 USD).[286] We have converted these costs to equivalent Canadian health care costs by reducing costs by 29% to reflect excess health care prices in the US.[287,288] This value was then adjusted to 2013 CAD based on differences in the value of the two currencies that year (see below) for an estimated cost of $3,826.[289]
- Gloede and coauthors in Australia estimated the ongoing annual costs (including informal care and out-of-pocket costs) associated with an ischemic stroke to be $7,996 (in 2010 AUD) while costs associated with a haemorrhagic stroke were

[279] Krueger H, Lindsay P, Cote R et al. Cost avoidance associated with optimal stroke care in Canada. *Stroke*. 2012; 43(8): 2198-206.
[280] Campbell and Cochrane Economics Methods Group. *CCEMG – EPPI-Centre Cost Converter*. 2016. Available at https://eppi.ioe.ac.uk/costconversion/. Accessed December 2016.
[281] de Oliveira C, Bremner K, Pataky R et al. Understanding the costs of cancer care before and after diagnosis for the 21 most common cancers in Ontario: a population-based descriptive study. *Canadian Medical Association Journal Open*. 2013; 1(1): E1-E8.
[282] Dehmer S, Maciosek M, LaFrance A et al. Health benefits and cost-effectiveness of asymptomatic screening for hypertension and high cholesterol and aspirin counseling for primary prevention. *The Annals of Family Medicine*. 2017; 15(1): 23-36.
[283] Anderson GF, Reinhardt UE, Hussey PS et al. It's the prices, stupid: why the United States is so different from other countries. *Health Affairs*. 2003; 22(3): 89-105.
[284] Reinhardt U. *Why Does US Health Care Cost So Much? (Part I)*. 2008. Available at https://economix.blogs.nytimes.com/2008/11/14/why-does-us-health-care-cost-so-much-part-i/. Accessed January 2017.
[285] The US and Canadian dollars were roughly on par during 2012. See http://www.bankofcanada.ca/rates/exchange/10-year-converter/. Accessed January, 2017.
[286] Dehmer S, Maciosek M, LaFrance A et al. Health benefits and cost-effectiveness of asymptomatic screening for hypertension and high cholesterol and aspirin counseling for primary prevention. *The Annals of Family Medicine*. 2017; 15(1): 23-36.
[287] Anderson GF, Reinhardt UE, Hussey PS et al. It's the prices, stupid: why the United States is so different from other countries. *Health Affairs*. 2003; 22(3): 89-105.
[288] Reinhardt U. *Why Does US Health Care Cost So Much? (Part I)*. 2008. Available at https://economix.blogs.nytimes.com/2008/11/14/why-does-us-health-care-cost-so-much-part-i/. Accessed January 2017.
[289] The US and Canadian dollars were roughly on par during 2012. See http://www.bankofcanada.ca/rates/exchange/10-year-converter/. Accessed January, 2017.

$10,251.[290] Based on a mix of 85% ischemic strokes,[291] the weighted cost would be $8,335. We converted this cost to 2013 CAD ($7,358).[292]

- For modelling purposes, we used the midpoint between $3,826 and $7,358 in the base case ($5,592, Table 3-3, row an) and the extremes in the sensitivity analysis.
- Maroun et al. estimated the lifetime costs of colorectal cancer management in Canada in 1998. Of those patients who survived the initial year following diagnosis, approximately 33% were subsequently treated for metastases, 10% for local recurrence and the remainder received well-patient follow-up, at a cost of $8,200 / $6,700 and $750, respectively.[293] The weighted lifetime cost of managing colorectal cancer for patients who survive at least one year would therefore be $3,804 ($8,200*33% + $6,700*10% + $750*57%) in 1998 CAD. We adjusted these costs to 2013 CAD using the health and personal care component of the BC Consumer Price Index (CPI) (+20.5%) for a cost of $4,583 (Table 3-3, row ao).[294]
- **Costs incurred** - In a study of 936 patients with acute upper gastrointestinal bleeding in the UK, the mean hospital stay was 5.34 days with total hospital costs of £2,458 (in 2012/13 £). Mean post hospital discharge costs to day 28 were £391. In addition, patients received an average of £357 in unpaid informal care.[295] We converted the total cost of £3,206 to $5,660 CAD (Table 3-3, row aw).[296]
- Specogna and colleagues found that the cost of hospital care in Calgary, Alberta for spontaneous intracerebral hemorrhage to be $10,544 (in 2008 USD), with significant variability in the range (from $364 to $265,470). Death in hospital was associated with a $5,093 (48%) reduction in costs.[297]
- For modelling purposes, we assumed that the cost of care associated with dying from a haemorrhagic stroke would be 48% lower than the estimated $18,571 costs of care in the first year following a stroke (or $9,657, Table 3-3, row ax).
- Discount rate of 3%.

Based on these assumptions, the CE associated with screening for and initiating use of low-dose aspirin for the primary prevention of CVD and CRC in adults between the ages of 50 and 69 years who have a 10% or greater 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years is $37,758 / QALY (Table 3-3, row bh).

[290] Gloede T, Halbach S, Thrift A et al. Long-term costs of stroke using 10-year longitudinal data from the North East Melbourne Stroke Incidence Study. *Stroke*. 2014: 1-8.
[291] Krueger H, Lindsay P, Cote R et al. Cost avoidance associated with optimal stroke care in Canada. *Stroke*. 2012; 43(8): 2198-206.
[292] Campbell and Cochrane Economics Methods Group. *CCEMG – EPPI-Centre Cost Converter*. 2016. Available at https://eppi.ioe.ac.uk/costconversion/. Accessed December 2016.
[293] Maroun J, Ng E, Berthelot J et al. Lifetime costs of colon and rectal cancer management in Canada. *Chronic Diseases and Injuries in Canada*. 2003; 24(4): 91-101.
[294] Statistics Canada. *Table 326-0021 Consumer Price Index*. 2002. Government of Canada. Available at http://www5.statcan.gc.ca/cansim/a26?id=3260021. Accessed February 2017.
[295] Campbell H, Stokes E, Bargo D et al. Costs and quality of life associated with acute upper gastrointestinal bleeding in the UK: cohort analysis of patients in a cluster randomised trial. *British Medical Journal Open*. 2015; 5(4): e007230.
[296] Campbell and Cochrane Economics Methods Group. *CCEMG – EPPI-Centre Cost Converter*. 2016. Available at https://eppi.ioe.ac.uk/costconversion/. Accessed December 2016.
[297] Specogna A, Patten S, Turin T et al. Cost of spontaneous intracerebral hemorrhage in Canada during 1 decade. *Stroke*. 2014; 45(1): 284-6.

Table 3-3: CE of Screening for and Initiating Use of Aspirin in Adults Between the Ages of 50 and 59 Years with an Intermediate or Higher Risk of CVD in a Birth Cohort of 40,000			
Row Label	**Variable**	**Base Case**	**Data Source**
a	# of individuals alive at age 54 in birth cohort	38,310	Table 3-1
b	# of life years lived between the ages of 50-59 in birth cohort	371,091	Table 3-2
c	% of life years at intermediate or high risk	32.8%	Table 3-2
d	# of life years at intermediate or high risk	121,739	= (b * c)
e	Lifetime number of screens	3.0	Assumed
f	Potential screens with 100% adherence	114,930	= (a * e)
g	Adherence with offers to receive screening	70%	Assumed
h	Total # of screens in birth cohort	80,451	= (e * f)
	Estimated cost of screening		
i	Number of office visits associated with screening - low risk	1	Assumed
j	Number of office visits associated with screening - medium or high risk	2	Assumed
k	Cost of 10-minute office visit	$34.00	√
l	Cost of a follow-up phone call	$15.00	√
m	Cost to measure cholesterol	$21.31	√
n	Health care costs of screening - low risk	$3,800,868	= (1 - c) * h * l * (k + l + m)
o	Health care costs of screening - medium and high risk	$2,357,118	= ((c * h) * j) * (k + m * 0.5)
p	Patient time required / office visit (hours)	2	√
q	Value of patient time (per hour)	$28.78	√
r	Value of patient time and travel for screening	$6,149,929	=(((c * h * j) + ((1 - c) * h * j))) * p * q
	Estimated cost of intervention		
s	Proportion of clinicians advising aspirin use for primary prevention	54%	Assumed
t	Proportion of patients complying with clinician recommendation to take aspirin	79%	√
u	Adherence with long-term aspirin therapy in intermediate & high risk cohort	30.0%	=1 * g * s * t
v	Years on aspirin therapy	36,522	= (d * u)
w	Cost of aspirin therapy / year	$54.70	√
x	Cost of aspirin therapy	$1,997,750	= (v * w)
y	Follow-up office visits / year on aspirin therapy	1.0	Assumed
z	Health care costs of intervention	$1,241,746	= v * y * k
aa	Value of patient time and travel for intervention	$2,102,203	= v * y * p * q
	Estimated costs avoided due to intervention		
ab	# of nonfatal cardiovascular events avoided	51.8	= Table 3-2, row am * u
ac	# of nonfatal cerebrovascular events avoided	14.3	= Table 3-2, row ap * u
ad	# of nonfatal colorectal cancer events avoided	61.1	= Table 3-2, row as * u
ag	# of fatal colorectal cancer events avoided	36.6	= Table 3-2, row n * Table 3-2, row au * u
ah	First year costs avoided per nonfatal cardiovascular event avoided	$26,337	√
ai	First year costs avoided per nonfatal cerebrovascular event avoided	$18,571	√
aj	First year costs avoided per nonfatal colorectal cancer event avoided	$37,945	√
ak	Costs avoided per fatal colorectal cancer event avoided	$46,703	√
al	First year costs avoided	$5,655,089	=(ab*ah)+(ac*ai)+(ad*aj)+(ae*ak)
am	Post-first-year annual costs avoided for nonfatal cardiovascular events avoided (per year)	$1,768	√
an	Post-first-year annual costs avoided for nonfatal cerebrovascular events avoided (per year)	$5,592	√
ao	Post-first-year annual costs avoided for nonfatal colorectal cancer events avoided (over lifetime)	$4,583	√
ap	Post-first-year costs avoided for nonfatal cardiovascular events avoided	$2,309,365	= (ab * Table 3-2, row r * am)
aq	Post-first-year costs avoided for nonfatal cerebrovascular events avoided	$2,018,325	= (x * Table 3-2, row x* ag)
ar	Post-first-year costs avoided for nonfatal colorectal cancer events avoided	$279,836	= (ad * ao)
as	Costs avoided due to intervention	$10,262,615	= al + ap + aq + ar
	Estimated costs incurred due to intervention		
at	# of gastrointestinal bleeds incurred	29.0	= Table 3-2, row be * u
au	# of nonfatal haemorrhagic strokes incurred	9.4	= (Table 3-2, row bf - Table 3-2, row bj) * u
av	# of fatal haemorrhagic strokes incurred	6.2	= Table 3-2, row bj * u
aw	Costs per nonfatal gastrointestinal bleed	$5,660	√
ax	Cost per fatal haemorrhagic stroke	$9,657	= ai * 0.52
ay	Costs incurred due to intervention	$1,542,726	= (at * aw) + (av * ax) + (an * Table 3-2, row x * an)
	CE Calculation		
az	Cost of intervention over lifetime of birth cohort	$17,649,613	= n + o + r + x + z + aa
ba	Costs avoided due to intervention over lifetime of birth cohort	$10,262,615	= as
bb	Costs incurred due to intervention over lifetime of birth cohort	$1,542,726	= ay
bc	Net QALYs saved	448	Table 3-2, row bv
bd	Cost of intervention over lifetime of birth cohort (3% discount)	$13,522,956	Calculated
be	Costs avoided due to intervention over lifetime of birth cohort (3% discount)	$5,798,900	Calculated
bf	Costs incurred due to intervention over lifetime of birth cohort (3% discount)	$925,979	Calculated
bg	Net QALYs saved (3% discount)	229	Calculated
bh	**CE ($/QALY saved)**	**$37,758**	= (bd + bf - be)/bg

√ = Estimates from the literature

For our sensitivity analysis, we modified a number of major assumptions and recalculated the CE as follows:

- Assume that decreased risk of cardiovascular disease events associated with aspirin use is reduced from 17% to 6% (Table 3-2, row al), the decreased risk of cerebrovascular disease events is reduced from 14% to 2% (Table 3-2, row ao), the decreased risk of incident CRC is reduced from 40% to 24% (Table 3-2, row ar) and the decreased risk of mortality due to CRC is reduced from 33% to 14% (Table 3-2, row au): CE = N**ot cost-effective as there is a net loss in QALYs**.
- Assume that decreased risk of cardiovascular disease events associated with aspirin use is increased 17% to 26% (Table 3-2, row al), the decreased risk of cerebrovascular disease events is increased from 14% to 24% (Table 3-2, row ao), the decreased risk of incident CRC is increased from 40% to 53% (Table 3-2, row ar) and the decreased risk of mortality due to CRC is increased from 33% to 48% (Table 3-2, row au): CE = $7,603.
- Assume that the disutility per year associated with taking pills for cardiovascular prevention is reduced from -0.0024 to -0.000 (Table 3-2, row ax): CE = $28,258.
- Assume that the disutility per year associated with taking pills for cardiovascular prevention is increased from -0.0024 to -0.0033 (Table 3-2, row ax): CE = $43,204.
- Assume that the rate of a major bleeding event in a 50-69 year old not taking aspirin is reduced from 1.99 to 1.82 per 1,000 person-years (Table 3-2, row az) while the rate of a major bleeding event in a 50-69 year old who is taking aspirin is reduced from 3.21 to 2.93 per 1,000 person-years (Table 3-2, row ba): CE = $34,914.
- Assume that the rate of a major bleeding event in a 50-69 year old not taking aspirin is increased from 1.99 to 2.18 per 1,000 person-years (Table 3-2, row az) while the rate of a major bleeding event in a 50-69 year old who is taking aspirin is increased from 3.21 to 3.53 per 1,000 person-years (Table 3-2, row ba): CE = $41,688.
- Assume that the proportion of patients complying with clinician recommendation to take aspirin is reduced from 79% to 71% (Table 3-3, row r): CE = $42,246.
- Assume that the proportion of patients complying with clinician recommendation to take aspirin is increased from 79% to 85% (Table 3-3, row r): CE = $34,914.
- Assume that the first year costs avoided per nonfatal cerebrovascular event avoided are reduced from $18,571 to $12,196 (Table 3-3, row ab): CE = $37,937.
- Assume that the first year costs avoided per nonfatal cerebrovascular event avoided are increased from $18,571 to $24,947 (Table 3-3, row ab): CE = $37,579.
- Assume that the post-first-year annual costs avoided for nonfatal cerebrovascular events avoided are reduced from $5,592 (per year) to $3,826 (per year) (Table 3-3, row ag): CE = $38,318.
- Assume that the post-first-year annual costs avoided for nonfatal cerebrovascular events avoided are increased from $5,592 (per year) to $7,358 (per year) (Table 3-3, row ag): CE = $37,198.

Summary

Table 3-4: Screening for and Initiating Use of Aspirin in Adults Aged 50 to 59 Years with an Intermediate or Higher Risk of CVD in a Birth Cohort of 40,000

Summary

	Base Case	Range	
CPB (Potential QALYs Gained)			
Gap between No Service and 'Best in the World' (30%)			
3% Discount Rate	229	-57	251
0% Discount Rate	448	-33	693
Gap between estimated B.C. Current (15%) and 'Best in the World' (30%)			
3% Discount Rate	115	-29	126
0% Discount Rate	224	-17	347
CE ($/QALY) **including** patient time costs			
3% Discount Rate	$37,758	Dominated (Not Cost-Effective)	$12,405
0% Discount Rate	$19,938		$4,467
CE ($/QALY) **excluding** patient time costs			
3% Discount Rate	$10,159		-$1,337
0% Discount Rate	$1,513		-$5,408

United States Preventive Services Task Force Recommendations (USPSTF; 2017)[298]

The USPSTF recommends that all women who are planning or capable of pregnancy take a daily supplement containing 0.4 to 0.8 mg (400-800µg) of folic acid (Grade A recommendation).

The critical period of supplementation starts at least 1 month before conception and continues through the first 2 to 3 months.

Canadian Task Force on Preventive Health Care (CTFPHC; 1994)[299]

For women at low risk of having a fetus with an NTD, there is fair to good evidence that supplementation with folic acid at a dosage of 0.4 mg/d (fair evidence from analytic studies) to 0.8 mg/d (good evidence from an RCT) reduces the risk of an NTD. To be effective, supplementation should begin at least 1 month before conception and continue during the first trimester. We do not know whether women whose diet meets the current recommended standards for folic acid consumption during pregnancy must also take vitamin supplements. Whether nutritional interventions to increase the level of folates in the diet of the population at risk would be as effective as supplementation is also unknown.

Given the lack of harmful effects of such supplementation and other benefits of a good diet, all women of childbearing age capable of becoming pregnant, including those taking oral contraceptives, should be advised to increase their daily intake of folic acid to meet the recommended periconceptional and pregnancy requirement of 0.4 mg. Supplementation appears to be the most practical way to achieve this goal (Grade A recommendation).

Utilization of This Clinical Preventive Service

Currently in British Columbia

In a survey conducted at Children's and Women's Health Center in BC in 1999, 71% of women surveyed knew that vitamins could prevent birth defects, however only 49.4% of all women took vitamins prior to pregnancy.[300]

Based on the Canadian Maternity Experiences Survey conducted between October of 2006 and January of 2007, 61.3% of women who were 5 to 14 months postpartum living in BC reported taking folic acid supplementation three months before pregnancy and 93.9% reported taking it during the first three months of pregnancy.[301]

[298] Bibbins-Domingo K, Grossman D, Curry S et al. Folic acid supplementation for the prevention of neural tube defects: US Preventive Services Task Force recommendation statement. *Journal of American Medical Association*. 2017; 317(2): 183-9.
[299] Goldbloom R, Battista R, Anderson G et al. Periodic health examination, 1994 update: 3. Primary and secondary prevention of neural tube defects. Canadian Task Force on the Periodic Health Examination. *Canadian Medical Association Journal*. 1994; 151(2): 159-66.
[300] Morin V, Mondor M and Wilson R. Knowledge on periconceptional use of folic acid in women of British Columbia. *Fetal Diagnosis and Therapy*. 2001; 16(2): 111-5.
[301] Nelson C, Leon J and Evans J. The relationship between awareness and supplementation: which Canadian women know about folic acid and how does that translate into use. *Canadian Journal of Public Health*. 2014; 105(1): e40-6.

Folic acid supplementation is just one source of folic acid. For example, folic acid is naturally available in some foods and is added to white flour, pasta and cornmeal during manufacturing. Fortification of grains began in 1996 as a response to the growing awareness of the benefits of folic acid. It is therefore important to consider all sources of folic acid.

One way to do this is by measuring the concentration of red blood cell folate. Based on the 2007 – 2009 *Canadian Health Measures Survey*, 22% of women of childbearing age (ages 15 to 45) exhibited a low concentration of red blood cell folate. Specifically, it was below the level considered to be the optimal level for minimizing the risk of neural tube defects (<906 nmol/L). The inverse argument could also be made, namely that 78% of Canadian women of reproductive age have sufficient folate intake to minimize the risk of NTDs.[302]

This result is for Canadian women and not specific to BC. Can we assume that the proportion of women in BC who have the recommended level of red blood cell folate is at least equivalent (or higher) than the national average? The BC Guidelines on *Folate Deficiency* note that over 99% of folate tests from two laboratories in BC in 2010 were normal. Serum folate and red blood cell folate tests are no longer being offered in BC except with special approval.[303]

Another approach to assessing the current levels of folic acid is to consider the prevalence of NTDs among live births, still births and terminations of pregnancies. In BC, these rates have historically been among the lowest in Canada. The very lowest rates have been demonstrated in the province of Ontario. During 2000 to 2002, the rate of NTDs in BC was 7.5 / 10,000 births[304] compared to a rate of 5.8 in Ontario between 1998 and 2000.[305]

Best in the World

Based on the Canadian Maternity Experiences Survey conducted between October of 2006 and January of 2007, 67.5% of women who were 5 to 14 months postpartum living in the Yukon reported taking folic acid supplementation three months before pregnancy.[306] This 67.5% is only minimally better than the 61.3% observed in BC noted above.

Data from the 2007 to 2012 US National Health and Nutrition Survey, 22.8% (95% CI of 21.1% to 24.6%) of women ages 12 to 49 in the US had a concentration of red blood cell folate below that considered to be optimal for minimizing the risk of neural tube defects.[307]

[302] Colapinto C, O'Connor D and Tremblay M. Folate status of the population in the Canadian Health Measures Survey. *Canadian Medical Association Journal*. 2011; 183(2): E100-E6.
[303] BCGuidelines. *Folate Deficiency- Investigation and Management*. 2012. Available at http://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/bc-guidelines/folate-deficiency. Accessed March 2017.
[304] De Wals P, Tairou F, Van Allen M et al. Reduction in neural-tube defects after folic acid fortification in Canada. *New England Journal of Medicine*. 2007; 357(2): 135-42.
[305] Ray J, Meier C, Vermeulen M et al. Association of neural tube defects and folic acid food fortification in Canada. *The Lancet*. 2002; 360(9350): 2047-8.
[306] Nelson C, Leon J and Evans J. The relationship between awareness and supplementation: which Canadian women know about folic acid and how does that translate into use. *Canadian Journal of Public Health*. 2014; 105(1): e40-6.
[307] Tinker S, Hamner H, Qi Y et al. US women of childbearing age who are at possible increased risk of a neural tube defect-affected pregnancy due to suboptimal red blood cell folate concentrations, National Health and Nutrition Examination Survey 2007 to 2012. *Birth Defects Research Part A: Clinical and Molecular Teratology*. 2015; 103(6): 517-26.

This is almost equivalent to the 22% observed in the 2007 – 2009 Canadian Health Measures Survey noted above. [308]

For modelling purposes, we assumed that it would be possible to lower the rate of NTDs in BC from 7.5 / 10,000 births to the 5.8 / 10,000 births observed in Ontario.[309]

Relevant British Columbia Population in 2013

In 2013, a total of 945,397 females between the ages of 15 and 45 were living in BC.[310]

Modelling CPB and CE

In this section, we will calculate the CPB and CE associated with advising all women of reproductive age to take a daily supplement containing 0.4 to 0.8 mg (400-800µg) of folic acid.

In estimating CPB, we made the following assumptions:

What are Neural Tube Defects?

- "NTDs are major birth defects of the brain and spine that occur early in pregnancy as a result of improper closure of the embryonic neural tube, which can lead to death or varying degrees of disability. The two most common NTDs are anencephaly and spina bifida." [311]
- Anencephaly is a serious birth defect in which a baby is born without parts of the brain and skull.
- "Spina bifida is a congenital malformation in which the spinal column is split (bifid) as a result of failed closure of the embryonic neural tube, during the fourth week post-fertilization."[312]
- NTDs are caused by a variety of genetic and non-genetic factors, although the contributing role of each is not fully known. Between 10% and 60% of NTDs have a genetic component. Lack of folic acid is perhaps the best known risk factor but there are a number of potential behavioural and environmental risk factors, such as alcohol use, smoking, poor nutrition, valproic acid use and indoor air pollution. Consequently, some women who take folic acid supplements in the periconceptional period still experience NTD-affected pregnancies.[313]
- The WHO has wrestled with determining what proportion of NTDs are preventable given optimal (<906 nmol/L) red blood cell folate concentrations in the population. If these levels are uniformly achieved, the rate of NTDs could fall somewhere within the range of 4 to 9 per 10,000 live births.[314, 315]

[308] Colapinto C, O'Connor D and Tremblay M. Folate status of the population in the Canadian Health Measures Survey. *Canadian Medical Association Journal*. 2011; 183(2): E100-E6.
[309] Ray J, Meier C, Vermeulen M et al. Association of neural tube defects and folic acid food fortification in Canada. *The Lancet*. 2002; 360(9350): 2047-8.
[310] See http://www.bcstats.gov.bc.ca/StatisticsBySubject/Demography/PopulationEstimates.aspx. Accessed January 2017.
[311] Williams J, Mai C, Mulinare J et al. Updated estimates of neural tube defects prevented by mandatory folic acid fortification - United States, 1995–2011. *Morbidity and Mortality Weekly Report*. 2015; 64(1): 1-5.
[312] Copp A, Adzick N, Chitty L et al. Spina bifida. *Nature Reviews Disease Primers*. 2015; 1: 1-45.
[313] Copp A, Adzick N, Chitty L et al. Spina bifida. *Nature Reviews Disease Primers*. 2015; 1: 1-45.
[314] World Health Organization. *Guideline: Optimal Serum and Red Blood Cell Folate Concentrations in Women of Reproductive Age for Prevention of Neural Tube Defects*. 2015. World Health Organization. Available at http://www.who.int/iris/handle/10665/161988. Accessed February 2017.

Prevalence of Neural Tube Defects

- Between 1993 and 2002, a total of 2,446 NTDs were among live births, still births and terminations of pregnancies in seven Canadian Provinces.[316] Of the 2,446 neural tube defects identified in seven Canadian provinces between 1993 and 2002, 1,466 (60%) were terminations of pregnancy, 112 (5%) were stillbirth and 868 (35%) were live birth. The majority of NTDs were either spina bifida (53%) or anencephaly (34%) (see Table 4-1).[317]

Table 4-1: NTDS by Diagnostic Category and Pregnancy Outcome In Seven Canadian Provinces, 1993 to 2002.

Diagnostic Category	*Pregnancy Outcome* Induced Abortion	Stillbirth	Live Birth	Total	% of Total
Spina bifida	595	35	656	1,286	53%
Anencephaly	668	67	95	830	34%
Encephalocele	160	8	115	283	12%
Unspecified NTD	24	0	0	24	1%
Iniencephaly	19	2	2	23	1%
All NTDs	**1,466**	**112**	**868**	**2,446**	
% of Total	60%	5%	35%		

- Based on data from these seven provinces between January 1, 1993 and September 30, 1997, the prevalence of NTDs among live births, still births and terminations of pregnancies was 15.8 per 10,000 live births.[318] BC's rate, at 9.6 per 10,000, was the lowest of the seven provinces (see Table 4-2).

Table 4-2: Prevalance of NTDS / 10,000 Births In Seven Canadian Provinces January 1, 1993 to September 30, 1997

Province	Rate
N/L	45.6
NS	27.2
PEI	20.8
PQ	17.7
MB	15.4
AB	11.2
BC	9.6
Combined	**15.8**

Evidence of the Effectiveness of Folic Acid Supplementation in Reducing the Prevalence of NTDs

- In Hungary in the mid-1980s, 7,540 women planning to conceive were randomly assigned to receive a prenatal vitamin supplement (including 0.8 mg of folic acid) or

[315] Tinker S, Hamner H, Qi Y et al. US women of childbearing age who are at possible increased risk of a neural tube defect-affected pregnancy due to suboptimal red blood cell folate concentrations, National Health and Nutrition Examination Survey 2007 to 2012. *Birth Defects Research Part A: Clinical and Molecular Teratology*. 2015; 103(6): 517-26.

[316] The seven provinces include Newfoundland & Labrador, Prince Edward Island, Nova Scotia, Quebec, Manitoba, Alberta and British Columbia.

[317] De Wals P, Tairou F, Van Allen M et al. Reduction in neural-tube defects after folic acid fortification in Canada. *New England Journal of Medicine*. 2007; 357(2): 135-42.

[318] De Wals P, Tairou F, Van Allen M et al. Reduction in neural-tube defects after folic acid fortification in Canada. *New England Journal of Medicine*. 2007; 357(2): 135-42.

a trace element supplement, starting one month prior to conception and for three months after conception. In the evaluation of 4,704 pregnancies and 4,122 live births, 28 congenital malformations were observed in the experimental group vs. 47 in the control group. Six of the congenital malformations in the control group were neural-tube defects (NTDs) vs. none in the experimental group.[319] Given the results of this trial, RCTs are no longer considered ethically possible because of the clear benefits of folic acid supplementation.[320]

- Other cohort and case control studies completed between 1976 and 1998 consistently found evidence of a protective effect associated with folic acid supplementation.[321]
- Case control studies since 1998 have not consistently demonstrated a protective association with folic acid supplementation, but these studies tend to be weakened by misclassification and recall bias.[322]

Fortification of Grain Products with Synthetic Folic Acids

- The evidence of the effectiveness of folic acid supplementation in reducing the prevalence of NTDs noted above led to a 1992 recommendation by the US Public Health Service that all women of childbearing age consume 400µg (0.4 mg) of folic acid daily, followed by the US Food and Drug Administration authorization to add synthetic folic acid to grain products in March of 1996 with mandatory compliance by January of 1998.[323]
- In Canada, the milling industry began fortification early in 1997 to meet US requirements for imported flour. On November 11, 1998, fortification of all types of white flour, enriched pasta and cornmeal became mandatory in Canada.[324, 325]
- The prevalence of NTDs among live births, still births and terminations of pregnancies declined from 10.7 cases per 10,000 live births before the implementation of food fortification in the US (1995 to 1996) to 7.0 cases per 10,000 live births after fortification.[326]
- In Canada, the prevalence of neural tube defects among live births, still births and terminations of pregnancies decreased from 15.8 to 8.6 per 10,000 live births between January 1, 1993 and December 31, 2002 (see Table 4-3).[327] The time period was divided into three 'fortification' periods. The pre-fortification period ran from January 1, 1993 to September 30, 1997 to coincide with the beginning of flour

[319] Czeizel A and Dudás I. Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. *New England Journal of Medicine*. 1992; 327(26): 1832-5.
[320] Viswanathan M, Treiman K, Kish-Doto J et al. Folic acid supplementation for the prevention of neural tube defects: an updated evidence report and systematic review for the US Preventive Services Task Force. *Journal of American Medical Association*. 2017; 317(2): 190-203.
[321] Viswanathan M, Treiman K, Kish-Doto J et al. Folic acid supplementation for the prevention of neural tube defects: an updated evidence report and systematic review for the US Preventive Services Task Force. *Journal of American Medical Association*. 2017; 317(2): 190-203.
[322] Viswanathan M, Treiman K, Kish-Doto J et al. Folic acid supplementation for the prevention of neural tube defects: an updated evidence report and systematic review for the US Preventive Services Task Force. *Journal of American Medical Association*. 2017; 317(2): 190-203.
[323] Williams L, Mai C, Edmonds L et al. Prevalence of spina bifida and anencephaly during the transition to mandatory folic acid fortification in the United States. *Teratology*. 2002; 66(1): 33-9.
[324] De Wals P, Tairou F, Van Allen M et al. Reduction in neural-tube defects after folic acid fortification in Canada. *New England Journal of Medicine*. 2007; 357(2): 135-42.
[325] Ray J. Efficacy of Canadian folic acid food fortification. *Food and Nutrition Bulletin*. 2008; 29(2): S225-30.
[326] Williams J, Mai C, Mulinare J et al. Updated estimates of neural tube defects prevented by mandatory folic acid fortification - United States, 1995–2011. *Morbidity and Mortality Weekly Report*. 2015; 64(1): 1-5.
[327] De Wals P, Tairou F, Van Allen M et al. Reduction in neural-tube defects after folic acid fortification in Canada. *New England Journal of Medicine*. 2007; 357(2): 135-42.

fortification in Canada. The partial fortification period ran from October 1, 1997 to March 31, 2000 based on evidence from Ontario that red-cell folate levels in the population started to increase in April 1997 and reached a plateau in February 1999.[328] The full fortification period ran from April 1, 2000 to December 31, 2002. The biggest reduction between the pre-fortification and full fortification periods was observed in Newfoundland and Labrador (from 45.6 to 7.6 per 10,000) while the smallest reduction was observed in BC (from 9.6 to 7.5 per 10,000). BC already had the lowest prevalence of NTDs (at 9.6 per 10,000) in the country before fortification (see Table 4-3).

Table 4-3: Prevalance of NTDS / 10,000 Births In Seven Canadian Provinces According to Fortification Period

	Fortification Period		
Province	Prefortification	Partial Fortification	Full Fortification
N/L	45.6	14.2	7.6
NS	27.2	13.2	12.6
PEI	20.8	10.6	0.0
PQ	17.7	12.7	9.7
MB	15.4	8.8	9.3
AB	11.2	7.3	6.7
BC	9.6	10.8	7.5
Combined	**15.8**	**10.9**	**8.6**

- The prevalence of neural tube defects among live births, still births and terminations of pregnancies declined from 11.3 cases per 10,000 live births before the implementation of food fortification in Ontario (1994 to 1997) to 5.8 cases per 10,000 live births after fortification (1998 to 2000).[329] Ontario's data was not included in Tables 4-1 to 4-3 because the review by De Wals et al focussed on seven provinces rather than all of Canada.

Modelling in a BC Birth Cohort of 40,000

- Based on BC life tables for 2009 to 2011,[330] an estimated 19,665 females would survive through to age 44 in a BC birth cohort of 40,000 (see Table 4-4). Note that the birth cohort includes both males and females. Our analysis focusses on just the females of reproductive age in this cohort. Based on age specific fertility rates,[331] an estimated 28,110 live births would occur between the ages of 15 and 44 in this cohort of females (see Table 4-4).

- For modelling purposes, we have assumed that the pre-fortification rate of NTDs in BC would be approximately 11 / 10,000 live births, followed by a rate of 7.5 / 10,000 live births post-fortification (see Table 4-3). We have chosen the higher rate of 10.8 (rounded to 11) seen during the partial fortification period in BC (see Table 4-3) rather than the 9.6 seen during prefortification as a conservative approach (recognizing that the lower 9.6 seen during prefortification in BC may be an anomaly as the rate was reduced from prefortification to partial fortification in all provinces except BC). Furthermore, we have assumed that this could be further reduced to 5.8 /

[328] Ray J, Vermeulen M, Boss S et al. Declining rate of folate insufficiency among adults following increased folic acid food fortification in Canada. *Canadian Journal of Public Health*. 2002; 93(4): 249-53.
[329] Ray J, Meier C, Vermeulen M et al. Association of neural tube defects and folic acid food fortification in Canada. *The Lancet*. 2002; 360(9350): 2047-8.
[330] See http://www.statcan.gc.ca/pub/84-537-x/2013005/tbl-eng.htm. Accessed January 2017.
[331] See http://www.bcstats.gov.bc.ca/StatisticsBySubject/Demography/VitalStatistics.aspx. Accessed February 2017.

10,000 live births based on Ontario's full fortification rate noted above.[332] In the sensitivity analysis, we modelled the effect of reducing this rate to 4.0 / 10,000, the lowest range considered achievable by the WHO given optimal red blood cell folate concentrations in the population.[333]

- We have also assumed that 39% (830 of 2,116) of pregnancies with NTD would be anencephaly and 61% (1,286 of 2,116) spina bifida (see Table 4-1). Furthermore, 11.4% of pregnancies with anencephaly and 51% of pregnancies with spina bifida would result in a live birth (see Table 4-1). Based on these assumptions, an estimated 9.6 live births with spina bifida would have occurred in the birth cohort pre-fortification. The estimated post-fortification status would be 6.5 live births with spina bifida with the potential to be further reduced to 5.1 live births with spina bifida if Ontario's rate of 5.8 / 10,000 were achieved (see Table 4-4). Likewise, an estimated 0.9 live births with anencephaly would occur post-fortification with the potential to reduce this to 0.7 live births with anencephaly if Ontario's rate of 5.8 / 10,000 were achieved (see Table 4-4).

Table 4-4: Females Ages 15-44, Live Births and Pregnancies with Neural Tube Defects
in a British Columbia Birth Cohort of 40,000

					Estimated Prefortification Status					***Estimated Current Status***					***Estimated Potential Status***				
Age Group	*Mean Survival* Females	*Females in Birth Cohort*	*Life Years Lived*	# of Live Births	Est. # of NTDs	Anen-cephaly	Spina Bifida	*Live Birth with* Anen-cephaly	Spina Bifida	Est. # of NTDs	Anen-cephaly	Spina Bifida	*Live Birth with* Anen-cephaly	Spina Bifida	Est. # of NTDs	Anen-cephaly	Spina Bifida	*Live Birth with* Anen-cephaly	Spina Bifida
15-19	0.995	19,899	99,495	759	0.8	0.3	0.5	0.0	0.3	0.6	0.2	0.3	0.0	0.2	0.4	0.2	0.3	0.0	0.1
20-24	0.994	19,872	99,361	3,241	3.6	1.4	2.2	0.2	1.1	2.4	1.0	1.5	0.1	0.8	1.9	0.7	1.1	0.1	0.6
25-29	0.992	19,839	99,197	7,489	8.2	3.2	5.0	0.4	2.6	5.6	2.2	3.4	0.3	1.7	4.3	1.7	2.6	0.2	1.3
30-34	0.990	19,803	99,014	9,895	10.9	4.3	6.6	0.5	3.4	7.4	2.9	4.5	0.3	2.3	5.7	2.3	3.5	0.3	1.8
35-39	0.987	19,744	98,721	5,573	6.1	2.4	3.7	0.3	1.9	4.2	1.6	2.5	0.2	1.3	3.2	1.3	2.0	0.1	1.0
40-44	0.983	19,665	98,324	1,152	1.3	0.5	0.8	0.1	0.4	0.9	0.3	0.5	0.0	0.3	0.7	0.3	0.4	0.0	0.2
Total			**594,112**	**28,110**	**30.9**	**12.1**	**18.8**	**1.4**	**9.6**	**21.1**	**8.3**	**12.8**	**0.9**	**6.5**	**16.3**	**6.4**	**9.9**	**0.7**	**5.1**

- A 2015 Cochrane Review found that there is high quality evidence that daily folic acid supplementation (alone or in combination with other vitamins and minerals) prevents NTDs when compared with no intervention/placebo or vitamins and minerals without folic acid (RR of 0.31, 95% CI of 0.17 to 0.58). The review also found no evidence of an increase in cleft palate, cleft lip, congenital cardiovascular defects, miscarriages or any other birth defects associated with daily folic acid supplementation.[334]
- The 2017 USPSTF review found no significant evidence of potential harms associated with folic acid supplementation.[335]
- "Spina bifida results from the incomplete closure of the tissue and bone surrounding the spinal cord. Children born with spina bifida can have mild to severe disabilities depending on the location of the lesion along the spinal cord."[336]

[332] Ray J, Meier C, Vermeulen M et al. Association of neural tube defects and folic acid food fortification in Canada. *The Lancet*. 2002; 360(9350): 2047-8.
[333] World Health Organization. *Guideline: Optimal Serum and Red Blood Cell Folate Concentrations in Women of Reproductive Age for Prevention of Neural Tube Defects*. 2015. World Health Organization. Available at http://www.who.int/iris/handle/10665/161988. Accessed February 2017.
[334] De-Regil L, Peña-Rosas J, Fernández-Gaxiola A et al. Effects and safety of periconceptional oral folate supplementation for preventing birth defects. *Cochrane Database of Systematic Reviews.* 2015.
[335] Bibbins-Domingo K, Grossman D, Curry S et al. Folic acid supplementation for the prevention of neural tube defects: US Preventive Services Task Force recommendation statement. *Journal of American Medical Association*. 2017; 317(2): 183-9.
[336] Tilford J, Grosse S, Robbins J et al. Health state preference scores of children with spina bifida and their caregivers. *Quality of Life Research*. 2005; 14(4): 1087-98.

- The mortality rate is substantially higher for individuals with moderate to severe spina bifida than for less severe cases. Oakeshott and colleagues have followed a cohort of individuals with spina bifida for 50 years and found that just 12% with moderate to severe spina bifida survived to age 50, while 54% of those with less severe spina bifida survived to age 50.[337, 338]
- We used this survival data to compare life expectancy in the general population vs. a population with a sacral lesion (least severe) or a lumbar lesion (moderate to severe) (see Table 4-5). If we use 100% to represent the normal life-span of the general population, a person with a sacral lesion will have a life expectancy of 60.6% (or a loss of 39.4% of a normal life expectancy, Table 4-6, row m) and a person with a lumbar lesion will have a life expectancy of 25.1% (or a loss of 74.9% of a normal life expectancy, Table 4-6, row n).

Table 4-5: Survival and Year of Life in a Birth Cohort of 40,000
The General Population Compared to Individuals with Spina Bifida

	General Population					*Individuals with Spina Bifida*					
						Lower Lesion (less severe)			***Higher Lesion (more severe)***		
Age Group	Mean Survival Rate Male	Female	Total	Individuals in Birth Cohort	Years of Life in Birth	Mean Survival Rate	Individuals in Birth Cohort	Years of Life in Birth	Mean Survival Rate	Individuals in Birth Cohort	Years of Life in Birth
0-4	0.996	0.996	0.996	39,846	199,230	0.818	32,727	163,636	0.649	25,965	129,825
5-9	0.995	0.996	0.996	39,823	199,115	0.764	30,545	152,727	0.526	21,053	105,263
10-14	0.995	0.995	0.995	39,809	199,043	0.745	29,818	149,091	0.491	19,649	98,246
15-19	0.994	0.995	0.994	39,773	198,864	0.691	27,636	138,182	0.456	18,246	91,228
20-24	0.991	0.993	0.992	39,683	198,417	0.673	26,909	134,545	0.368	14,737	73,684
25-29	0.987	0.992	0.989	39,572	197,859	0.655	26,182	130,909	0.333	13,333	66,667
30-34	0.983	0.990	0.986	39,451	197,253	0.618	24,727	123,636	0.298	11,930	59,649
35-39	0.977	0.987	0.982	39,293	196,463	0.600	24,000	120,000	0.211	8,421	42,105
40-44	0.971	0.983	0.977	39,075	195,375	0.545	21,818	109,091	0.175	7,018	35,088
45-49	0.961	0.977	0.969	38,765	193,826	0.545	21,818	109,091	0.123	4,912	24,561
50-54	0.947	0.969	0.958	38,310	191,551	0.534	21,363	106,816	0.111	4,457	22,286
55-59	0.926	0.955	0.941	37,627	188,136	0.517	20,680	103,401	0.094	3,774	18,872
60-64	0.894	0.935	0.915	36,591	182,955	0.491	19,644	98,220	0.068	2,738	13,690
65-69	0.847	0.904	0.875	35,009	175,045	0.452	18,062	90,310	0.029	1,156	5,780
70-74	0.776	0.854	0.815	32,600	162,999	0.391	15,653	78,265		0	0
75-79	0.673	0.777	0.725	28,992	144,961	0.301	12,045	60,226		0	0
80+	0.531	0.659	0.595	23,809	119,047	0.172	6,862	34,312		0	0
Total					**3,140,140**			**1,902,458**			**786,945**
% Compared to General Population								60.6%			25.1%

- The research by Oakeshott and colleagues was based on 117 consecutive infants born with spina bifida between 1963 and 1971 in the UK who have been followed until 2013. Of these 117 infants, 40 (34%) died before the age of 5.[339] The 1-year survival of infants born with spina bifida in the US has improved from 87.1% during 1983 to 1987 to 93.6% during 1998 to 2002.[340] To take into account the possibility of better

[337] Oakeshott P, Hunt G, Poulton A et al. Expectation of life and unexpected death in open spina bifida: a 40-year complete, non-selective, longitudinal cohort study. *Developmental Medicine & Child Neurology*. 2009; 52(8): 749-53.
[338] Oakeshott P, Reid F, Poulton A et al. Neurological level at birth predicts survival to the mid-40s and urological deaths in open spina bifida: a complete prospective cohort study. *Developmental Medicine & Child Neurology*. 2015; 57(7): 634-8.
[339] Oakeshott P, Reid F, Poulton A et al. Neurological level at birth predicts survival to the mid-40s and urological deaths in open spina bifida: a complete prospective cohort study. *Developmental Medicine & Child Neurology*. 2015; 57(7): 634-8.
[340] Shin M, Kucik J, Siffel C et al. Improved survival among children with spina bifida in the United States. *Journal of Pediatrics*. 2012; 161(6): 1132-7.e3.

long-term survival of infants currently born with spina bifida, we increased the calculated life expectancy of infants with both a sacral (Table 4-6, row m) and lumbar lesion (Table 4-6, row n) by 25% in the sensitivity analysis.

- Based on a consecutive cohort of 117 children with spina bifida in the UK, the distribution of children were 33.9% (Table 4-6, row g) with a sacral lesion, 28.6% (Table 4-6, row h) with a lower lumbar lesion and 37.5% (Table 4-6, row i) with a higher lumbar lesion.[341]
- Based on a study of 98 children with spina bifida in Arkansas, the average loss in QoL associated with spina bifida was 41%, ranging from 34% (6% to 62%) for the sacral lesion (Table 4-6, row j), 42% (22% to 62%) for the lower lumbar lesion (Table 4-6, row k) and 52% (25% to 78%) for the upper lumbar lesion (Table 4-6, row l). We used plus or minus one standard deviation provided by Tilford et al. in the sensitivity analysis.[342] There was also a modest 5% reduction in the QoL of caregivers. This reduction, however, was only significantly different from control caregivers for the group of parents caring for the most severe children (10% reduction in QoL). A subsequent, more in depth analysis of these caregivers identified less sleep and less frequent engagement in leisure and social activities as key differences compared with a sample of control caregivers.[343]
- Verhoef and colleagues used the SF-36 to compare the QoL in 164 young adults (ages 16 to 25) with spina bifida in Holland. Compared to the average Dutch population ages 16-25, young adults with spina bifida experienced a significant decrement in physical functioning (51%), role limitations due to physical health problems (22%), bodily pain (9%) and general health (17%). No significant differences were observed in vitality, social functioning and role limitations due to emotional health problems or mental health.[344]
- The life expectancy of an infant born in BC of 82 years (Table 4-6, row o) is based on life tables for 2009 to 2011 for BC.[345]
- De Wals and colleagues found that there were 656 live births with spina bifida in seven Canadian provinces between 1993 and 2002. At the same time, 1,466 pregnancies with a diagnosed NTD resulted in an induced abortion (see Table 4-1).[346] We have assumed that for every live birth with spina bifida avoided, an estimated 2.23 abortions (1,466 / 656) would be avoided.

Based on these assumptions, the CPB associated with advising all women who are planning or capable of pregnancy to take a daily supplement containing 0.4 to 0.8 mg (400-800µg) of folic acid is 94 QALYs (see Table 4-6, row ac). The 94 QALYs is based on moving from the current NTD rate in BC of 7.5 per 10,000 births to 5.8 per 10,000 births, the post fortification rate observed in Ontario.

[341] Oakeshott P, Hunt G, Poulton A et al. Expectation of life and unexpected death in open spina bifida: a 40-year complete, non-selective, longitudinal cohort study. *Developmental Medicine & Child Neurology*. 2009; 52(8): 749-53.
[342] Tilford J, Grosse S, Robbins J et al. Health state preference scores of children with spina bifida and their caregivers. *Quality of Life Research*. 2005; 14(4): 1087-98.
[343] Grosse S, Flores A, Ouyang L et al. Impact of spina bifida on parental caregivers: findings from a survey of Arkansas families. *Journal of Child and Family Studies*. 2009; 18(5): 574-81.
[344] Verhoef M, Post M, Barf H et al. Perceived health in young adults with spina bifida. *Developmental Medicine & Child Neurology*. 2007; 49(3): 192-7.
[345] See http://www.statcan.gc.ca/pub/84-537-x/2013005/tbl-eng.htm. Accessed January 2017.
[346] De Wals P, Tairou F, Van Allen M et al. Reduction in neural-tube defects after folic acid fortification in Canada. *New England Journal of Medicine*. 2007; 357(2): 135-42.

Table 4-6: CPB Associated with Advising Women Ages 15 to 44 to Take a Daily Supplement Containing 0.4 to 0.8 mg of Folic Acid in a Birth Cohort of 40,000			
Row Label	**Variable**	**Base Case**	**Data Source**
a	Average # of females ages 15-44 in birth cohort	19,767	Table 5-3
b	Life years lived between the ages of 15 and 44	594,112	Table 5-3
c	Live births between the ages of 15 and 44	28,110	Table 5-3
d	Estimated live births with spina bifida prefortification	9.6	Table 5-3
e	Estimated live births with spina bifida currently	6.5	Table 5-3
f	Estimated potential live births with spina bifida post fortification	5.1	Table 5-3
g	Proportion of children with spina bifida with a sacral lesion (least severe)	33.9%	√
h	Proportion of children with spina bifida with a lower lumbar lesion	28.6%	√
i	Proportion of children with spina bifida with a higher lumbar lesion (most severe)	37.5%	√
j	Loss in QoL with a sacral lesion	34.0%	√
k	Loss in QoL with a lower lumbar lesion	42.0%	√
l	Loss in QoL with a upper lumbar lesion	52.0%	√
m	Reduction in life expectancy with a sacral lesion	39.4%	√
n	Reduction in life expectancy with a lumbar lesion	74.9%	√
o	Average life expectancy in BC at birth (in years)	82.0	√
p	Births with sacral lesion spina bifida avoided (9.6 to 5.1)	1.5	= (d - f) * g
q	Births with lumbar lesion spina bifida avoided (9.6 to 5.1)	3.0	= (d - f) - p
r	Life years gained due to sacral lesion spina bifida avoided	49.6	= m * o * p
s	Life years gained due to lumbar lesion spina bifida avoided	184.0	= n * o * q
t	QALYs gained due to sacral lesion spina bifida avoided	26.0	= p * (1 - m) * o * j
u	QALYs gained due to lumbar lesion spina bifida avoided	29.0	= q * (1 -n) * o * (k + l) / 2
v	**Total QALYs gained due to spina bifida avoided (9.6 to 5.1)**	**289**	= r + s + t + u
w	Births with sacral lesion spina bifida avoided (6.5 to 5.1)	0.5	= (e - f) * g
x	Births with lumbar lesion spina bifida avoided (6.5 to 5.1)	1.0	= (e - f) - w
y	Life years gained due to sacral lesion spina bifida avoided	16.2	= m * o * w
z	Life years gained due to lumbar lesion spina bifida avoided	60.1	= n * o * x
aa	QALYs gained due to sacral lesion spina bifida avoided	8.5	= w * (1 - m) * o * j
ab	QALYs gained due to lumbar lesion spina bifida avoided	9.5	= x * (1 -n) * o * (k + l) / 2
ac	**Total QALYs gained due to spina bifida avoided (6.5 to 5.1)**	**94**	= y + z + aa + ab

√ = Estimates from the literature

For our sensitivity analysis, we modified a number of major assumptions and recalculated the CPB as follows:

- Assume that the loss in QoL associated with a sacral lesion is reduced from 34% to 6% (Table 4-6, row j), the loss in QoL associated with a lower lumbar lesion is reduced from 42% to 22% (Table 4-6, row k) and the loss in QoL associated with an upper lumbar lesion is reduced from 52% to 25% (Table 4-6, row l): CPB = 83.
- Assume that the loss in QoL associated with a sacral lesion is increased from 34% to 62% (Table 4-6, row j), the loss in QoL associated with a lower lumbar lesion is increased from 42% to 62% (Table 4-6, row k) and the loss in QoL associated with an upper lumbar lesion is increased from 52% to 78% (Table 4-6, row l): CPB = 106.
- Assume that the reduction in life expectancy with either a sacral and lumbar lesion is increased by 25%, giving people with spina bifida a longer lifespan. (Table 4-6, rows m & n): CPB = 105.
- Reduce the incidence of NTDs from 5.8 to 4.0 / 10,000 live births: CPB = 194.

In estimating CE, we made the following assumptions:

- Approximately half of all pregnancies are unplanned. Therefore clinicians should advise all women who are capable of pregnancy to take daily folic acid supplements.[347]
- In a survey of 499 women, the majority (95%) indicated that they prefer to receive information about preconception health from their primary care physician. Only 39% of these women, however, could recall their physician ever discussing this topic.[348]
- Mazza and colleagues in Australia found that low levels of engagement between primary care providers and women regarding preconception care are due to a number of perceived barriers, including "time constraints, the lack of women presenting at the preconception stage, the numerous competing preventive priorities within the general practice setting, issues relating to the cost of and access to preconception care, and the lack of resources for assisting in the delivery of preconception care guidelines."[349]
- Does a clinician's advice increase the uptake of daily folic acid supplements during the periconceptional period? In a study of 1,173 women with a median age of 32 in the UK, 51% reported receiving advice on issues such as smoking, alcohol use, healthy diet and folic acid intake from a health professional prior to becoming pregnant. Women who received this advice were significantly more likely to take folic acid supplements (76%) than women who did not receive this advice (37%).[350]
- For modelling purposes, we assumed that 70% (ranging from 60% to 80% in the sensitivity analysis) (Table 4-7, row b) of clinicians would advise women ages 15 to 44 to take a daily supplement containing 0.4 to 0.8 mg of folic acid and that 76% (ranging from 66% to 86%) (Table 4-7, row e) of women would follow this advice.
- For modelling purposes, we assumed this advice would need to be given every three years (Table 4-7, row c) and modified this from every one to five years in the sensitivity analysis.
- **Cost of an office visit** - We estimated the average cost of a visit to a General Practitioner to be $34.00 (Table 4-7, row i).[351] We assumed that 50% of a 10-minute office visit (Table 4-7, row j) would be required in providing advice to take a daily supplement of folic acid and modified this from 30% to 70% in the sensitivity analysis.
- **Patient time and travel costs** - For patient time and travel costs, we assumed an hourly wage of $24.39 (the BC average in 2013)[352] plus 18% benefits for a cost per

[347] Bibbins-Domingo K, Grossman D, Curry S et al. Folic acid supplementation for the prevention of neural tube defects: US Preventive Services Task Force recommendation statement. *Journal of American Medical Association*. 2017; 317(2): 183-9.
[348] Frey K and Files J. Preconception healthcare: what women know and believe. *Maternal and Child Health Journal*. 2006; 10(1): 73-7.
[349] Mazza D, Chapman A and Michie S. Barriers to the implementation of preconception care guidelines as perceived by general practitioners: a qualitative study. *BioMed Central Health Services Research*. 2013; 13(36): 1-8.
[350] Stephenson J, Patel D, Barrett G et al. How do women prepare for pregnancy? Preconception experiences of women attending antenatal services and views of health professionals. *Plos One*. 2014; 9(7): e103085.
[351] Medical Services Commission. *Payment Schedule: Section 7 General Practice*. 2013. Available at http://www.health.gov.bc.ca/msp/infoprac/physbilling/payschedule/pdf/7-general-practice.pdf. Accessed December 2013.
[352] Statistics Canada. *Average Hourly Wages of Employees by Selected Characteristics and Occupation, Unadjusted Data, by Province (Monthly) (British Columbia)*. 2013. Available at http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/labr69k-eng.htm. Accessed December 2013.

hour of $28.78 (Table 4-7, row m) applied to the estimated two hours of patient time required for a cost per physician visit (Table 4-7, row l).

- **Cost of folic acid supplements** – The cost of folic acid supplements averages $0.043 per tablet at London Drugs.[353] We assumed an annual cost of $15.70 (Table 4-7, row g).
- **Costs avoided** – Average incremental medical expenditures comparing patients with spina bifida and those without are $41,460 (in 2003 US$) in the first year of life, $14,070 per year from ages 1 -17, $13,339 per year from ages 18-44 and $10,134 per year from ages 45-64.[354]
- Based on a study of the same 98 children and their caregivers, the caregivers worked an average of 7.5 to 11.3 hours less per week (depending on their children's disability severity) than matched control caregivers.[355]
- Grosse and co-authors estimated the lifetime costs associated with spina bifida to be $791,900 (in 2014 USD). This includes $513,500 in medical costs, $63,500 in special education and developmental service costs and $214,900 in parental time costs.[356] We converted the medical costs to equivalent Canadian health care costs by reducing costs by 29% to reflect excess health care prices in the US.[357,358] All costs were then adjusted to 2013 Canadian dollars for a lifetime cost of $442,600 in medical costs (Table 4-7, row r), $77,100 in special education and developmental service costs (Table 4-7, row s) and $260,900 in parental time costs (Table 4-7, row t).[359]
- Parental time costs are excluded from the base model (Table 4-7, row t) but included in the sensitivity analysis. The literature on 'spillover effects' (e.g. when the illness of a child or family member has an economic or quality of life impact on the broader family or caregiver(s) is nascent and further work is required before these effects can be relied upon with confidence.[360,361]
- For every live birth with spina bifida avoided, an estimated 2.23 abortions would be avoided (Table 4-7, row v). The cost of an abortion is estimated at $609 (Table 4-7, row w).[362]

[353] See http://www.londondrugs.com/search/?q=Folic+acid&lang=default. Accessed February 2017.
[354] Ouyang L, Grosse S, Armour B et al. Health care expenditures of children and adults with spina bifida in a privately insured US population. *Birth Defects Research Part A: Clinical and Molecular Teratology*. 2007; 79(7): 552-8.
[355] Tilford J, Grosse S, Goodman A et al. Labor market productivity costs for caregivers of children with spina bifida: a population-based analysis. *Medical Decision Making*. 2009; 29(1): 23-32.
[356] Grosse S, Berry R, Tilford J et al. Retrospective assessment of cost savings from prevention: folic acid fortification and spina bifida in the US. *American Journal of Preventive Medicine*. 2016; 50(5S1): S74-S80.
[357] Anderson GF, Reinhardt UE, Hussey PS et al. It's the prices, stupid: why the United States is so different from other countries. *Health Affairs*. 2003; 22(3): 89-105.
[358] Reinhardt U. *Why Does US Health Care Cost So Much? (Part I)*. 2008. Available at https://economix.blogs.nytimes.com/2008/11/14/why-does-us-health-care-cost-so-much-part-i/. Accessed January 2017.
[359] Campbell and Cochrane Economics Methods Group. *CCEMG – EPPI-Centre Cost Converter*. 2016. Available at https://eppi.ioe.ac.uk/costconversion/. Accessed December 2016.
[360] Wittenberg E and Prosser L. Disutility of illness for caregivers and families: a systematic review of the literature. *Pharmacoeconomics*. 2013; 31(6): 489-500.
[361] Wittenberg E, Ritter G and Prosser L. Evidence of spillover of illness among household members EQ-5D scores from a US sample. *Medical Decision Making*. 2013; 33(2): 235-43.
[362] Black A, Guilbert E, Hassan F et al. The cost of unintended pregnancies in Canada: estimating direct cost, role of imperfect adherence, and the potential impact of increased use of long-acting reversible contraceptives. *Journal of Obstetrics and Gynaecology Canada*. 2015; 37(12): 1086-97.

- Anencephaly is uniformly fatal. However, an estimated 11.4% of pregnancies with anencephaly result in live births (Table 4-1). These infants survive an average of 2.11 days.[363] According to the Canadian Institute for Health Information's *Patient Cost Estimator*, the average cost per day in BC in 2014 for CMG 599 (Neonate 2500+ grams, ages 0-28 days, other major problem) was $2,085.[364] We therefore calculated an avoided cost of $4,399 (2.11 * $2,085) per anencephaly live birth avoided (Table 4-7, row p).
- Discount rate of 3%.

Based on these assumptions, the CE associated with advising all women of reproductive age to take a daily supplement containing 0.4 to 0.8 mg (400-800µg) of folic acid is $237,088 / QALY (Table 4-7, row ad).

Table 4-7: CE Associated with Advising Women Ages 15 to 44 to Take a Daily Supplement Containing 0.4 to 0.8 mg of Folic Acid in a Birth Cohort of 40,000

Row Label	Variable	Base Case	Data Source
a	Life years lived between the ages of 15 and 44	594,112	Table 4-6, row b
b	Clinician adherence in offering advice re: folic acid supplementation	70%	Assumed
c	Frequency of offering advice re: folic acid supplementation (every x years)	3	Assumed
d	Life years covered by advice re: folic acid supplementation	415,879	= a * b
e	Proportion of women taking folic acid supplementation after receiving advice	76%	√
f	Life years covered by folic acid supplementation	316,068	= d * e
g	Annual cost of folic acid supplementation	$15.70	√
h	Cost of folic acid supplementation	$4,962,263	= f * g
i	Cost of 10-minute office visit	$34.00	√
j	Portion of 10-minute office visit for offering advice	33%	Assumed
k	Costs of office visits	$1,555,386	= (d / c) * i * j
l	Patient time required per office visit (hours)	2	Assumed
m	Value of patient time (per hour)	$28.78	√
n	Value of patient time and travel for intervention	$2,633,177	= (d / c) * l * m * j
o	**Estimated cost of the intervention**	**$9,150,825**	= h + k + n
p	Medical care costs avoided per anencephaly live birth avoided	-$4,399	√
q	Cases of anencephaly live births avoided with intervention	0.21	Table 4-4
r	Medical care costs avoided per case of spina bifida avoided	-$442,600	√
s	Special education and developmental service costs avoided per case of spina bifida avoided	-$77,100	√
t	Parental time costs avoided per case of spina bifida avoided	$0	√
u	Cases of spina bifida avoided with intervention	1.48	Table 4-6, row w + x
v	Abortions avoided per spina bifida live birth	2.23	√
w	Costs avoided per abortion avoided	-$609	√
	CE Calculation		
x	Cost of intervention over lifetime of birth cohort	$9,150,825	= o
y	Costs avoided over lifetime of birth cohort	-$772,876	= ((r + s + t) * u)+(u * v * w)+(p * q)
z	QALYs saved	94	Table 4-6, row ac
aa	Cost of intervention over lifetime of birth cohort (3% discount)	$9,150,825	Calculated
ab	Costs avoided over lifetime of birth cohort (3% discount)	-$616,532	Calculated
ac	QALYs saved (3% discount)	36	Calculated
ad	**CE ($/QALY saved)**	**$237,088**	= (aa + ab) / ac

√ = Estimates from the literature

[363] Jaquier M, Klein A and Boltshauser E. Spontaneous pregnancy outcome after prenatal diagnosis of anencephaly. *British Journal of Obstetric and Gynaecology: An International Journal of Obstetrics & Gynaecology*. 2006; 113(8): 951-3.

[364] Canadian Institute for Health Information. *Patient Cost Estimator*. Available online at https://www.cihi.ca/en/spending-and-health-workforce/spending/patient-cost-estimator. Accessed January 2017

For our sensitivity analysis, we modified a number of major assumptions and recalculated the CE as follows:

- Assume that the loss in QoL associated with a sacral lesion is reduced from 34% to 6% (Table 4-6, row j), the loss in QoL associated with a lower lumbar lesion is reduced from 42% to 22% (Table 4-6, row k) and the loss in QoL associated with an upper lumbar lesion is reduced from 52% to 25% (Table 4-6, row l): CE = $270,739.
- Assume that the loss in QoL associated with a sacral lesion is increased from 34% to 62% (Table 4-6, row j), the loss in QoL associated with a lower lumbar lesion is increased from 42% to 62% (Table 4-76 row k) and the loss in QoL associated with an upper lumbar lesion is increased from 52% to 78% (Table 4-6, row l): CE = $211,078.
- Assume that the reduction in life expectancy with either a sacral and lumbar lesion is increased by 25% (Table 4-6, rows m & n): CE = $213,043.
- Reduce the incidence of NTDs from 5.8 to 4.0 / 10,000 live births: CE = $106,349.
- Assume that clinician adherence in offering advice re: folic acid supplementation is reduced from 70% to 60% (Table 4-6, row b): CE = $200,771.
- Assume that clinician adherence in offering advice re: folic acid supplementation is increased from 70% to 80% (Table 4-7, row b): CE = $273,404.
- Assume that the frequency of offering advice re: folic acid supplementation is increased from every 3 years to every year (Table 4-7, row c): CE = $469,810.
- Assume that the frequency of offering advice re: folic acid supplementation is decreased from every 3 years to every 5 years (Table 4-7, row c): CE = $190,554.
- Assume the proportion of women taking folic acid supplementation after receiving advice is decreased from 76% to 66% (Table 4-7, row e): CE = $218,949.
- Assume the proportion of women taking folic acid supplementation after receiving advice is increased from 76% to 86% (Table 4-7, row e): CE = $255,227.
- Assume that the portion of 10-minute office visit required for offering advice is reduced from 33% to 25% (Table 4-7, row j): CE = $208,879.
- Assume that the portion of 10-minute office visit required for offering advice is increased from 33% to 50% (Table 4-7, row j): CE = $297,031.
- Include parental time costs avoided per case of spina bifida avoided (Table 4-7, row t): CE = $228,522

Summary

Table 4-8: Advising Women Ages 15 to 44 to Take a Daily Supplement Containing 0.4 to 0.8 mg of Folic Acid in a Birth Cohort of 40,000
Summary

	Base Case	Range	
CPB (Potential QALYs Gained)			
3% Discount Rate	36	32	40
0% Discount Rate	94	83	106
CE ($/QALY) **including** patient* time costs			
3% Discount Rate	$237,088	$106,349	$469,810
0% Discount Rate	$88,818	$38,926	$177,627
CE ($/QALY) **excluding** patient time costs			
3% Discount Rate	$163,937	$70,818	$250,356
0% Discount Rate	$60,903	$25,367	$93,881

** Patient time costs do not normally include caregiver time costs (spillover effects). In this model, however, we have included caregiver time costs but only in the sensitivity analysis and not in the base case analysis.*

While the approach modelled above involving regular clinic-based reminders for women ages 15 to 44 to take a daily supplement containing folic acid is not cost-effective, folic acid supplementation is still highly recommended before conception and throughout pregnancy. The BC Perinatal Health Program's *Maternity Care Pathway*, for example, recommends "supplementation with folic acid before conception and throughout pregnancy. Folic acid supplementation as per patient risk (0.4 mg – 5 mg per day pre pregnancy)." [365]

Behavioural Counselling to Promote a Healthful Diet and Physical Activity in Adults

In this section of the report, we are considering the effectiveness of behavioural counselling in the clinical setting to promote a healthful diet and physical inactivity in the ***general, asymptomatic adult population. This does not include individuals who are obese (a body mass index of >30 kg/m^2) or who have a pre-existing condition such as diabetes or cardiovascular disease.*** [366]

2002/2003 USPSTF Review and Recommendations

In 2002, the USPSTF asked the question, "Does behavioural counselling by clinicians in primary care improve physical activity?" The Task Force acknowledged that there are numerous health benefits associated with even modest levels of physical activity and wondered "whether routine counseling and follow-up by primary care physicians (would)

[365] BC Perinatal Health Program, *Maternity Care Pathway*, February 2010. Available online at http://www.perinatalservicesbc.ca/Documents/Guidelines-Standards/Maternal/MaternityCarePathway.pdf. Accessed July 2017.

[366] In their 2017 update, the USPSTF specifically noted that "this recommendation applies to adults age 18 years or older who are normal weight or overweight, with a BMI between 18.5 and 30 kg/m2. It does not apply to persons who have known CVD risk factors (hypertension, dyslipidemia, abnormal blood glucose, or diabetes) or persons who have obesity or are underweight."
US Preventive Services Task Force. *Draft Recommendation Statement- Healthful Diet and Physical Activity for Cardiovascular Disease Prevention in Adults Without Known Risk Factors: Behavioral Counseling*. 2017. Available at https://www.uspreventiveservicestaskforce.org/Page/Document/draft-recommendation-statement/healthful-diet-and-physical-activity-for-cardiovascular-disease-prevention-in-adults-without-known-risk-factors-behavioral-counseling. Accessed March 2017.

result in increased physical activity among adult patients".[367] A review of the available evidence found eight studies involving 9,054 adults which met their inclusion criteria.[368] Most of the included studies still had at least one methodological limitation. Based on the available evidence, the USPSTF concluded that "the evidence is insufficient to recommend for or against behavioural counseling in primary care settings to promote physical activity (Grade I recommendation)" while calling for more research.[369]

In 2003, the USPSTF asked the question, "Does behavioural counselling by clinicians in primary care promote a healthy diet?" Once again the task force acknowledged that there are numerous health benefits associated with a healthy diet but that few people follow such a diet.[370] A review of the available evidence found 21 studies which met their inclusion criteria.[371] The authors of the review found that dietary counseling produces modest changes in self-reported consumption of saturated fat, fruits and vegetables, and possibly dietary fiber. More-intensive interventions were more likely to produce important changes than brief interventions, but they may be more difficult to apply to typical primary care patients. They concluded that "brief counseling of unselected patients by primary care providers appears to produce small changes in dietary behavior, but its effect on health outcomes is unclear".[372] Based on this review, the USPSTF concluded that "the evidence is insufficient to recommend for or against routine behavioural counseling to promote a healthy diet in unselected patients in a primary care setting (Grade I recommendation)".[373]

2012 USPSTF Review and Recommendations

In 2012, the USPSTF asked a more specific question, namely, "Does behavioural counselling by clinicians in primary care promote a healthful diet and/or physical activity which results in cardiovascular disease prevention?"[374] A review of the available evidence found 26 studies (14,172 patients) testing the effects of counseling persons to increase physical activity, 24 studies (70,969 patients) testing the effect of counseling persons to eat a healthy diet and 15 studies (4,475) testing the effects of counselling persons for both physical activity and healthful diet.[375] The review assessed the evidence from the perspective of three levels of changes. Namely, they looked at changes in behavioural outcomes (e.g. an increase in physical activity, fruit and vegetable consumption, etc.), changes in intermediate health outcomes (e.g. a reduction in body mass index, blood pressure, etc.) and changes in long-term

[367] US Preventive Services Task Force. Behavioral counseling in primary care to promote physical activity: recommendation and rationale. *Annals of Internal Medicine*. 2002; 137(3): 205-7.
[368] Eden K, Orleans C, Mulrow C et al. Does counseling by clinicians improve physical activity? A summary of the evidence for the US Preventive Services Task Force. *Annals of Internal Medicine*. 2002; 137(3): 208-15.
[369] US Preventive Services Task Force. Behavioral counseling in primary care to promote physical activity: recommendation and rationale. *Annals of Internal Medicine*. 2002; 137(3): 205-7.
[370] US Preventive Services Task Force. Behavioral counseling in primary care to promote a healthy diet: recommendations and rationale. *American Journal of Preventive Medicine*. 2003; 24(1): 93-100.
[371] Pignone M, Ammerman A, Fernandez L et al. Counseling to promote a healthy diet in adults: a summary of the evidence for the US Preventive Services Task Force. *American Journal of Preventive Medicine*. 2003; 24(1): 75-92.
[372] Pignone M, Ammerman A, Fernandez L et al. Counseling to promote a healthy diet in adults: a summary of the evidence for the US Preventive Services Task Force. *American Journal of Preventive Medicine*. 2003; 24(1): 75-92.
[373] US Preventive Services Task Force. Behavioral counseling in primary care to promote a healthy diet: recommendations and rationale. *American Journal of Preventive Medicine*. 2003; 24(1): 93-100.
[374] Moyer V. Behavioral counseling interventions to promote a healthful diet and physical activity for cardiovascular disease prevention in adults: US Preventive Services Task Force recommendation statement. *Annals of Internal Medicine*. 2012; 157(5): 367-72.
[375] Lin J, O'connor E, Whitlock E et al. Behavioral counseling to promote physical activity and a healthful diet to prevent cardiovascular disease in adults: a systematic review for the US Preventive Services Task Force. *Annals of Internal Medicine*. 2010; 153(11): 736-50.

health outcomes (i.e., a reduction in morbidity and /or mortality related to cardiovascular disease).

Behavioural Outcomes

In general, physical activity and lifestyle (combined physical activity and healthful diet interventions) counselling resulted in a small increase of 38.3 minutes per week (95% CI of 25.9 to 50.7) in self-reported physical activity, especially in trials that provided at least medium-intensity interventions. Interventions were grouped into three levels of intensity as follows:

- Low - 30 minutes or less of contact
- Medium – 31 minutes to 6 hours of contact
- High - >6 hours of contact

Healthful dietary counselling resulted in a self-reported increase of between 0.4 to 2 servings per day of fruit and vegetable intake at all three levels.

Healthful dietary counselling resulted in a reduction in self-reported total fat intake at all levels of intervention although the reduction was the greatest with high-intensity interventions (e.g. a 5.9% to 11% decrease in energy from total fat).

A challenge with all studies included in the review is the limited follow-up period to assess whether the beneficial results are maintained over time. For example, just two of the 37 studies included in the meta-analysis of physical activity assessed outcomes beyond one year following the intervention. These two, however, found that increased levels of physical activity were maintained for 18 and 24 months following the intervention. Only two of the 17 studies included in the meta-analysis of fruit and vegetable intake assessed outcomes beyond one year. These two, however, also found a persistent increase at 24 and 72 months of follow-up. Four of 24 studies included in the meta-analysis of fat intake assessed outcomes for up to 72 months. All involved a high-intensity intervention with reduction in total and saturated fats remaining significantly lower in the intervention group for up to 72 months.

Intermediate Health Outcomes

Medium to high-intensity dietary interventions, with or without concomitant physical activity counselling, decreased body mass index (BMI) at 12 months of follow-up. High-intensity interventions led to a decrease in BMI of between 0.3 to 0.7 kg/m^2. Five of the 26 studies had a follow-up period of longer than 12 months. They found that the reduction in BMI persisted for up to 72 months, although the result was slightly decreased over time.

High-intensity dietary and lifestyle interventions decreased systolic blood pressure by 1.5 mm Hg (95% CI 0.9 to 2.1) and diastolic blood pressure by 0.7 mm Hg (95% CI 0.6 to 0.9). Reductions in blood pressure were still significantly reduced, although somewhat attenuated, at 36 months in the three (of 26) studies with longer-term follow-up. Six medium-intensity physical activity interventions did not improve blood pressure.

High-intensity dietary and lifestyle interventions decreased total cholesterol levels by -0.17 mmol/L (95% CI -0.09 to -0.25) and low-density lipoprotein (LDL) cholesterol levels by -0.13 mmol/L (95% CI -0.06 to -0.21). Reductions in total and low-density lipoprotein cholesterol levels were still reduced at up to 54 months in the three (of 21) studies with longer-term follow-up. Medium-intensity trials did not improve lipid levels on average.

Longer-Term Health Outcomes

Data on the morbidity and mortality related to cardiovascular disease was limited to two large, good-quality trials.

The women's health initiative randomized controlled dietary modification trial (WHI) randomly assigned 19,541 women ages 50 to 79 years to a dietary intervention group and 29,294 to a control group.[376] The intervention group received 18 group sessions in the first year followed by quarterly maintenance sessions thereafter. Group activities were supplemented by individual interviews and telephone/email follow-up. The intervention resulted in a significant decrease in fat intake, an increase in fruit / vegetable and grain intake, as well as a reduction in low-density lipoprotein cholesterol, diastolic blood pressure and factor VIIc levels by year six. At 8.1 years of follow-up, however, no differences were observed between the intervention and control groups in the proportion of women with either fatal or non-fatal coronary heart disease (RR = 0.93, 95% CI 0.83 to 1.05) or fatal or non-fatal stroke (RR = 1.02, 95% CI 0.90 to 1.17).

The second trial consists of the long-term observational follow-up of the two phases of the trials of hypertension prevention (TOHP I & II).[377] TOHP I consisted of 327 persons ages 30-54 with prehypertension randomly allocated to an intervention group and 417 to the control group. The intervention lasted 18 months and focused on sodium reduction. TOHP II consisted of 1,191 persons ages 30-54 with prehypertension in the intervention group and 1,191 in the control group. This time the intervention lasted three years with the intervention group divided into three sub-groups. The first sub-group focused on sodium reduction. The second sub-group focused on weight loss and the third sub-group focused weight loss and sodium reduction. In general, the intervention in the larger and longer TOHP II consisted of 14 weekly 90-minute group sessions of 11 to 34 participants led by trained instructors. This was followed by six bi-weekly sessions. Participants were then encouraged to take a refresher course of between three and six sessions during the second and third years. Throughout the intervention, participants were also encouraged to contact an interventionist through mail or face-to-face interactions.[378]

Sodium levels were significantly reduced in the intervention groups in both TOHP I & II.[379] Follow-up of between 10 and 15 years suggest that the risk of cardiovascular disease (a composite of myocardial infarction, stroke, coronary artery bypass graft [CABG], percutaneous transluminal coronary angioplasty [PCTA], or death with a cardiovascular cause) is reduced by 30% (RR = 0.70, 95% CI of 0.53 to 0.94) in the group receiving intensive sodium restriction counselling. If a more conservative cardiovascular disease composite outcome is used (excluding CABG and PCTA), then the reduction in risk is no

[376] Howard B, Van Horn L, Hsia J et al. Low-fat dietary pattern and risk of cardiovascular disease: the women's health initiative randomized controlled dietary modification trial. *Journal of American Medical Association*. 2006; 295(6): 655-66.
[377] Cook NR, Cutler JA, Obarzanek E et al. Long term effects of dietary sodium reduction on cardiovascular disease outcomes: observational follow-up of the trials of hypertension prevention (TOHP). *British Medical Journal*. 2007; 334: 885.
[378] Lasser V, Raczynski J, Stevens V et al. Trials of hypertension prevention, phase II structure and content of the weight loss and dietary sodium reduction interventions. *Annals of Epidemiology*. 1995; 5(2): 156-64.
[379] Cook NR, Cutler JA, Obarzanek E et al. Long term effects of dietary sodium reduction on cardiovascular disease outcomes: observational follow-up of the trials of hypertension prevention (TOHP). *British Medical Journal*. 2007; 334: 885.

longer statistically significant (RR = 0.72, 95% CI of 0.50 to 1.03). No difference was observed in total mortality (RR = 0.80, 95% CI of 0.51 to 1.26).[380]

Reviewer Conclusions

After reviewing the available evidence for the USPSTF, Lin and colleagues draw some overall conclusions.[381]

- Most of the trials reporting on behavioural outcomes used self-reported outcome measures.
- The evidence for changes in intermediate outcomes is strongest for high-intensity counselling interventions.
- Interventions showing benefits beyond 12 months were all from high-intensity interventions with group, phone or mail contact throughout the intervention.
- Most of the high-intensity intervention involved a minimum of 12 sessions. This level of resource use is likely not available at a population level.

USPSTF Conclusion

Based on the information summarized above, the USPSTF concluded that "although the correlation among healthful diet, physical activity, and the incidence of CVD is strong, existing evidence indicates that the health benefit of initiating behavioral counseling in the primary care setting to promote a healthful diet and physical activity is small. Clinicians may choose to selectively counsel patients rather than incorporate counseling into the care of all adults in the general population (Grade C recommendation)."[382]

The task force also noted that behavioural counselling may be more effective if delivered in the context of broader public health interventions that encourage healthy lifestyles.

2017 USPSTF Review and Recommendations

The USPSTF is currently in the process of updating its review of the literature and recommendations, with the draft literature review[383] and recommendation statement[384] available online. The 2017 review and update addresses the question, "Do primary care–relevant counseling interventions to promote a healthful diet, physical activity, or both improve health outcomes, intermediate outcomes associated with CVD, or dietary or physical

[380] Lin J, O'connor E, Whitlock E et al. Behavioral counseling to promote physical activity and a healthful diet to prevent cardiovascular disease in adults: a systematic review for the US Preventive Services Task Force. *Annals of Internal Medicine*. 2010; 153(11): 736-50.

[381] Lin J, O'connor E, Whitlock E et al. Behavioral counseling to promote physical activity and a healthful diet to prevent cardiovascular disease in adults: a systematic review for the US Preventive Services Task Force. *Annals of Internal Medicine*. 2010; 153(11): 736-50.

[382] Moyer V. Behavioral counseling interventions to promote a healthful diet and physical activity for cardiovascular disease prevention in adults: US Preventive Services Task Force recommendation statement. *Annals of Internal Medicine*. 2012; 157(5): 367-72.

[383] Patnode C, Evans C, Senger C et al. *Behavioral Counseling to Promote a Healthful Diet and Physical Activity for Cardiovascular Disease Prevention in Adults Without Known Cardiovascular Disease Risk Factors: Updated Systematic Review for the U.S. Preventive Services Task Force*. 2016. Available at https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryDraft/healthful-diet-and-physical-activity-for-cardiovascular-disease-prevention-in-adults-without-known-risk-factors-behavioral-counseling. Accessed March 2017.

[384] US Preventive Services Task Force. *Draft Recommendation Statement- Healthful Diet and Physical Activity for Cardiovascular Disease Prevention in Adults Without Known Risk Factors: Behavioral Counseling*. 2017. Available at https://www.uspreventiveservicestaskforce.org/Page/Document/draft-recommendation-statement/healthful-diet-and-physical-activity-for-cardiovascular-disease-prevention-in-adults-without-known-risk-factors-behavioral-counseling. Accessed March 2017.

activity behaviors in adults?" The literature review reconsidered the 65 trials include in the 2012 review and carried forward 50 of these 65 trials for the current review. They also identified an additional 38 trials completed since the previous review for inclusion in the current review.[385]

Intervention Intensity

Within the 88 trials, there were 121 distinct intervention arms. Forty arms included **low-intensity** interventions. The majority of these consisted of mailed, print-based interventions in which participants received tailored feedback regarding their dietary choices and / or physical activity choices with specific recommendations and tools for behaviour change. Only seven low-intensity interventions involved primary care provider in-person or telephone counselling lasting from 3 to 15 minutes.

Of the 121 intervention arms, 55 were of **medium-intensity**. The majority of medium-intensity interventions consisted of at least one face-to-face individual counseling session lasting from 20 to 60 minutes followed by booster telephone counseling call, emails or text messages. The majority of interactions were provided by research staff, health educators, dietitians or nutritionists. Just 10 of the 55 interventions included a component delivered by a primary care provider.

Of the 121 intervention arms, 26 were of **high-intensity**. These generally included at least 15 group sessions ranging from 45 minutes to 2.5 hours in length over a 4 week to 6 year time period. The active component of the intervention (vs. maintenance) tended to last six months. Only one intervention involved primary care staff while the others were provided by dietitians or nutritionists, behavioural health specialists or research staff.

Participant adherence was highest in the low- and medium-intensity interventions with 70% to 98% of participants involved in most of the planned intervention. Participant adherence in the high-intensity interventions tended to be somewhat lower at 50% to 60%.

Behavioural Outcomes

Physical activity interventions (with or without dietary messages) resulted in an approximate 35-minute increase (95% CI of 22 to 47) in self-reported physical activity per week. In addition, intervention group participants had a 32% higher odds (95% CI of 12% to 56%) of meeting physical activity recommendations compared to those in the control group. There was no evidence of effect modification based on the level of intensity of the intervention (i.e. low, medium or high).

Healthful dietary counselling resulted in a change in self-reported intake of fruits and vegetables of between -0.2 servings (favouring the control group) to 2.2 servings per day. All six trials that focused dietary messages exclusively on fruit and vegetable intake found a statistically significant increase in consumption in the intervention group.

Healthful dietary counselling resulted in a change in self-reported percent of energy from total fat of between 0.8% (favouring the control group) to -11%. For saturated fat, the reduction was from -0.3% to -4.1%.

[385] Patnode C, Evans C, Senger C et al. *Behavioral Counseling to Promote a Healthful Diet and Physical Activity for Cardiovascular Disease Prevention in Adults Without Known Cardiovascular Disease Risk Factors: Updated Systematic Review for the U.S. Preventive Services Task Force*. 2016. Available at https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryDraft/healthful-diet-and-physical-activity-for-cardiovascular-disease-prevention-in-adults-without-known-risk-factors-behavioral-counseling. Accessed March 2017.

Healthful dietary counselling led to statistically significant reductions of sodium intake in the five trials that specifically focused on this outcome, with evidence of persistence in the effects after up to three years of follow-up.

Intermediate Health Outcomes

Healthful diet and physical activity interventions were associated with a reduction in BMI but this reduction was only statistically significant for high-intensity interventions (-0.81 kg/m^2, 95% CI -0.99 to -0.63).

Healthful diet and physical activity interventions were associated with a decrease of -1.26 mm Hg (95% CI -1.77 to -0.75) in systolic blood pressure and a decrease of -0.49 mm Hg (95% CI -0.82 to -0.16) in diastolic blood pressure at approximately six to 12 months compared to controls. The largest reductions (-1.55 and -0.67 mm Hg in systolic and diastolic blood pressure respectively) were seen in the high-intensity interventions.

Healthful diet and physical activity interventions were associated with a reduction in LDL cholesterol levels but this decrease was only statistically significant for high-intensity interventions (-4.51 mg/dL; 95% CI of -6.85 to -2.16). The results for total cholesterol were concordant with finding for LDL cholesterol. The meta-analysis of results found a reduction in total cholesterol levels of -2.85 mg/dL (95% CI of -4.95 to -0.75). The largest effect was again seen among the high-intensity interventions (-5.32 mg/dL; 95% CI of -8.84 to -1.81).

A statistically significant reduction in fasting glucose of -1.35 mg/dL (95% CI -2.24 to -0.45) was only observed in high-intensity interventions.

Longer-Term Health Outcomes

Data on the morbidity and mortality related to cardiovascular disease was still limited to the WHI[386] and the TOHP I & II[387] trials covered in the 2012 recommendations, as noted above.

The 2017 literature review did include 10 fair- to good-quality studies assessing the effect of a healthful diet and/or physical activity intervention on a participants QoL. Overall, the self-reported measurers of QoL (primarily the 36-Item Short Form Health Survey or SF-36) appeared to improve more among the intervention participants than those in the control groups over six to 12 months, although the specific QoL domains that were measured and the results of the individual trials were mixed.

USPSTF Conclusion

Based on the information summarized above, the USPSTF concluded that "primary care professionals individualize the decision to offer or refer adults without obesity who do not have hypertension, dyslipidemia, abnormal blood glucose, or diabetes to behavioral counseling to promote a healthful diet and physical activity. Existing evidence indicates a positive but small benefit of behavioral counseling for the prevention of cardiovascular disease (CVD) in this population. Individuals who are interested and ready to make

[386] Howard B, Van Horn L, Hsia J et al. Low-fat dietary pattern and risk of cardiovascular disease: the women's health initiative randomized controlled dietary modification trial. *Journal of American Medical Association*. 2006; 295(6): 655-66.

[387] Cook NR, Cutler JA, Obarzanek E et al. Long term effects of dietary sodium reduction on cardiovascular disease outcomes: observational follow-up of the trials of hypertension prevention (TOHP). *British Medical Journal*. 2007; 334: 885.

behavioral changes may be most likely to benefit from behavioral counseling (Grade C recommendation)."[388]

The task force also noted that it "recognizes the important contributions of public health approaches to improving diet, increasing physical activity levels, and preventing CVD. The Community Preventive Services Task Force recommends several community-based interventions to promote physical activity, including communitywide campaigns, social support interventions, school-based physical education, and environmental and policy approaches." [389]

Summary and Conclusions

- Despite the addition of evidence from 38 trials completed since the evidence review for the 2012 USPSTF recommendation, the results of the evidence review guiding the 2017 USPSTF recommendations have not changed materially.
- Healthful diet and physical activity interventions tend to improve self-reported behavioural outcomes such as changes in physical activity and fat, sodium or fruit and vegetable consumption.
- Improvements in measured, intermediate health outcomes such as changes in weight, blood pressure and cholesterol levels tend to require high-intensity interventions.
- High-intensity interventions generally include at least 15 group sessions ranging from 45 minutes to 2.5 hours in length over a six month period with a maintenance phase after six months for a period of up to six years.
- Data on morbidity and mortality related to cardiovascular disease are restricted to longer-term follow-up from two trials, with mixed results. The TOHP I & II trials suggest that a 30% reduction in cardiovascular disease may be achievable with reductions in sodium intake. Achieving the targeted reductions in sodium intake, however, required between 26 and 32 90-minute group sessions over a three-year period, with contact by an interventionist throughout this period.
- Interventions rarely include the direct involvement of primary care staff. They are usually provided by dietitians or nutritionists, behavioural health specialists or research staff.

It is likely a combination of the above that led the USPSTF to maintain a Grade C recommendation in 2017. A Grade C recommendation means that "the USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small." For a CPS to be considered for inclusion on the Lifetime Prevention Schedule, it must receive an effectiveness grade of an 'A' or 'B' from the USPSTF or an equivalent grade from the CTFPHC.

[388] US Preventive Services Task Force. *Draft Recommendation Statement- Healthful Diet and Physical Activity for Cardiovascular Disease Prevention in Adults Without Known Risk Factors: Behavioral Counseling*. 2017. Available at https://www.uspreventiveservicestaskforce.org/Page/Document/draft-recommendation-statement/healthful-diet-and-physical-activity-for-cardiovascular-disease-prevention-in-adults-without-known-risk-factors-behavioral-counseling. Accessed March 2017.

[389] US Preventive Services Task Force. *Draft Recommendation Statement- Healthful Diet and Physical Activity for Cardiovascular Disease Prevention in Adults Without Known Risk Factors: Behavioral Counseling*. 2017. Available at https://www.uspreventiveservicestaskforce.org/Page/Document/draft-recommendation-statement/healthful-diet-and-physical-activity-for-cardiovascular-disease-prevention-in-adults-without-known-risk-factors-behavioral-counseling. Accessed March 2017.

While behavioural counselling in the clinical setting to promote a healthful diet and physical inactivity in the general, asymptomatic adult population may be limited in its effectiveness, there are a number of *community-based* interventions that are considered to be effective by the US Community Preventive Services Task Force. Examples include:

- Worksite programs intended to improve diet and/or physical activity behaviors to promote healthy weight. [390]
- Built environment strategies that combine one or more interventions to improve pedestrian or bicycle transportation systems with one or more land use and environmental design interventions to increase physical activity.[391]
- Interventions that actively engage families to increase physical activity by combining activities to build family support with health education.[392]

Additional information on effective community-based interventions can be found at the US Community Preventive Services Task Force website (https://www.thecommunityguide.org /task-force-findings).

[390] Anderson L, Quinn T, Glanz K et al. The effectiveness of worksite nutrition and physical activity interventions for controlling employee overweight and obesity: a systematic review. *American Journal of Preventive Medicine*. 2009; 37(4): 340-57.

[391] The Community Preventive Services Task Force. *Physical Activity: Built Environment Approaches Combining Transportation System Interventions with Land Use and Environmental Design*. 2016. The Community Guide. Available at https://www.thecommunityguide.org/sites/default/files/assets/PA-Built-Environments.pdf. Accessed July 2017.

[392] The Community Preventive Services Task Force. *Physical Activity: Family-Based Interventions*. 2016. The Community Guide. Available at https://www.thecommunityguide.org/sites/default/files/assets/PA-Family-based-Interventions.pdf. Accessed July 2017.

The Lifetime Prevention Schedule

Establishing Priorities among Effective Clinical Prevention Services in British Columbia

Summary and Technical Report

March 2017 Update

Screening for hearing loss in newborns, screening for cardiovascular disease risk in adults, routine aspirin use and folic acid supplementation

Participating partner organizations:

BC Cancer Agency
CARE + RESEARCH
An agency of the Provincial Health Services Authority

BRITISH COLUMBIA

BC Centre for Disease Control
An agency of the Provincial Health Services Authority

CHILD HEALTH BC
LEAD BENEFACTOR
save on foods

GPSC
General Practice Services Committee

Perinatal Services BC
An agency of the Provincial Health Services Authority

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