ReFlections

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IN THIS ISSUE

FROM THE EDITORS

We hope this issue of *ReFlections* finds you safe and well, despite the ongoing hardships and challenges the COVID-19 pandemic is causing. It is during such times as these that we continue to see the value and benefit the insurance industry provides to policyholders and their families.

In this final edition of *ReFlections* for 2020, we bring you articles written by three experienced and authoritative RGA subject matter experts. **Dr. Georgiana Willwerth-Pascutiu**, Vice President, Global Medical Director, walks us through the complex topic of cannabis, its derivatives, its prevalence of use, and insurance industry implications. **Hilary Henly**, Head of Underwriting, Ireland and Director, Divisional Underwriting Research, provides a deep dive on e-cigarettes and the practice of vaping, especially as it pertains to younger users, and its health complications. Finally, **Dr. Karneen Tam**, Medical Consultant, Asia Pacific, explains the concept of herd immunity – a very timely topic in the context of the ongoing COVID-19 pandemic.

The **Longer Life Foundation (LLF)** update announces the 2020-2021 grant award recipients and describes the innovative research being funded. LLF is especially proud to have provided an unprecedented interim grant to Dr. Jeffrey Henderson, one of our alumni grant recipients, to support his research: "Prognostic Biomarkers of Severe Disease in COVID-19 Patients."

As always, please be sure to check out **ReCite** for highlights and RGA's perspectives on recent medical literature. Finally, we provide links to several new and informative articles by our thought leaders that are available on **RGA's Knowledge Center**.

Thank you and be well,

Dan and Adela

CANNABIS – A COMPLEX AND RAPIDLY EVOLVING LANDSCAPE

Abstract

The humble Cannabis sativa *plant, cultivated for millennia for its psychoactive properties and more, is today considered one of the most controversial and complex plants in the world.*

Starting in the early to mid-20th century, much of its use became recreational, but by the early 1970s discoveries began to emerge around its potential medical efficacies.

This article will discuss current knowledge of how cannabis engages with the brain and the endocannabinoid system (ECS) and provide an overview of the new market landscapes brought about by changes in governing laws and regulations, which are affecting usage by our current and potential customers. It will also explore the additional hazards, concerns, and considerations of cannabis use in countries where it remains illegal.

Introduction

Naturally occurring psychoactive substances have been part of human life for millennia. One of the most frequently utilized plant sources of these substances, *Cannabis sativa,* is also the best-known worldwide. For the past half-century, scientific and medical interest in its many compounds, known as cannabinoids, has been increasing. Today, the two best-known, delta-9 tetrahydrocannabinol (THC), its psychoactive chemical, and cannabidiol (CBD), which does not have psychoactive properties, are some of the most commonly used in the world.[1]

Laws and regulations governing cannabis – both its products and its use – differ from market to market. Although possession and use are still illegal in most of the world's countries, many do not enforce their laws. Several of the world's developed countries have decriminalized and even legalized medical and, in some cases, recreational use.

In Canada, for example, cannabis has been legal for medical use for nearly 20 years and for recreational use since October 2018, and today it is widely available.[1] In the U.S., however, cannabis possession and use continue to be illegal on the federal level. The U.S. government maintains cannabis' classification as a Schedule 1 substance under the Controlled Substances Act. (Schedule 1 drugs are considered to have high potential for abuse and no currently accepted medicinal use.) Still, conditional legalization for medical cannabis use exists in several U.S. states as well as the District of Columbia, and a few states have even legalized it for recreational use.

In South Africa, cannabis for private use only has been decriminalized, but its commercial cultivation and sale remains illegal. Medical for private use only is legal in Australia as well but is subject to qualifying conditions by state, and recreational use has mostly been decriminalized and is legal in some states for personal use. In India, both medical and recreational

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use are illegal, but *bhang*, a traditional edible cannabis preparation commonly used in Hindu religious ritual and in Ayurvedic medicine, is excepted.

As research into cannabis and its compounds proceeds, new discoveries are being made about potential pharmacological efficacies. At the same time, prevalence of use is continuing to grow worldwide, and its legal status is evolving as well. Because of this, the insurance industry needs to stay up to date on research, governing laws and regulations, and how they are impacting market characteristics.

Prevalence of Use

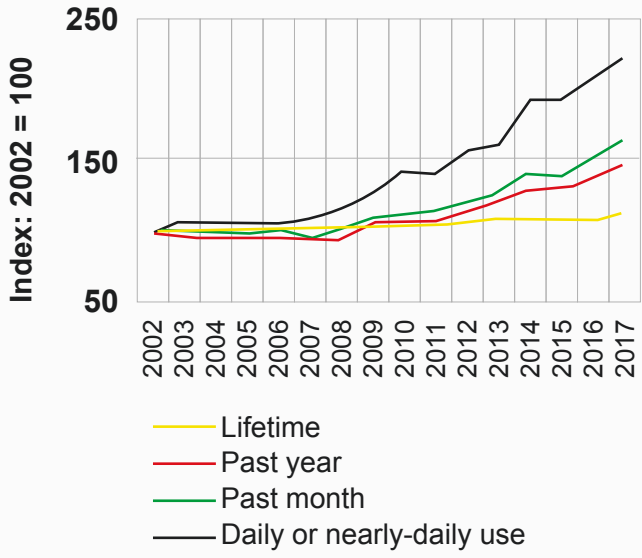
Today, an estimated 188 million individuals worldwide use cannabis, according to the European Drug Report 2019.[1] Prevalence of use varies in accordance with location, age, gender, and sociodemographics. It is important to recognize that prevalence of use is high in countries where cannabis is still illegal. Clearly, it does not need to be legal to be used.

In Asia, the highest prevalence of use is found in India and Pakistan, most likely due to consumption of *bhang*. Prevalence of use in Europe ranges considerably, from 7.4% among adults ages 15-64 to 14.4% among younger adults (ages 15-34). Among younger European adults, prevalence of use also varies widely from country to country. In Hungary, for example, where cannabis is illegal for any use, 3.5% of younger adults are users, whereas in France, where recreational use is illegal but certain cannabis-derived medical preparations are legal, young adult prevalence of use is 21.8%.[2]

What are the additional challenges and hazards in regions where cannabis use and/or possession is still illegal, and what has been observed in countries where it has been legalized or decriminalized?

Two lessons from markets with populations indicating more experience with cannabis use are that prevalence of use appears to increase in response to legalization or decriminalization, and the demographics change. In the U.S., for example, individuals age 18 and older indicating daily or near-daily use of cannabis doubled between 2002 and 2017.[1]

Figure 1: U.S. cannabis use trends, age 18 and older, 2002-2017



Source: United States, Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality, Results from the 2017 National Survey on Drug Use and Health: Detailed Tables (Rockville, Marlyland, 2018).

In the past, cannabis use was associated with certain population characteristics, with average users being young adults, and greater use was reported among males than females. The easing of laws and regulations governing cannabis over the past few decades has been creating new user demographics. Data from the Canadian Survey on Cannabis shows that the number of female and older users is high and rising. Seniors (age >65 years) have the most growth in cannabis usage – a 10-fold increase since 2012. In addition, according to the survey, more than 400,000 seniors were using cannabis by the end of 2019. Increased cannabis use among these older adults has also contributed to a rise in the average age of cannabis users in Canada, from 29.4 in 2004 to 38.1 in 2019. Most of the seniors are new users who purchase it for medicinal purposes and from legal sources.[3] Among younger adults (ages 15-24), however, use is mainly recreational, and for those in the 45-64 age group, motivation for use is almost equally divided into recreational, medicinal, and mixed-use.

How is the mixed-use category defined? Is cannabis used to treat serious medical conditions or minor ailments? Is it done under medical supervision?

Even though cannabis is more widely accepted today than ever, most healthcare professionals are still not comfortable authorizing it. Most times, medical cannabis use is patient-driven. In Canada, cannabis is not prescribed as it has no drug identification number (D.I.N.); rather, it is authorized by physicians. There is also no detailed drug information, no official monograph, and it does not come with clear recommendations in terms of initial dose, titration methodology, or proper use. The authorization form provides some guidance, such as “start low and go slow,” that the initial dose should not be not more than 0.5-1 g/day, and that the maximum authorized dose is 3 grams of dried plant/day and up to 25 mg THC/day.[4] This information can certainly generate polarizing conversations, drive further analysis, and does not provide much comfort when insurance applicants are underwritten, especially those who are regular cannabis users.

The cannabis world is evolving rapidly, its legal landscape is changing, the prevalence of use is increasing, and the insurance industry needs good data to guide risk stratification. For example. based on a 2016 Clinical Reference Laboratory study which tested 574,541 insurance applicants during the period of 1995-2014 for the presence of THC-COOH metabolite, the prevalence of cannabis use in the U.S. insurance applicant pool was quite substantial. It ranged from 1.1% in female non-smokers to 14.8% in male smokers. The latter approaches the prevalence reported in the U.S. general population in 2017.[8] Newer data confirms that cannabis test positivity is climbing in the general U.S. population. In 2009, it was reported that 2-3% of all drug tests and across all employee testing categories showed positivity for cannabis, an almost 17% increase since 2014.[9]

Does all this information mean cannabis is ready for prime time? Some believe it might be a universal remedy – the new super-drug. Others, however, are skeptical of the many claims for its efficacy. Most users seek it out for the chronic pain triad: physical pain, mood disorder (anxiety and depression), and insomnia. Often it is self-prescribed rather than authorized or recommended by a physician.

People with severe medical conditions, such as cancer patients, may prefer it over opioids for pain relief. This is one good reason cannabis should be clinically studied. Indeed, scientists are actively researching this complex plant, which has hundreds of chemical entities, with more than 800 ongoing studies.

Cannabinoid Science

Scientists first isolated THC and CBD, the two best-known cannabinoid molecules, in the 1960s. In the years since, research has determined cannabis to have some medical efficacy, such as easing interocular pressure from glaucoma and reducing chemotherapy-induced nausea. However, only in the 1990s did researchers begin to understand how cannabis exerts its effect on the body and brain.

In 1996, scientists discovered the body's own natural cannabinoids—anandamide (AEA) and 2-arachidonoyl glycerol (2-AG). These two chemicals, called endocannabinoids, along with their receptors, make up the endocannabinoid system (ECS). Indeed, research into the effects of the two major cannabinoids led to the discovery of the ECS and its function.[16] This fascinating system plays a critical role in regulating mood, pleasure, memory, thinking and concentration, body movement, awareness of time, appetite, pain, and the five senses

The two ECS receptors found thus far, CB1 and CB2, are located throughout the body. CB1 receptors are found mainly in the brain and central nervous system and are in many peripheral organs as well, and CB2 receptors are found primarily in the immune system.

AEA is a neurotransmitter secreted by the brain and is the body's own version of exogenous THC. The name "anandamide" comes from the Sanskrit word *ananda*, which means bliss. AEA and THC molecules are very similar, which is why AEA is also called the natural THC, or bliss, molecule.

The breakthrough discovery of AEA broadened science's understanding of how cannabis exerts its effect. AEA's close relationship with dopamine may explain its important role in mood regulation.[15] Dopamine is released by the brain when experiencing pleasurable activities and as a reward for behavior that, historically, has improved humanity's chance of survival. As the reward system uses AEA to release dopamine in small amounts, AEA directly affects energy, mood, sleep, appetite, and more.

Does more THC mean more dopamine? Not long-term. As THC resembles AEA, habitual cannabis use disrupts the AEA-dopamine cycle by frequently signaling for dopamine release. If excessive dopamine levels continue, the brain's dopaminergic receptors downregulate. This is the reason chronic cannabis users need increasingly more potent products (as well as more frequency of use) to achieve the same effects.[14]

The growing importance of the ECS is now recognized in human health and well-being.

Is Cannabis Safe or Hazardous?

The growing importance of the ECS is now recognized in human health and well-being. While cannabis use is not without risks, scientists agree that there is no risk of lethal overdose from plant-based cannabis products. The reason is the neuroanatomical distribution of cannabinoid receptors. While ECS receptor concentration is high in the frontal cortex, amygdala, basal ganglia, and cerebellum, which are the brain regions involved in learning, emotion processing, and body movement, concentration is low in the brain stem. Opioids and alcohol can impair the respiratory and circulatory systems, which are located in the lower brain stem, but cannabis does not have the ability to affect this critical area of the brain. In addition, cannabis has a very large therapeutic index (TI). The TI of a drug is the ratio that compares the blood concentration at which a drug becomes toxic and the concentration at which the drug is effective – the larger the TI, the safer the drug.[12]

Therefore, while one can overdo cannabis intake, as is commonly seen with edibles, it is not possible to die from a cannabis overdose.[13]

Does this mean cannabis is safe for medical use? That is still unknown. Insufficient high-quality studies, addiction risk, and lack of reliable information about its interactions with other medications and side effects are important challenges, but lack of user knowledge is a prime reason for concern. The known health hazards of cannabis can be moderated through a user's behavior and choices. Cannabis products from illegal sources may be highly potent and not quality controlled and properly labeled, and their use brings additional challenges.

Available literature attests that frequent or intensive (i.e., daily or near-daily) cannabis use is strongly associated with higher risks of experiencing use-related adverse health and social outcomes, and higher risks of various acute as well as chronic problematic mental and behavioral outcomes.[10, 11]

However, with new legislation and wider acceptance, the profile of cannabis users might change. More people may use it for milder medical conditions such as anxiety, depression, back pain, and insomnia. Medical cannabis users also tend to buy the products legally, whether from dispensaries or online, in order to access higher-quality products in more reliable doses. Motivation of use is also changing: for many newer users it is not to get high but to assist their ability to recover from underlying conditions. The risk of graduating from cannabis to harder drugs is lower as the newer providers have a broad range of choices. Also, shopping at a dispensary allows relationships to develop. The purchase is less about the user getting what they want than it is about someone listening to their problems and offering solutions that meet their need.

Because of all these factors, the risk profiles of newer medical cannabis users are likely better than in the past. Assuming no other unfavorable risk factors, these individuals might actually have better risk profiles than recreational users. However, the insurance disability risk might be higher due to the underlying condition(s) for which the medical cannabis is being used.

In addition, available studies thus far have produced controversial results, so the individual perspective on cannabis will guide how the evidence of benefits and harms is viewed.

Health hazards attributable to cannabis use depend on the individual users, their health profiles, and the company their usage keeps, e.g., whether they use alcohol and/or other illicit drugs, driving criticism, and overall high-risk behavior.

As cannabis is now legal (or at least decriminalized) in many markets, this extraordinarily complex plant must continue to be scientifically studied and assessed. Cannabis is clearly not a mono-molecule: it consists of numerous compounds which can and do interact in unexpected and sometimes opposite ways, and their effects are yet to be determined through high-quality studies. Cannabis falls into the category of substances which are tolerated and discouraged at the same time. Knowledge is key and awareness is power. The potential harms can be mitigated by collaborating and knowledge-sharing to increase awareness surrounding the nature and composition of cannabis products.

Cannabinoids vs. Opioids

Could cannabis be a safer alternative than opioids for patients with chronic pain?

The growing interest in cannabinoid science may be a collateral effect of the opioid epidemic. Available U.S. research from 2014 and 2019 found a 25% decrease in opioid overdose death rates reported in states permitting medicinal cannabis use versus those that did not.[5, 7] In addition, a 2017 survey demonstrated that 69% of older adults (ages 50-80) in the U.S. believed that cannabis provides pain relief and 70% believed its side effects were tolerable compared to those of opioids.[6]

Today

Is cannabis yet ready for prime time?

Cannabis plant products affect users in different ways, depending on the type of product used, the interaction between the product and the user's brain chemistry and genetics, and the motivation for use.

While attending the first Canadian cannabis conference, this author underwent pharmacogenetic testing to determine how THC was personally metabolized and the risk for cannabis-related health hazards. The results showed normal (or average) metabolism. These tests seem to support the theory that not everyone is affected in the same way.

Cannabinoid science is surely captivating and is generating substantial and increasing interest. Research into its many compounds is still in the early stages, but esteemed universities are currently running hundreds of studies to understand the pharmacological properties of this controversial plant and determine its risks, hazards, and possible benefits.

The ECS seems to play an essential role in both health and disease. Cannabis-derived drugs that interact with the ECS could have important therapeutic applications if used with medical supervision. Unfortunately, there could also be severe adverse consequences.

Today, many therapeutic interventions are available for people with chronic pain. However, before resorting to a drug-only therapy, remember that humans can recalibrate their minds and bodies in natural ways. For example, balanced levels of dopamine and AEA, which are responsible for mental and emotional health, can be stimulated in natural, healthy, and safer ways, through items as simple as laughter, exercise, healthy food, yoga, mindful meditation, and music.

A growing body of research has started to provide evidence of the pharmacological potential of cannabis on a wide range of disorders. But it should be recalled that motor vehicle accidents are a prime reason for early mortality risk, and that any drug that mimics a substance naturally produced by the body could affect us in ways that are yet to be completely understood.

Information about cannabinoids and the ECS gathered from scientific study will surely help insurers underwrite applicants who are regular users of cannabis, whether medically or recreationally. ReF

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TODAY'S VAPERS, TOMORROW'S SMOKERS?

Abstract

The use of e-cigarettes, often referred to as vaping, has been rising at worrying rates, particularly among adolescents and young adults. E-cigarette use increases the risk of ever using combustible tobacco cigarettes as well as heavier use of both products over time. Progression towards more frequent use of e-cigarettes and combustible tobacco use increases the risk of nicotine dependence and it is important that insurers have a thorough understanding of the evolving health risks.

Introduction

Tobacco use continues to be one of the world's biggest health problems. One in every five adults worldwide today smokes tobacco.[1]

Although tobacco's global burden of disease is extremely high, many countries have put smoking-related restrictions in place that are successfully reducing mortality from smoking-related diseases. Indications are, however, that the smoking epidemic may be shifting into to one of vaping. The fast-rising use of electronic nicotine delivery systems (ENDS), more commonly referred to as e-cigarettes, especially among the young, is causing considerable concern among health authorities. E-cigarette use has been shown to reduce several health risks among former smokers, but the use of e-cigarettes should be temporary as the long-term adverse effects are yet to be established.

Prevalence of Use

In Europe alone, approximately 48.5 million individuals have used an e-cigarette at least once. About 7.5 million are current users, and the largest subgroup consists of those who use both e-cigarettes and conventional cigarettes.[2]

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In the U.S., adult e-cigarette use rose from 5.2% in 2017 to 7.6% in 2018 – a 46.2% increase.[3] While older U.S. adults may still be more likely to smoke conventional cigarettes, adults under age 30 are increasingly more likely to use e-cigarettes.

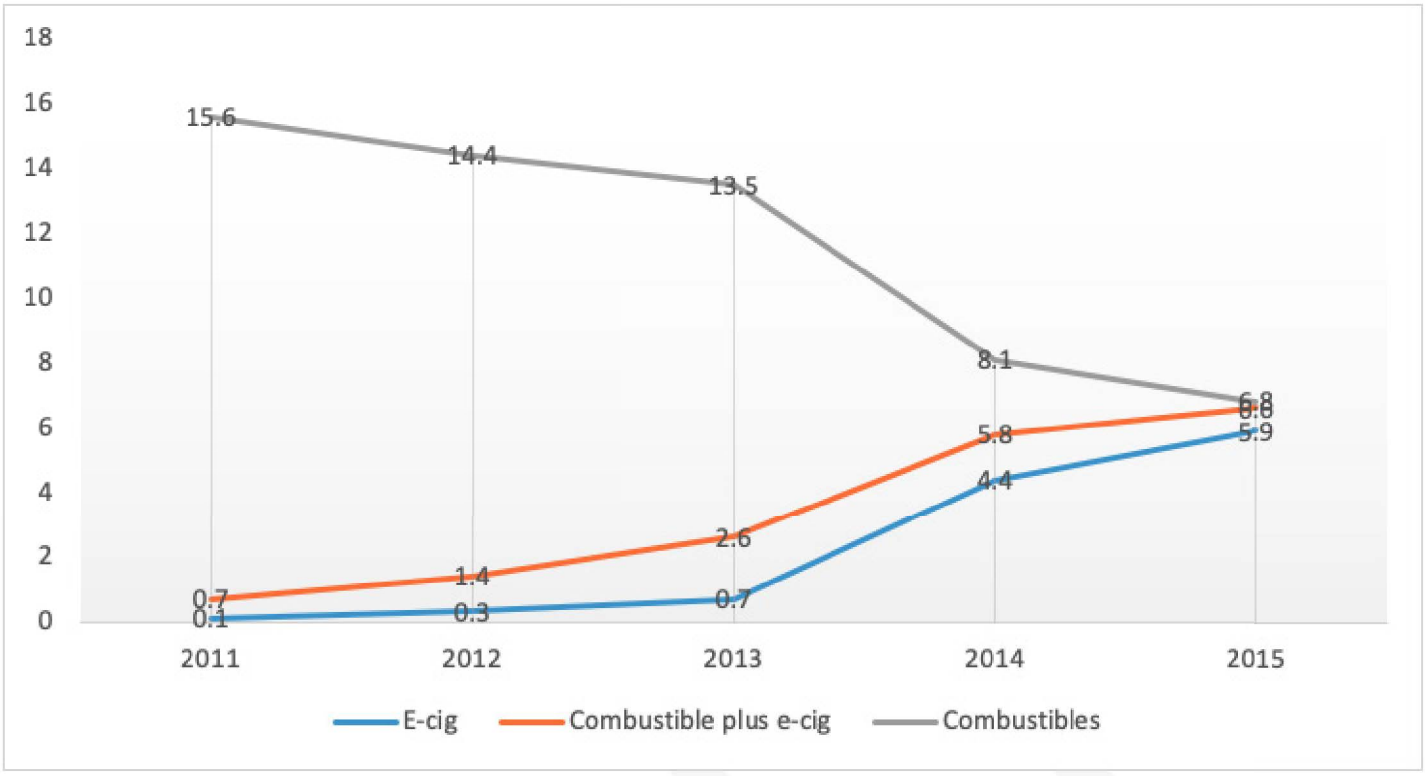
Table 1: U.S. Smoking Habits 2019[4]

Category	Cigarette smoking (%)	E-cigarettes (%)
By Gender		
Men	15	9
Women	15	6
By Age Range		
18-29	14	19
30-49	19	8
50-64	18	3
65+	7	<1

Source: Gallup

The 2018 National Youth Tobacco Survey (NYTS) found a sharp reversal of overall past declines in youth tobacco use between 2015 and 2017.[5] In 2018, 20.8% of high school students and 4.9% of middle school students reported current e-cigarette use. By 2019, this had increased to 27.5% and 10.5% respectively. Even though the newly released figures for 2020 show a decrease to 19.6% and 4.7%, 3.6 million U.S. youths still currently use e-cigarettes.[6]

Figure 1: Percentage of U.S. high school students who have ever used tobacco products, by product type (2011-2015)[5]



Source: FDA

The Switch to e-Cigarettes

E-cigarettes were originally designed as a smoking cessation aid, but many young people now begin smoking with e-cigarettes unrelated to quitting conventional cigarettes. Among adolescents, vaping is strongly associated with increased risk of future cigarette smoking and moderately associated with long-term cigarette use.

While e-cigarettes are promoted as being less harmful than conventional cigarettes, this does not mean that they are free of health risks.[7] The World Health Organization (WHO) is recommending that its members which have not yet banned e-cigarettes consider treating them as a harmful product.[4] More than 30 countries around the world have already banned the sale of e-cigarettes, and several more have banned only the sale of flavored e-cigarettes.[8]

Health Effects

The liquid used in e-cigarettes, known as e-liquid, e-juice, or vape juice, contains four major compounds: nicotine, in average concentrations of 11 mg/ml; glycerol (average concentration 37 g/100 g); propylene glycol (average concentration 57 g/100 g); and ethylene glycol (average concentration 10 g/100 g). Flavorings such as banana or vanilla are added to e-liquids to make them more attractive, which risks encouraging adolescents to try e-cigarettes. Many users start with tobacco-flavored e-cigarettes, but later switch to other flavors.[9]

Evidence to date shows that e-cigarette use can cause several adverse health effects. Long-term exposure to carbonyl compounds such as formaldehyde, which are present in e-cigarettes, are known to increase the risk of cancer in humans. Formaldehyde is also associated with the increased cardiovascular risk of tobacco smoking.[10]

The nicotine in e-cigarette liquid can increase risk of tachycardia as well as ventricular arrhythmias.[11] A study by Bhatta, et al. on e-cigarette use and myocardial infarction (MI) in the U.S. found that every-day (adjusted odds ratio [OR] 2.25) and some-day (OR 1.99) e-cigarette use were independently associated with increased odds of having had an MI. It also noted that dual use of e-cigarettes and conventional cigarettes was more harmful than use of either product alone, as users are exposed to high levels of toxicants.[12]

Alzahrani, et al., in their 2018 study, found that daily e-cigarette use was independently associated with a 70% increased risk of MI compared to those who have never used e-cigarettes. It also found that the risk of MI in a current daily dual user was more than four times that of a never-smoker, indicating that dual use of e-cigarettes and conventional cigarettes may be more harmful than using only one product.[13]

A study by Parekh, et al. published in January 2020 found that current dual use was associated with nearly a threefold risk of stroke compared to non-smokers, and that dual use was associated with almost double the risk of stroke versus only conventional cigarette use.[14]

Product Use

User habits such as puff duration, puff intervals, and the power of the e-cigarette device, in addition to the concentration of liquid nicotine, affect the amount of aerosolized nicotine inhaled, making it difficult to quantify adverse effects of e-cigarette consumption. Puff duration is directly related to the nicotine content of the e-cigarette, and blood nicotine levels are influenced by the way an e-cigarette is puffed. The ability of e-cigarettes to deliver high doses of nicotine compared to conventional cigarettes is of particular concern in adolescents and young adults.[15]

There is still considerable uncertainty surrounding the potential health impacts of e-cigarettes.

Newer generation e-cigarette devices can achieve nicotine levels that are the same or higher than conventional cigarettes, increasing the potential for nicotine addiction as well as its adverse effects. One e-cigarette product delivers more than 50 mg/mL of nicotine in the standard U.S. and Canadian version, but in Europe, the European Tobacco Product Directive limits nicotine levels in e-cigarettes to 20 mg/mL, so the product contains less than half that nicotine concentration.[15]

If rates of e-cigarette use continue to rise in young adults and adolescents, the long-term harmful consequences of nicotine exposure are likely to rise accordingly. Early exposure to nicotine increases the risk of long-term dependency and the ability to quit becomes less likely. Studies have also shown that nicotine has negative influences on adolescent brain development, resulting in deficits in attention and cognition as well as mood disorders.[10]

The extraction process of nicotine from tobacco, as well as poor quality control of e-liquid products, may leave harmful impurities such as lead and nickel in the end product. Aerosolized solvents produced by e-cigarettes such as propylene glycol are known respiratory irritants. Inhaling propylene glycol can increase the risk of developing asthma, while high volumes of particles resulting from vaping liquid's aerosolized solvents can deposit in the respiratory system and cause toxic effects on the lung epithelium.

Flavoring agents such as diacetyl and acetyl propionyl, both of which are known to adversely affect lung function if inhaled, have been associated with a decline in respiratory function in e-cigarette users. A number of people in the U.S. have developed a severe pulmonary disease named e-cigarette or vaping product use-associated lung injury, or EVALI. The disease was first recognized and identified in 2019. Vitamin E acetate, also found in vaping liquid samples tested by the U.S. Food and Drug Administration, is strongly linked to the EVALI outbreak. Previous research suggests that when vitamin E acetate is inhaled, it may interfere with normal lung functioning. As of the final update published in February 2020, EVALI has resulted in 2,807 cases and 68 deaths.[10]

Conclusions

Smoking patterns continue to change over time, including daily consumption amounts, the type of product used, and dual use of nicotine products.

There is still considerable uncertainty surrounding the potential health impacts of e-cigarettes. To date, evidence of the short-term risks of e-cigarette use is limited and long-term risks cannot yet be identified. New e-cigarette and e-liquid products are attracting more young adults and adolescents, exposing them to the harmful effects of nicotine and increasing their risk of long-term dependence. Studies to date also indicate an

increased risk to health from dual use. Preventing tobacco use and the use of e-cigarettes among young people is a key component to ending the tobacco-use epidemic.

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HERD IMMUNITY IN THE CONTEXT OF THE COVID-19 PANDEMIC

Introduction

An individual gains immunity to an infectious pathogen either by natural infection or by vaccination.[1] A population can also develop resistance to an infectious pathogen when it achieves "herd immunity" or "community immunity." This phrase – one we are hearing with increasing frequency – refers to a state reached when a large enough proportion of a population has become immune to a pathogen that ongoing transmission of it slows or halts.[2]

Immune individuals act as breaks in a chain of infection. If enough of these individuals are among an infected person's contacts during the period of infectivity, transmissibility of the infection cannot be sustained. This confers the added benefit of potential protection to susceptible members of a population even if they themselves have no individual immunity.[1, 3]

What population immunity threshold is required to achieve herd immunity?

This varies from disease to disease, depending on biological and epidemiological factors. In the simplest model, the population immunity threshold is represented mathematically as

$$1 - (1/ R_o),$$

where R_o refers to the basic reproduction number of the pathogen.[1] The basic reproduction number is defined as the average number of secondary infections introduced by a single infected person into a completely susceptible population. This equation shows that the population immunity threshold rises if the pathogen has a higher R_o, i.e., if it is more communicable.

A slight shift in the concept occurs when applying the above to a population where some individuals have pre-existing immunity. Under this circumstance, the population immunity threshold is

$$1 - (1/ R_e),$$

where R_e is the effective reproduction number of a pathogen in a population that has achieved partial immunity.[3] This equation offers a closer approximation to the current realities experienced by most countries at this stage of the COVID-19 pandemic.

In a real world scenario, the R_o and R_e of a pathogen depends on its transmission dynamics and the population in which it circulates. In addition to the pathogen's biological characteristics, other factors can include varying innate susceptibility to the infection from individual to individual, density and social structure of the population, and contact rates across demographic groups. Several parameters are in turn influenced by behavioral practices such as social distancing, personal

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hygiene etiquette, and mask-wearing. Consequently, the threshold for herd immunity varies both for different pathogens and for different populations responding to the same pathogen.[2, 3]

Another consideration is the durability of the immunity established after natural infection or vaccination. Many infectious pathogens do not generate lifelong immunity in humans, therefore compromising the preservation of community immunity.[3]

How does this apply to SARS-CoV-2?

It is challenging right now to estimate the R_o for SARS-CoV-2. Using 12 studies, Liu and colleagues[4] arrived at a mean and median estimated R_o of 3.28 and 2.79, respectively, within a range of 2 - 6. The corresponding calculated herd immunity thresholds ranged quite widely, from 50% to 83.3%, illustrating that such thresholds are conceptual. More detailed modeling would need to incorporate additional considerations, including population and behavioral dynamics, as well as transmission dynamics of the pathogen specific to the various region.[1, 3]

Achieving herd immunity against SARS-CoV-2

Whether herd immunity to SARS-CoV-2 can be successfully achieved depends on various considerations around its two main modalities: natural infection and vaccination.[2]

The immunity that can be triggered by a safe and effective vaccine would need to stop both disease manifestation and transmission. To do this, the vaccine would have to enable acquisition of persistent long-term immunity, otherwise revaccination will be necessary. Receptiveness to vaccination campaigns among populations is also a factor, as it could influence the immunity generated and would be critical to their success.[3]

Natural infection stimulates antibody production against SARS-CoV-2, but it is still not clear at this stage whether the resultant immunity acquired by those who recover persists beyond the short term, and if so, for what absolute length of time.[3] Using Liu's median R_o of 2.79, the threshold for herd immunity of SARS-CoV-2 is 64.15%. This means that just under two-thirds of populations would have to become immune either by surviving natural infection or by being successfully vaccinated for herd immunity to be achieved. At this point, according to serotracker.com,[5] which calculates seroprevalence of populations in various regions based on available studies, estimated prevalence rates as of mid-August included an 8.6% national prevalence rate for the United Kingdom, a prevalence range of 2.7% to 6.4% for Spain, a range of 0.26% to 23% for different regions across the U.S., a 14% rate for Germany, and a 28.5% rate for Italy. Clearly, most countries are still far from approaching herd immunity thresholds.

In the absence of an effective vaccine, a still higher COVID-19 infection rate would theoretically be required to enable the world's population to move toward achieving herd immunity. The cost of the associated mortality, morbidity, and possible resultant long-term complications, as well as the overwhelming burden on healthcare systems, could be challenging worldwide.

Conclusion

Understanding and applying the principles of herd immunity will be an essential component of bringing the COVID-19 pandemic to an end. While there may be barriers to establishing herd immunity, it is hoped that effective treatments that reduce COVID-19-related mortality, as well as the development and deployment of vaccines that can confer durable and long-lasting immunity, will successfully achieve this goal.

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Longer Life Foundation

An RGA/Washington University Collaboration

LONGER LIFE FOUNDATION'S 2020-2021 RESEARCH GRANT RECIPIENTS

The Longer Life Foundation (LLF) is proud to announce its newest research grant recipients. These individuals are investigating some of the most important health issues of the day, including COVID-19.

To find out more about LLF and the research funded to date, please visit www.longerlife.org or reach out to Dr. Dan Zimmerman at dzimmerman@rgare.com or Dr. Dave Rengachary at drengachary@rgare.com.

Investigator/Title of Research Project	Description
Jeffrey Henderson, M.D., Ph.D.* Prognostic Biomarkers of Severe Disease in COVID-19 Patients	The aim of this novel study is to discover biomarkers that identify COVID-19 patients at high risk for progressing to severe disease. This will improve mortality and morbidity by directing high-risk patients to closer medical monitoring, identifying patients who will benefit from early treatment, and optimizing use of limited treatment doses.
*Award effective June 1, 2020 through May 31, 2021. All other awards effective October 1, 2020 through September 30, 2021.	
Cynthia Herrick, M.D., MPHS Clinic to Community Connections: Type 2 Diabetes Prevention Among Low-Income Women with Gestational Diabetes	The central objective of this project is to test a program that teaches practical skills to prevent diabetes. The program focuses on women who have high blood sugar first detected during pregnancy (gestational diabetes).
Alex Holehouse, M.Sc., Ph.D. Predicting the Functional Impact of Genetic Variation with Intrinsically Disordered Protein Regions	A major roadblock toward personalized medicine is the inability to predict the clinical significance of arbitrary mutations detected in a person's genome. This proposal is centered on a novel approach for predicting the functional impact of mutations by studying intrinsically disordered proteins (IDRs) and protein regions.
Devesha Kulkarni, M.Sc., Ph.D. Defining the Role of Intestinal Immune Cell Balance and its Association with Obesity	In the last 10 years, researchers have identified the role of dysbiosis (imbalance in gut microbiota) in the development of obesity and its related comorbidities. The results of this study will form the scientific basis for therapeutic approaches to prevent or reverse obesity and associated diseases.

Kathryn Lindley, M.D. Angiogenic Imbalance and Diastolic Dysfunction in Pre-Eclampsia	Pre-eclampsia (PE) during pregnancy is associated with the development of future cardiovascular disease (CVD). Recent epidemiologic studies suggest that rather than being a marker of CVD, PE is mechanistically linked to the development of CVD. The goal of this study is to identify PE-related biomarkers associated with left ventricular diastolic dysfunction, which may help identify women at high risk for future CVD.
Bettina Mittendorfer, Ph.D. Director, Longevity Research Program (LRP) Dietary Protein and Cardiovascular Health (Year 2)	The goal of this three-year LRP project is to evaluate the effect of dietary protein (plant vs. animal origin) on cardiovascular health and to determine the physiological and cellular mechanisms involved. This topic is particularly important because consumption of protein-fortified plant-based foods is now a popular trend.
Carolina Soriano-Tarraga, M.Sc., Ph.D. DNA methylation in Alzheimer's disease (AD)	This study will examine changes in blood DNA methylation, a modification of the DNA, in AD patients and controls at two time points (at early and late stages of the disease), and compare these results to brain DNA methylation from the same individuals. This information could be used as a biomarker of AD diagnosis, progression, and prognosis, or to improve the understanding of what causes AD. It may also serve as a new way to identify drug targets.

The Longer Life Foundation invites you to click below to view a short (4:04) interview with Dr. Bettina Mittendorfer to learn more about her research and work as Director of the Longevity Research Program.

ReCite

Interesting and relevant articles to the field of insurance medicine recently appearing in the literature...

Association of Healthy Lifestyle with Years Lived Without Major Chronic Diseases

Nyberg T, et al.
JAMA Internal Medicine. 2020 Apr 6; 180(5): 760-8.
https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2763720

Many studies have explored the association of lifestyle factors with mortality and morbidity risk. Findings to date suggest that healthy lifestyle choices, such as being active, maintaining a low body mass index (BMI), avoiding smoking, and consuming modest amounts of alcohol, confer the lowest risk of mortality and chronic, non-communicable diseases, specifically cardiovascular diseases. What is yet to be discovered is how combinations of these factors can impact disease-free life-years.

This study sought to estimate the association between healthy lifestyles and the number of disease-free life-years. Disease-free life-years refer to the number of life-years between ages 40 and 75 years that an individual is free from a diagnosis of any of the following noncommunicable diseases: type 2 diabetes, coronary heart disease, stroke, cancer, asthma, and chronic obstructive pulmonary disease (COPD).

The analytic sample included 12 European cohorts from the Individual-Participant-Data Meta-Analysis in Working Populations (IPD-Work) Consortium. The 12 that had data on all risk factors at baseline and follow-up of noncommunicable diseases were included in this analysis. In all, the sample comprised 116,043 participants for whom there was data on height, weight, smoking, physical activity, and alcohol consumption, and who, at baseline, had no history of cancer, coronary heart disease, stroke, diabetes, asthma, or COPD.

The main finding of this study was that a high overall healthy lifestyle score and a lifestyle profile characterized by the four optimal factors was associated with significant gains in life-years without major noncommunicable diseases for both sexes.

Editor's Note: *These findings may be useful for strengthening the evidence base to support healthy choices in everyday life as well as underwriting decisions.*

Dietary Intake of Total, Animal, and Plant Proteins and Risk of All Cause, Cardiovascular, and Cancer Mortality: Systematic Review and Dose-Response Meta-analysis of Prospective Cohort Studies

Naghshi S, et al.
BMJ. 2020 Jul 22; 370: m2412.
https://www.bmj.com/content/370/bmj.m2412

Cardiovascular disease and cancer are two leading causes of death. Diet is an important factor in both conditions. A global transition toward more protein in diets has occurred in the past few decades. More recently, high-protein diets have again become popular because of possible positive effects on weight loss, preservation of muscle mass, and increased strength.

The aim of this study was to examine the association between intake of dietary protein as well as types of dietary protein and risk of all-cause mortality as well as mortality due to cardiovascular disease and cancer.

A two-stage, random effects dose-response meta-analysis was applied to examine a possible non-linear association between protein intake and mortality.

The study found that high total intake of protein was associated with a lower risk of all-cause mortality. Intake of plant protein was also associated with a lower risk of all-cause and cardiovascular disease mortality. This is consistent with the beneficial effects of increasing plant intake on cardiometabolic risk factors, including blood lipid and lipoprotein profiles, blood pressure, and glycemic regulation.

Editor's Note: *These findings may have important public health implications as intake of plant protein could have a large effect on human longevity. This study strongly supports the existing dietary recommendations to increase consumption of plant proteins. Assessment of dietary profiles could become crucial to underwriting decisions in the future.*

Incidence of Stress Cardiomyopathy During the Coronavirus Disease 2019 Pandemic

Jabri A, et al.
JAMA Network Open. 2020 Jul 9; 3(7): e2014780
https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2768093

The global effects of COVID-19 have been linked with increasing stress and anxiety worldwide. Clinicians have noted a rise in stress cardiomyopathy (also known as Takotsubo syndrome or Takotsubo cardiomyopathy) worldwide since the COVID-19 pandemic began early this year.

This observation warranted further investigation to determine if there might be a plausible pathogenic mechanism associated with COVID-19 causing Takotsubo syndrome, such as cardiomyopathy, versus a true increase in its incidence due to the associated psychological, social, and economic stresses of imposed quarantine, lack of social interaction, strict physical distancing rules, and the pandemic's economic impact on people's lives.

The study investigated the incidence of stress cardiomyopathy during the COVID-19 pandemic in comparison with its incidence in historical cohorts, its association with the viral infection, and related outcomes.

Researchers analyzed electronic medical records of all patients presenting with acute coronary syndrome (ACS), including ST-segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction, and unstable angina, from two hospitals in the Cleveland Clinic Health System in Ohio (U.S.). Control groups included patients seen during March 1 to April 30, 2018, January 1 to February 28, 2019, March 1 to April 30, 2019, and January 1 to February 29, 2020. The study group consisted of patients from March 1 to April 30, 2020, i.e., patients who presented during the COVID-19 pandemic.

The incidence of stress cardiomyopathy was significantly higher in patients presenting with ACS between March 1 and April 30, 2020, compared with the four control groups from before the pandemic. The incidence of stress cardiomyopathy in the control groups was similar to that reported in the literature, ranging from 1.0% to 2.0% in patients presenting with acute myocardial infarction. The study group outcomes were similar to those of the control groups with regard to mortality and 30-day rehospitalization. However, patients with stress cardiomyopathy who needed hospitalization during the pandemic had significantly longer length of stays.

The study determined that the psychological, social, and economic distress accompanying the pandemic, rather than direct viral involvement and sequelae of the infection, were factors more likely associated with the increase in stress cardiomyopathy cases. This was further supported by negative COVID-19 testing results in all patients diagnosed with stress cardiomyopathy in the study group.

Editor's Note: *The indirect long-term psychological effects of the COVID-19 pandemic are likely to have significant impacts on many conditions, including stress cardiomyopathy, for years to come. These factors will need to be considered for risk assessment going forward.*

The Impact of the COVID-19 Pandemic on Cancer Deaths Due to Delays in Diagnosis in England, UK: a National, Population-Based, Modelling Study

Maringe C, et al.
The Lancet Oncology. 2020 Jul 20; 21(8): 1023-34
https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(20)30388-0/fulltext

A lockdown was introduced across the U.K. on March 23, 2020, as part of the national strategy to flatten the curve of the COVID-19 pandemic and reduce the potential impact on the U.K.'s National Health Service (NHS). Similar protocols occurred worldwide, which resulted in the suspension of cancer screening activities and the deferral of routine diagnostic investigations. Additionally, the urgent two-week wait referrals from NHS general practitioners in the U.K. for patients with suspected cancer decreased by up to 80% in response to physical distancing requirements.

This study is the first of its kind to estimate the impact of delays in diagnostic pathways stemming from the pandemic's lockdown measures on cancer survival for four major tumor types (breast, colorectal, esophageal, and lung). National cancer registration and hospital datasets were used, which provided a robust template for understanding the impact of current and predicted changes in availability, access, and health-seeking behavior in response to the COVID-19 pandemic on cancer survival.

The study estimated years of life lost (YLLs) due to premature deaths to understand the wider effects resulting from avoidable cancer deaths, and how this varied according to tumor type and the age profile of men and women diagnosed with these cancers. Data was collected for 32,583 patients with breast cancer, 24,975 with colorectal cancer, 6,744 with esophageal cancer, and 29,305 with lung cancer. Across the four different scenarios, compared with pre-pandemic figures, the study projected increases in the number of additional deaths after diagnosis and within five years would generate total additional YLLs of an estimated 59,204 to 63,229 years.

Editor's Note: *Substantial increases in the number of avoidable cancer deaths in England are to be expected as a result of diagnostic delays due to the COVID-19 pandemic. This is expected to be similar worldwide, and is likely to impact future life and health insurance pricing and product development.*

RGA THOUGHT LEADERSHIP PUBLICATIONS

RGA publishes content on many topics of interest to insurers. Here are links to some recent publications:

HbA1c Levels – Mortality Biomarker or Random Fluctuation?
By Dr. Guizhou Hu, Vice President, Head of Risk Analytics, Global Data and Analytics, RGA, Dr. Dave Rengachary, DBIM, FALU, FLMI, Senior Vice President and Chief Medical Director, U.S. Mortality Markets, RGA, and Yunus Piperdy, FCII, Vice President and Head of Underwriting Innovation Strategy, RGA UK
https://www.rgare.com/knowledge-center/media/articles/hba1c-levels-mortality-biomarker-or-random-fluctuation

Global Claims Views: COVID-19/SARS-CoV-2 and the Impact on Disability - A Focus on Fatigue
By Dr. Paul Davis, FRACP, Chief Medical Officer, RGA Australia
https://www.rgare.com/knowledge-center/media/covid-19/global-claims-views-covid-19-sars-cov-2-and-the-impact-on-disability-a-focus-on-fatigue

What Can Insurers Learn About COVID-19 Risk Factors From OpenSAFELY, the Largest Cohort Study to Date?
By Anna Currie, Underwriting Research and Development Manager, RGA UK, and John Ng, FIA, Senior Data Scientist, Global Data and Analytics, RGA
https://www.rgare.com/knowledge-center/media/covid-19/what-can-insurers-learn-about-covid-19-risk-factors-from-opensafely-the-largest-cohort-study-to-date

COVID-19 Brief: Do Your Genes Carry the Secret to Disease Response?
By Carmela Tedesco, Vice President, Underwriting Solutions, RGAX, and Gayathri Ravi Shankar, Knowledge Management and Information Specialist, RGA
https://www.rgare.com/knowledge-center/media/covid-19/covid-19-brief-do-your-genes-carry-the-secret-to-disease-response

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Alzheimer's Disease: Epidemiology, Risks, and Testing

By Hilary Henly, Chartered Insurer / FCII (DLDU/DLDC), Head of Underwriting Ireland, Director, Divisional Underwriting Research, RGA International Reinsurance Company dac

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